When citing an abstract from the 2022 annual meeting, please use the format below.

[Authors]. [Abstract Title]. Program No. XXX.XX. 2022 Neuroscience Meeting Planner. San Diego, CA: Society for Neuroscience, 2022. Online.

Poster

107. Postnatal Neurogenesis

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 107.01

Topic: A.02. Postnatal Neurogenesis

Title: Role of EPH/EFN in the Regulation of Neuroblast Fate and Topographical Mapping

Authors: *D. YEROSHENKO[1], M. MASHWIYAT[1], I. LIVINGSTON[2], S. BELLIZZI[1], J. C. CONOVER[3];
[1]Dept Physiol & Neurobiol, [2]Univ. of Connecticut, Storrs Manfld, CT; [3]Dept Physiol & Neurobiol, Univ. Connecticut, Storrs Manfld, CT

Abstract: Here, we identify Eph-ephrin signaling as a mechanism that supports cell-cell physical interactions to direct migration and topographical mapping in the postnatal brain. In rodents, the only postnatal long-range pathway is the forebrain rostral migratory stream (RMS). It is known that this migration pathway consists of fasciculated chains of neuroblasts that migrate through a dense meshwork of astrocytes prior to dispersal and then integration within the olfactory bulb. However, the molecular cues that coordinate this extensive migration and guide new neuron distribution are unclear.Receptor tyrosine kinases Ephs and their ephrin ligands are known for coordinating and directing cell migration through direct cell-cell contact and are abundantly expressed at the ventricular-subventricular zone (birthplace of migratory neuroblasts), RMS (migratory pathway), and the olfactory bulb (final destination), making them candidates for regulating the neuroblast migration and integration. Previously, our group found that EphA4 is a key player in RMS organization, as EphA4$^{-/-}$ mice show disorganization of the astrocyte meshwork, loss of neuroblast fasciculation and aberrant neuroblast migration - neuroblasts deviate from the tight confines of the RMS. Immunohistochemistry and single-cell analysis also revealed unique neuroblast and astrocyte subpopulations based on EphA4/ephrin expression patterns.Here, we present Eph/ephrin distribution patterns within the olfactory bulb, including the specific localization of activated (phosphorylated) receptors and ligands. Using single-cell expression transcriptomics and proteomics, we infer migration patterns for each neuroblast/interneuron subpopulation across olfactory bulb development. In summary, we propose that differential co-expression of specific Ephs/ephrins in migratory neuroblast subpopulations act as guidance cues in forebrain migration and then in olfactory bulb distribution.

Disclosures: D. Yeroshenko: None. **M. Mashwiyat:** None. **I. Livingston:** None. **S. Bellizzi:** None. **J.C. Conover:** None.

Poster

107. Postnatal Neurogenesis

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 107.02

Topic: A.02. Postnatal Neurogenesis

Support: ENDpoiNTs (grant no. 825759)
ATHENA (grant no. 666869)
NeurATRIS, ACACIA

Title: Developmental thyroid-hormone disruption and long-lasting consequences on neural stem cell fate

Authors: P. VANCAMP[1], K. LE BLAY[2], ***S. REMAUD**[1];
[1]CNRS MNHN 7221, PARIS, France; [2]CNRS UMR 7221, Paris, France

Abstract: The subventricular zone (SVZ) of the adult mammalian brain harbors neural stem cells (NSCs) that generate neurons and oligodendrocytes throughout life. Our previous work demonstrated that the thyroid hormone (TH) signaling pathway tightly modulated NSC fate in the young adult mouse brain. Our recent work is focused on the modulation of NSC behavior underlying TH during the early post-natal life. Indeed, single-cell RNA-Seq analysis on mouse SVZ-NSCs isolated at different developmental stages established they gradually acquire their adult neurogliogenic identity between postnatal day (P) 7 and 20. We hypothesized that TH could fulfil this role. TH serum levels rise postnatally and peak around P15. Re-analysis of single-cell data from the P2 and P20 SVZ revealed a dynamically increased expression of the TH transporters *Mct8* and *Oatp1c1*, as well as the TH-(in)activating deiodinases *Dio2* and *Dio3* in NSCs, signs that the majority of NSCs possess the machinery to auto-regulate their intracellular TH concentration, allowing for TH action. Moreover, immunostainings showed a concomitant burst in SVZ-neurogenesis in vivo. Then, to study what occurs if TH synthesis is blocked, we fed dams a 0.15% propylthiouracil-enriched diet from embryonic day 15 to P21. *n vivo* analysis showed decreased SVZ-neuroblast and OPC generation at P21, as well as reduced uncommitted progenitor proliferation following this perinatal hypothyroidism. Interestingly, in 3-month-old young adult mice, that regained a normal diet following developmental PTU exposure, the neuro-gliogenesis is permanently impaired in the adult SVZ resulted in a lasting altered neuro/glia output. Related to that were behavioural alterations: a reduced ability to remember earlier-presented odors indicates impaired olfaction, a behavior strongly depending on SVZ-neurogenesis. Taken together our data indicate that perinatal hypothyroidism affects postnatal SVZ remodeling and permanently alters NSC lineage commitment. Our work reflects the idea of the Barker hypothesis (i.e. developmental origins of health and disease), and prompts the question whether ubiquitous environmental toxicants, notably endocrine disruptors, might evoke irreversible effects on the brain.

Disclosures: P. Vancamp: None. **K. Le Blay:** None. **S. Remaud:** None.

Poster

107. Postnatal Neurogenesis

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 107.03

Topic: A.02. Postnatal Neurogenesis

Support: NIH 1R01NS114578 (E.J.B)
NIH T32HD094671 (A.A.E)
Jean and George Brumley Jr. Endowment (to E.J.B)
Zeist Foundation (E.J.B)
American Academy of Pediatrics (AAP) Marshall Klaus Research Award (A.A.E.)

Title: Postnatal neurogenesis is disrupted by inflammatory injury in the subventricular zone following modelled intestinal perforation

Authors: *A. A. EPSTEIN[1], V. JAIN[4], A. S. CHAO[1], K. ABDI[4], K. PEGRAM[2], C. M. MAXFIELD[3], S. GREGORY[4], E. J. BENNER[1];
[1]Dept. of Pediatrics, Div. of Neonatology, [3]Radiology, [2]Duke Univ. Sch. of Med., Durham, NC; [4]Duke Mol. Physiol. Inst., Duke Univ., Durham, NC

Abstract: Intestinal perforation in preterm infants has been linked to neurodevelopmental impairment. Novel evidence of brain injury using cranial ultrasound surveillance in neonates identified SVZ echogenicity (SVE) following intestinal perforations predictive of motor impairment. The subventricular zone (SVZ) is a transient neural stem cell niche residing in the germinal matrix that generates glial progenitors required for proper myelination and neuronal progenitors that migrate to the frontal lobes postnatally. However, the mechanism(s) coupling systemic inflammatory disease to SVE needs to be defined. Here, we investigated structural and functional changes in the SVZ using neonatal modeled intestinal perforation (MIP) in rodents. MIP led to increased macrophage/microgliosis and increased proinflammatory cytokines in the SVZ compared to littermate controls. Disruption of multiciliated ependymal cell organization was seen in SVZ whole mounts using FoxJ1-EGFP tg-mice, as well as decreased cilia on the ventricular surface visualized using scanning electron microscopy. We employed single nuclear transcriptomic profiling ($snRNA^{seq}$) to study discrete SVZ niche cell populations in both MIP and littermate control mice. Using cluster specific differentially expressed genes we manually annotated 15 segregated clusters using established SVZ niche cell types. *In silico* pathway analysis showed ependymal cell and macrophage populations significantly upregulate multiple inflammatory pathways. Analysis of the neural progenitor lineages demonstrated decreased cell frequency and downregulation of metabolic pathways while also showing increased EGF receptor signaling following MIP. Deficits in postnatal neurogenesis were confirmed using confocal microscopy of doublecortin (DCx)-positive cell chain organization across the lateral ventricular wall in young adult mice. Our animal data suggests that SVZ injury following intestinal perforation leads to deficits in neurogenesis during a critical time of neurodevelopment. This previously undescribed injury may be an important molecular mechanism linking inflammatory complications following preterm birth and poor neurodevelopmental outcomes.

Disclosures: **A.A. Epstein:** None. **V. Jain:** None. **A.S. Chao:** None. **K. Abdi:** None. **K. Pegram:** None. **C.M. Maxfield:** None. **S. Gregory:** None. **E.J. Benner:** None.

Poster

107. Postnatal Neurogenesis

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 107.04

Topic: A.02. Postnatal Neurogenesis

Support: NIEHS R01ES027078

Title: Copper Modulates Adult Neurogenesis in the Subventricular Zone: Evidence from Copper Chelation by Intracerebroventricular Infusion of D-Penicillamine

Authors: *L. L. LIU, W. ZHENG;
Purdue Univ., West Lafayette, IN

Abstract: Early studies from this group provide strong evidence for selective Cu enrichment in adult brain subventricular zone (SVZ) as compared to the rest of brain regions. Our more recent data further reveal an increased neural proliferation in the SVZ, but with impaired olfaction, in experimentally Cu-deficient adult rats. However, the question as to whether Cu directly affected SVZ adult neurogenesis remained unanswered. This study was designed to investigate if reducing SVZ Cu level by Cu chelation altered the SVZ neurogenesis in adult mice. An intracerebroventricular (icv) infusion technique was established to deliver Cu chelator D-Penicillamine (D-Pen), which was stored in a pump reservoir implanted under back skin, directly into the cerebrospinal fluid (CSF) by lateral ventricle cannulation. AAS analyses verified the efficacy of icv infusion of D-Pen, showing that the Cu levels in SVZ were reduced by 7.5% ($p=0.17$) and 21.4% ($p<0.05$), when adult mice received icv-infusions of D-Pen at low (0.075 μg/h) and high (0.75 μg/h) doses for 28 days, respectively, as compared to saline-infused controls. Confocal immunohistochemical studies into the SVZ-rostral migratory stream (RMS)-olfactory bulb (OB) axis revealed that the 7-day low-dose D-Pen infusion significantly increased Ki67(+)/Nestin(+) cell counts in SVZ by 28% ($n=3$, $p<0.05$). Quantification of BrdU(+)/DCX(+) neuroblasts in the RMS and OB further revealed that the short-term, low-dose D-Pen infusion resulted in more BrdU(+)-neuroblasts in OB; however, the high-dose D-Pen infusion showed fewer labeled neuroblasts in OB but with more in the RMS ($n=3$, $p<0.05$) compared to controls. The long-term (28-day) infusion studies revealed similar outcomes, i.e., a significant increase of the newly generated neurons in OB by 37.8% ($p<0.05$) in the low-dose D-Pen group but no changes in the high-dose group. Additionally, the long-term, low-dose D-Pen infusion upregulated the activation ratio of NPSCs in the SVZ. Further investigation on critical Cu regulatory proteins indicated that both CTR1 and MT3 expressed as clusters in SVZ and their expression was altered in response to Cu chelation. Noticeably also, CTR1 expression in the choroid plexus, a tissue nearby SVZ modulating CSF Cu homeostasis, was upregulated by long-term D-Pen infusion. In conclusion, this study provides first-hand evidence that a reduced Cu

level in SVZ by Cu chelation appears likely to activate adult neurogenesis in this largest neurogenic zone in the adult brain. *Supported by NIEHS R01ES027078.*

Disclosures: L.L. Liu: None. **W. Zheng:** None.

Poster

107. Postnatal Neurogenesis

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 107.05

Topic: A.02. Postnatal Neurogenesis

Support: National Key Research and Development Program 2016YFA0100801
NIH/NIMH Grant 5R21MH115382
NIH Grant U54D087101
Intellectual and Developmental Disabilities Research Center at the University of California, Los Angeles

Title: Prenatal stress (PNS) promotes adult onset neurogenesis in the ependymal- subventricular zone of adult male offspring

Authors: *L. L. LIU[1], Z. WANG[2], L.-Q. ZHOU[2], C.-M. LEE[1], J.-Y. SHI[2], X.-J. YANG[2], Y.-X. DENG[2], J.-P. LIU[2], J.-B. WANG[3], W.-M. ZHU[2], Y. E. SUN[2], Q. LIN[1];
[1]Dept. of Psychiatry and Behavioral Sciences, Intellectual Develop. and Disabilities Res., UCLA, Los Angeles, CA; [2]Shanghai Institue of Stem Cell Res. and Clin. Translation, Shanghai East Hospital, Tongji Univ., Shanghai, China; [3]Orthopedic Dept., Sch. of Medicine, Tongji Univ., Shanghai, China

Abstract: It is well established that disturbances during critical stages of prenatal development can lead to adverse functional consequences in postnatal life. Here, we found that prenatal maternal stress (PNS) promotes late onset neurogenesis in the lateral ependymal-subventricular zone (E-SVZ) of male offspring (C57BL/6). One critical intrinsic biological mechanism PNS triggers to promote late onset neurogenesis is the upregulation of the MAP kinase (MAPK) pathway. Unexpertedly, immunostaining of prenatally stressed (STR) and unstressed (UNSTR) male offspring at different postnatal stages revealed an increase in the number of $MKI67^+$ proliferating cells in the E-SVZ ($p<0.001$) including proliferating ependymal cells ($MKI67^+/PROM1^+$, $p= 0.0312$) in the STR group beginning from P60. BrdU pulse labeling in adult P180 offspring revealed a higher number of $BrdU^+$ proliferating cells in the E-SVZ ($BrdU^+$, $p<0.0001$), proliferating ependymal cells ($MKI67^+/PROM1^+$, $p=0.0002$, $BrdU^+/PROM1^+$, $p=0.0002$), and proliferating neuroblasts ($MKI67^+/TUBB3^+$, $p=0.0071$, $BrdU^+/TUBB3^+$, $p<0.0001$) in the STR group. An increased number of proliferating cells in the rostral migratory stream (RMS) and subsequent mature neurons in the olfactory bulb (OB) with few cell deaths were also observed in the STR group. Bulk and single nuclei RNAseq data revealed an upregulation in genes involved in the down regulation of the negative regulation of

both phosphorylation (p<10^-7) and transferase activity (p<10^-7.5). Past studies have implicated the MAPK pathway in playing an essential role in the upregulation of neurogenesis . Rescue assays targeting either MAPK 3/1 or MAP2K 1/2, crucial kinases of the MAPK pathway, showed a decrease in the number of proliferating ependymal cells and neuroblast cells to baseline control levels, suggesting that the upregulation of the MAPK pathway was critical to increasing neuronal cell proliferation in the STR group. Behavioral assessments by the buried food test showed largely normal olfaction in the STR group, while the habituation/dishabituation test revealed normal olfaction for nonsocial cues, but impaired olfaction for social cues in the STR group. Although our study demonstrates the ability of prenatal maternal stress (PNS) to influence behavioral changes postnatally by upregulating the MAP kinase pathway that in turn upregulates cell proliferation in the E-SVZ, it remains to be understood the extrinsic cues that PNS elicits to upregulate neurogenesis and brings to question the source of actively proliferating cells in the E-SVZ.

Disclosures: **L.L. Liu:** None. **Z. Wang:** None. **L. Zhou:** None. **C. Lee:** None. **J. Shi:** None. **X. Yang:** None. **Y. Deng:** None. **J. Liu:** None. **J. Wang:** None. **W. Zhu:** None. **Y.E. Sun:** None. **Q. Lin:** None.

Poster

107. Postnatal Neurogenesis

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 107.06

Topic: A.02. Postnatal Neurogenesis

Support: Swiss National Science Foundation grant n° 146632
the Department of Surgery of Basel University Hospital
Department of Biomedicine of Basel

Title: Doublecortin is released from differentiating rat neural stem cells and consists predominantly of fragments

Authors: *C. BREGERE, B. SCHWENDELE, T. DITTMAR, P. BUSTOS, R. GUZMAN; Univ. Hosp. Basel, Univ. Hosp. Basel, Basel, Switzerland

Abstract: Background: Doublecortin (DCX) is a microtubule-associated protein often used as a marker of adult hippocampal neurogenesis. While predominantly intracellular, studies indicate that DCX is also present in the extracellular space, such as the cerebrospinal fluid (CSF) from rodent neonates and human infants. We showed that DCX concentration in the CSF increases after neonatal hypoxic-ischemic brain injury in the rat. Nevertheless, fundamental aspects concerning extracellular DCX remain currently unexplored: (i) the molecular forms are not characterized, (ii) it is unclear whether DCX can be released physiologically, and if so, (iii) the putative mechanism(s) of release are elusive. Methods: To address these issues, cortical neural stem/progenitor cells (NSPCs) isolated from embryonic day E14.5 rat embryos were expanded

with FGF-2 *in vitro*, and allowed to differentiate for 9 days in the absence of mitogen. Cell lysates and conditioned medium (CM) from 100 mm dishes were collected every 3 days, and cells cultured in ibidi chambers were paraformaldehyde-fixed in parallel for immunocytochemistry purposes. Cellular lysates and CM were analyzed by western blots. Quantification of intra- and extracellular DCX was also performed by specific immunoassays, and percent DCX release was calculated. Results: Immunocytochemistry of differentiating rat NSPCs clearly showed an increase in DCX staining with time, and the majority of DCX positive cells appeared to remain negative for cleaved caspase-3, a marker of cell death. Immunoblot analysis of cell lysates confirmed this steep increase in DCX levels with differentiation time, together with a rise in GFAP (astrocytic marker) and NeuN (neuronal marker), thereby attesting that differentiation did occur upon FGF-2 withdrawal. Intracellular DCX concentration and percent DCX release increased concomitantly as differentiation proceeded. While immunoblot analysis showed that full length doublecortin (~50 kDa) was the major species present in cell lysates, fragmented forms of DCX (~25 and 13 kDa) were detected and represented the most abundant species in concentrated CM. Conclusions: Our results suggest that DCX is released extracellularly independently of cell death, and that DCX undergoes cleavage prior to or during its passage to the extracellular space. Future studies will address the mechanisms of release of DCX and the potential functions of extracellular DCX.

Disclosures: C. Bregere: None. **B. Schwendele:** None. **T. Dittmar:** None. **P. Bustos:** None. **R. Guzman:** None.

Poster

107. Postnatal Neurogenesis

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 107.07

Topic: A.02. Postnatal Neurogenesis

Support: This work was supported by funds from the NINDS IRP.

Title: Neuregulin signaling in the development and physiology of fear learning related circuits

Authors: *L. JIANG, P. RAJEBHOSALE, N. DESAI, L. ROLE, D. TALMAGE;
NINDS, NIH, Bethesda, MD

Abstract: Type III Neuregulin (Nrg) 1 is important for neuronal development and function. Type III Nrg 1 mutant mice have defective fear learning. Our earlier studies have shown Nrg1 signaling is required for multiple aspects of the modulation of excitatory plasticity at cortical-BLA synapses and activation of cholinergic input from basal forebrain can enhance fear learning. However, the contribution of Nrg1 signaling to cholinergic modulation of fear-learning is not clear. In this study, we are using a mouse model with a psychosis-related Nrg1 mutation that impairs γ-secretase-mediated nuclear signaling. We are using optogenetic techniques to dissect the role of Nrg1 during the maturation of synaptic plasticity and cholinergic modulation of

specific synapses involved in threat learning (anterior cingulate to BLA, entorhinal cortex to DG, DG to CA3). In preliminary studies alterations in synaptic plasticity and cholinergic modulation in the Nrg1 mutants compared to wild type littermates. We have also found substantial alterations in fundamental physiological properties of mutant DG neurons. Our current study is helping to understand how Nrg1 local and nuclear back signaling can change neuronal development and affect fear learning related circuits.

Disclosures: L. Jiang: None. **P. Rajebhosale:** None. **N. Desai:** None. **L. Role:** None. **D. Talmage:** None.

Poster

107. Postnatal Neurogenesis

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 107.08

Topic: A.02. Postnatal Neurogenesis

Support: NIH T32 ES007148
NIH P30 ES005022
New Jersey Governor's Council for the Medical Research andTreatment of Autism CAUT20AFP004

Title: Caesarean delivery alters postnatal brain development in a mouse model of autism

Authors: *J. K. LESSING[1], X. ZHOU[2], H. SUN[1], M. G. DOMINGUEZ-BELLO[1], E. M. DICICCO-BLOOM[3];
[1]Biochem. and Microbiology, Rutgers Univ., New Brunswick, NJ; [2]Neurosci. & Cell Biol., [3]Neurosci & Cell Biol / Pediatrics (Child Neuro. & Neurodev. Diseases), Rutgers Univ., Piscataway, NJ

Abstract: Neurodevelopmental diseases - including autism spectrum disorder, attention deficit hyperactivity disorder (ADHD), and learning disability - are thought to be caused by a combination of genetic susceptibility and environmental triggers. Caesarean-section delivery (CS) may be an environmental trigger of developmental disorders. Human cohort studies correlate CS to a 20% increased risk of developing autism and a 17% increased risk of ADHD. Though CS is a medical necessity, the World Health Organization estimates CS rates above 10% do not improve outcomes in healthy mothers or neonates; the current US rate is 32%. Disorders associated with CS may be caused by many factors, including perinatal distress, maternal anesthesia, altered hormonal environment, and disrupted transmission of microbiome from mother to neonate. We designed a system in a genetic model of autism to study effects of CS on neurodevelopment and investigate gene x environment interactions. In humans, the 16p11.2 copy number variant (CNV) is responsible for approximately 1% of autism cases, and carriers have an increased risk of ADHD and intellectual disability. This CNV is conserved in mice. These mice exhibit many behavioral phenotypes and cytoarchitectural abnormalities associated with autism,

including: restrictive, stereotyped, and non-coordinated motor patterns, hyperactivity, and altered brain volumes, including reduced basal ganglia and increased hypothalamus. These phenotypes were generally stronger in male mice. Timed-pregnant dams were allowed to give birth vaginally (control) or underwent terminal CS at gestational day 19. Pups from both groups were cross-fostered by dams giving birth in the previous 24-hours. Following sacrifice on P7, we isolated cerebellum and hippocampus based on associations with neurodevelopmental diseases and periods of neurogenesis. Cerebellar external germinal layer proliferation peaks from P5-P10 and continues to P18 while hippocampal dentate gyrus precursors proliferate throughout life. Neurodevelopmental markers were assessed by immunoblotting. Preliminary data in hippocampus shows male mice that underwent CS had higher levels of proliferation marker cyclin E and potentially increased doublecortin. Conversely, the cerebellum in female mice that underwent CS had markedly increased levels of doublecortin and potentially increased cyclin E. In sum, CS was found to increase levels of neural stem cell markers in the hippocampus and cerebellum. Interestingly, this effect was sex and brain region dependent. Future studies will analyze transcriptional and microbiome-based mechanisms underlying these effects.

Disclosures: **J.K. Lessing:** None. **X. Zhou:** None. **H. Sun:** None. **M.G. Dominguez-Bello:** None. **E.M. DiCicco-Bloom:** None.

Poster

107. Postnatal Neurogenesis

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 107.09

Topic: A.02. Postnatal Neurogenesis

Support: NIH R15CA235749
UC-CRCC C21CR2007

Title: Regulation of Hedgehog signaling by ciliary PKA in health and disease

Authors: *E. CAI, J. ZHANG, X. GE;
Univ. of California, Merced, Merced, CA

Abstract: Abstract Precise regulation of Sonic Hhedgehog (Hh) signaling is essential for the proper formation of the brain. in the primary cilium of mammalian cells is responsible for brain patterning. Dysregulated Hh signaling in granule neural progenitors (GNP) of the developing cerebellum leads to medulloblastoma, a malignant pediatric brain cancer. Previous research show that Hh signaling is negatively regulated by PKA in the primary cilium, a cell surface organelle that acts as the signaling hub for the cell. We hypothesize that activating PKA in the cilium selectively inhibits Hh signaling and Hh-related medulloblastoma without interfering with other pathways. We found that , is a potent negative regulator of Hh signaling. PKA was previously thought to regulate Hh signaling at the centrosome, however, new research shows PKA signaling components within the cilium itself. This research explores the role of ciliary PKA signaling and

its effects on the Hh pathway. specifically targetingExpression of PKA catalytic subunit targeted to the cilium in wild type cells of 3T3 cells reveal that ciliary PKA inhibits Hh signaling and through Gli protein phosphorylation and proteolytic processingGNP proliferation. However, ciliary PKA is necessary but not sufficient to fully suppress Hh signaling. Full suppression of Hh signaling requires the cooperated action of PKA at the centrosome and in the cilium. Our results revealed the thorough regulatory mechanism of Hh signaling by PKA, and highlighted a new avenue to selectively inhibit Hh signaling in cancer therapeutics. In the developing cerebellum, GNP with overexpressed ciliary PKA had lower proliferation rates than control cells. In disease, medulloblastoma cells stem from GNP that overproliferate in response to abnormally high levels of Hh signaling. We will overexpress PKA at the cilium of these cancer cells to inhibit proliferation.

Disclosures: **E. Cai:** None. **J. Zhang:** None. **X. Ge:** None.

Poster

107. Postnatal Neurogenesis

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 107.10

Topic: A.02. Postnatal Neurogenesis

Support: Department of Biotechnology, Ministry of Science and Technology, Government of India (BT/PR8793/AGR/36/746/2013)

Title: Regulation of hypothalamic feeding circuitry by miRNA-mediated adult neurogenesis

Authors: *B. SRINIVASAN, S. SAMADDAR, A. GHOSH, D. ROY, S. BANERJEE;
Natl. Brain Res. Ctr., Gurgaon, India

Abstract: Body weight is regulated by energy homeostasis and is critical to maintain the metabolic demand required for physiological functions. Although, much is known about the functions of the feeding circuitry in the adult hypothalamus, little is known regarding the changes to the established circuitry in response to metabolites present in the diet. Neurogenesis has been observed in tanycytic cells located along the third ventricle and known to influence the functional hypothalamic feeding circuitry. High Fat Diet (HFD) feeding paradigm promotes neurogenesis from a specialized β2 trancytes located in the median eminence of the female mouse. However, mechanistic details of diet-induced neurogenesis and its impact on the function of feeding circuitry remain elusive. Of particular interest, we investigated the role of miRNAs in regulation of adult hypothamalic neurogenesis involving β2 trancytes. We analyzed miRNA expression profile from the neurogenic population of β2 trancytes following BrdU labelling, which was delivered via the intracerebroventricular method. Our miRNA array analysis identified differentially expressed miRNAs from the neurogenic population post HFD feeding compared to normal chow diet (NCD) fed mice. We observed that the expression of miRs-1894, 382, 145, 196 and let-7b were upregulated in the HFD fed mice brains, while miRNAs let-7e, 7i

and 7d were downregulated in the same. Further, we used *in silico* network analysis to identify the transcripts that are targeted by all miRNAs upregulated by HFD feeding. Our analysis identified transcripts involved in neurogenic and metabolic processes, such as IGF1, NTRK2, CAMK2B and ERBB4. We have inhibited functions of the miRNAs by synthesizing a sponge construct and delivered it *via* adeno-associated viruses. Sequestration of all miRNAs by sponge led to enhancement of luciferase reporter expression in a heterologous cell system. We investigated the identity of newborn neurons in the hypothalamus upon HFD feeding, by immunostaining for pro-opiomelanocortin and agouti related peptide, which mark the expressions of anorexigenic and orexigenic neurons that regulate hunger and satiety physiological states respectively. Furthermore, we have evaluated functional integration of these newborn neurons in hypothalamic feeding circuit by detecting c-fos expression following sequestration of miRNAs in the tanycytic cells. Our study highlighted the role of miRNA-regulated adult neurogenesis of the tanycytic population located in the median eminence and identified an emerging factor that influences feeding circuit modifications *via* homeostatic feedbacks to changes caused by a diet-induced obesity.

Disclosures: B. Srinivasan: None. **S. Samaddar:** None. **A. Ghosh:** None. **D. Roy:** None. **S. Banerjee:** None.

Poster

107. Postnatal Neurogenesis

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 107.11

Topic: A.02. Postnatal Neurogenesis

Support: F31DK132944-01
DK108230

Title: Investigating the role of Shh, Wnt, and Notch signaling on tanycyte neurogenic competence in the postnatal hypothalamus

Authors: *L. DUNCAN, S. BLACKSHAW;
The Solomon H. Snyder Dept. of Neurosci., Johns Hopkins Sch. of Med., Baltimore, MD

Abstract: Hypothalamic tanycytes are radial glial cells that closely resemble neural progenitors in morphology and gene expression profiles. Tanycytes retain limited neurogenic competence in juvenile and young adult mice**.** However, the exact molecular mechanisms controlling neurogenic competence in tanycytes, and the physiological function of tanycyte-derived neurons, are still poorly understood. Much emphasis has been placed on showing that dietary and hormonal cues can regulate tanycyte-derived neurogenesis, and tanycyte-derived neurons may regulate body weight. However, overall levels of both tanycyte proliferation and tanycyte-derived neurogenesis are very low, and are essentially undetectable in adulthood mice. Recently, our lab has identified that the *Nuclear Factor One* (*Nfi*) family transcription factors (TFs),

Nfia/b/x, play a critical role in regulating neurogenic competence in tanycytes. Under normal dietary conditions in male mice, *Nfia/b/x*-deficient tanycytes proliferate and undergo neurogenesis (a 50-fold increase compared to wildtype). Single-cell RNA-sequencing (scRNA-seq) analysis of *Nfia/b/x*-deficient tanycytes and tanycyte-derived cells indicates the majority of the tanycyte-derived neurons are GABAergic, expresses the *Leptin* receptor (*Lepr*), and are leptin-sensitive. Our lab has also shown that tanycyte-derived neurons survive, integrate into hypothalamic circuits, and fire spontaneous action potentials. Moreover, differential gene expression patterns between control and *Nfia/b/x*-deficient tanycytes identified multiple extrinsic pathways such as Shh, Wnt, and Notch, which are upregulated or downregulated following *Nfia/b/x* loss of function.

Disclosures: L. Duncan: None. **S. Blackshaw:** None.

Poster

107. Postnatal Neurogenesis

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 107.12

Topic: A.02. Postnatal Neurogenesis

Title: Involvement of prostaglandin E_2in psychobehavioral and neuronal impairments induced by perinatal exposure to environmental risk factor of psychiatric disorders

Authors: *H. HIDA[1,2], A. MOURI[3], S. HOTTA[1,2], M. UCHIDA[1,2], T. FURUYASHIKI[4], S. NARUMIYA[5], A. YOSHIMI[2,6], T. NABESHIMA[3], N. OZAKI[7], K. YAMADA[1], Y. NODA[1,2,6]; [1]Nagoya Univ. Hosp., Dept. of Neuropsychopharm. and Hosp. Pharmacy, Nagoya Univ. Hosp., Nagoya, Japan; [2]Div. of Clin. Sci. and Neuropsychopharm., Grad. Sch. of Pharmacy, Meijo Univ., Nagoya, Japan; [3]Dept. of Regulatory Sci. for Evaluation & Develop. of Pharmaceuticals and Devices, Fujita Hlth. Univ. Grad. Sch. of Hlth. Sci., Toyoake, Japan; [4]Div. of Pharmacol., Kobe Univ. Grad. Sch. of Med., Kobe, Japan; [5]Dept. of Drug Discovery Med., Kyoto Univ. Grad. Sch. of Med., Kyoto, Japan; [6]Clin. OMICs and Translation Res. Ctr., Meijo Univ., Nagoya, Japan; [7]Dept. of Psychiatry, Nagoya Univ. Grad. Sch. of Med., Nagoya, Japan

Abstract: Epidemiological studies indicate that perinatal exposure to environmental risk factors of psychiatric disorders could affect neurodevelopment in offspring. Inflammatory mediators such as cytokines and free radicals are induced by the exposure to environmental risk factors. However, neurodevelopmental effects of prostaglandin E_2 (PGE_2), one of the inflammatory mediators, are not clear. In the present study, we developed the animal models of exposure to environmental risk factor on viral infection, hypoxia, and child neglect during the perinatal period. We also investigated the involvement of PGE_2 in psychobehavioral and anatomical phenotypes in adulthood of these animal models. PGE_2 levels were significantly increased in whole brain of perinatal mice injected viral mimic [polyriboinosinic-polyribocytidylic acid (polyI:C)] during PD 2-6 and exposed to hypoxia (CO_2) at PD 2 or neglect (separation from the dams) during PD 2-21, compared to those in control mice. The mice injected polyI:C exhibited

the impairment of sociality, object recognition memory or pre-pulse inhibition (PPI), and further, significant decreased the spine density of the medial prefrontal cortex (mPFC) in adult at PD 70. Exposure to CO_2 and separation from dams exhibited the impairment of PPI and the decrease of the mPFC spine density in adult mice. These psychobehavioral impairments induced by polyI:C were recovered by an inhibition of PGE_2-EP1 (PGE_2 receptor subtype) signaling and of cyclooxygenase. Our findings suggest that PGE_2 is associated with vulnerability to neurodevelopmental disruptions induced by environmental factors, and plays a crucial role in the development of psychobehavioral and neuronal abnormalities related to activation of PGE_2-EP1 signaling.

Disclosures: H. Hida: None. **A. Mouri:** None. **S. Hotta:** None. **M. Uchida:** None. **T. Furuyashiki:** None. **S. Narumiya:** None. **A. Yoshimi:** None. **T. Nabeshima:** None. **N. Ozaki:** None. **K. Yamada:** None. **Y. Noda:** None.

Poster

108. Multimodal Imaging Studies in Youth: Identifying Trajectories and Sources of Variability

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 108.01

Topic: A.09. Adolescent Development

Support: NIH grants R01AG060054
NIH grants R01AG070227
NIH grants R01EB031080-01A1
NIH grants P41EB029460-01A1
NIH grants 1UL1TR003098

Title: Long-lasting effects of insufficient sleep on neurocognitive development in early adolescence

Authors: *F. N. YANG[1], W. XIE[2], Z. WANG[1];
[1]Diagnos. Radiology, Univ. of Maryland Baltimore, Baltimore, MD; [2]NIH, NIH, Bethesda, MD

Abstract: Background Although the American Academy of Sleep Medicine suggests at least 9 hours of sleep per day for 6- to 12-year-olds, children in recent generations often report sleeping less than the suggested duration. As early adolescence is a critical period for neurocognitive development, we investigated how insufficient sleep has impacted children's mental health, cognition, brain function and structure over two years. **Methods** We obtained large-scale data from the ongoing Adolescent Brain Cognitive Development study and included 8,323 eligible participants aged 9-10 years from 21 U.S. study sites. Participants were separated into two groups, namely sufficient sleep (SS) versus insufficient sleep (IS) groups based on a cutoff of 9 hours of sleep. Using propensity score matching (PSM), we matched these two groups of participants on 11 key covariates, including sex, socioeconomic status, puberty status, etc. The

outcome measures are behavioral problems, mental health, cognition, structural and resting-state functional brain measures, assessed at baseline and at two-year follow-up (FL2). We examined group differences on these outcomes and the stability of these group differences over those 2 years. **Results** We identified 3,021 matched SS-IS pairs at baseline and 749 matched pairs at FL2, and observed similar SS-IS differences in behavior and neural measures at both points in time. For example, the effect sizes of SS-IS differences in behavioral measures at these two timepoints were significantly correlated with each other (r = 0.85, 95% CI 0.73-0.92, p < 0.0001). A similar pattern was observed in resting-state functional connectivity (r = 0.54, 95% CI 0.45-0.61, p < 0.0001) and in structural measures (r = 0.52, 95% CI 0.40-0.61, p < 0.0001). These results suggest the temporal stability of compromised neurocognitive development is associated with insufficient sleep. We then performed mediation analyses to reveal the neural correlates of behavioral changes induced by insufficient sleep. We found that cortico-basal ganglia functional connections mediate the effects of insufficient sleep on depression, thought problems, and crystallized intelligence, and that structural properties of the anterior temporal lobe mediate the impact of insufficient sleep on crystallized intelligence. **Conclusions** These results provide population-level evidence for the long-lasting impact of insufficient sleep on neurocognitive development in early adolescence. These findings highlight the value of early sleep intervention to improve early adolescents' long-term developmental outcomes.

Disclosures: F.N. Yang: None. **W. Xie:** None. **Z. Wang:** None.

Poster

108. Multimodal Imaging Studies in Youth: Identifying Trajectories and Sources of Variability

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 108.02

Topic: A.09. Adolescent Development

Support: NIA Grant RO1 AG064247

Title: Association between executive functions and resting-state functional connectivity of the hippocampus and prefrontal cortex in periadolescent children: Preliminary findings from the PRANK study

Authors: *A. L. ZATKALIK[1], C. J. PHIPPS[1], M. RAMIREZ[1], J. SEXTON[1], A. HELLER[1], L. BEHM[1], K. NICKOLAS[1], A. C. MAERLENDER[2], V. S. PHATAK[1], J. A. CRAMER[1], J. BLAIR[3], D. L. MURMAN[1], D. E. WARREN[1];
[1]Univ. of Nebraska Med. Ctr., Omaha, NE; [2]Univ. of Nebraska Lincoln, Lincoln, NE; [3]Boys Town Natl. Res. Hosp., Omaha, NE

Abstract: Objective: Executive functions (EFs) consist of a diverse range of cognitive abilities, including working memory, inhibitory processes, and mental flexibility. Dysfunction in EF due to neurodevelopmental disorders or neurodegenerative disease can result in attention deficits,

decreased inhibition, and impaired decision-making abilities. EFs have historically been linked to the prefrontal regions of the brain, but recent studies of brain networks and their functional connectivity have broadened these links to include brain regions such as the hippocampus (Hc). Building upon recent findings, the current project investigated the association between decision making and hippocampal resting state functional connectivity (rs-FC) in periadolescent children. **Methods:** A cohort of healthy periadolescent children aged 8-13 (N = 75, 37 F) was sampled from the ongoing NIA-funded Polygenic Risk of Alzheimer's Disease in Nebraska Kids (PRANK) study. PRANK participants completed an array of cognitive and behavioral measures, in addition to an MRI of the brain that included resting-state fMRI. Executive functions were operationalized as performance on the NIH Toolbox Dimensional Change Card Sorting (DCCS) task. The resting state functional connectivity (rs-FC) between the Hc and regions of the prefrontal cortex (PFC) was measured, and its covariance with DCCS was assessed. **Results:** Hippocampal rs-FC covaried with performance on the DCCS in the left dorsolateral prefrontal cortex (dlPFC) and dorsal anterior cingulate cortex (dACC). These anatomical regions are in line with larger intrinsic brain networks, such as the frontoparietal network (FPN) and the cingulo-opercular network (CON). **Conclusion:** These preliminary results suggest the Hc is associated with anatomical regions and intrinsic brain networks that are important for EFs. A better characterization of how EFs are supported by functional brain networks including the hippocampus could offer insight regarding interventions for treatment of executive dysfunction in developmental or older populations.

Disclosures: A.L. Zatkalik: None. **C.J. Phipps:** None. **M. Ramirez:** None. **J. Sexton:** None. **A. Heller:** None. **L. Behm:** None. **K. Nickolas:** None. **A.C. Maerlender:** None. **V.S. Phatak:** None. **J.A. Cramer:** None. **J. Blair:** None. **D.L. Murman:** None. **D.E. Warren:** None.

Poster

108. Multimodal Imaging Studies in Youth: Identifying Trajectories and Sources of Variability

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 108.03

Topic: A.09. Adolescent Development

Support: RO1 AG064247

Title: Association Between Spatial Working Memory and Hippocampal Volume: Preliminary Findings from the PRANK Study

Authors: *J. SEXTON[1], M. RAMIREZ[1], C. J. PHIPPS[1], A. HELLER[1], L. BEHM[1], A. ZATKALIK[1], K. NICKOLAS[1], A. MAERLENDER[3], V. PHATAK[1], J. CRAMER[1], J. R. BLAIR[4], D. MURMAN[1], D. E. WARREN[2];
[2]Neurosciences, [1]Univ. of Nebraska Med. Ctr., Omaha, NE; [3]Univ. of Nebraska at Lincoln, Lincoln, NE; [4]nimh, Bethesda, MD

Abstract: Significant changes in cognition and brain structure are known to occur during childhood development, including the periadolescent epoch. The development of spatial working memory (SWM), for example, continues throughout adolescence. Recent findings have shown that the hippocampus is necessary for normal SWM. For example, hippocampal pathology in neurological patients such as people with Alzheimer's disease (AD) has been associated with significant SWM deficits. Understanding the developmental relationship between hippocampal volume and SWM would provide an important baseline for comparing different trajectories of putatively healthy brain development, including in children who have different genetic risk profiles for AD.
Using preliminary data from the Polygenic Risk for Alzheimer's disease in Nebraska Kids study (PRANK, R01 AG064247), we investigated the association between hippocampal volume, SWM, and age. Our sample included typically developing children (N = 80, M = 42, F = 38, age 8-13 years) recruited from the Eastern Nebraska region and tested at University of Nebraska Medical Center. SWM was measured using the Spatial Working Memory Task (between error term) from the Cambridge Neuropsychological Battery. Structural MRI data were collected using a 3T Siemens Prisma instrument. Hippocampal volume (HcV) was measured using automated segmentation from Freesurfer.
SWM was associated with age, $r(80) = -.334$, $p = .002$, such that older children showed fewer SWM errors than younger children. Hippocampal volume was not significantly associated with SWM, controlling for age, $r(77) = -.027$, $p = .813$. However, the direction of the relationship between HcV and SWM (larger HcV associated with fewer SWM errors) was consistent with previous literature. These preliminary results suggest that increasing age is associated with improvements in SWM; findings for hippocampal volume were non-significant in the current dataset. Although beyond the scope of our analysis, we expect that our study's full sample will provide sufficient statistical power to rigorously test the association of SWM with hippocampal volume. In future research, we will investigate this association as it relates to polygenic risk for Alzheimer's disease and whether these results generalize to children with Down syndrome.

Disclosures: **J. Sexton:** None. **M. Ramirez:** None. **C.J. Phipps:** None. **A. Heller:** None. **L. Behm:** None. **A. Zatkalik:** None. **K. Nickolas:** None. **A. Maerlender:** None. **V. Phatak:** None. **J. Cramer:** None. **J.R. Blair:** None. **D. Murman:** None. **D.E. Warren:** None.

Poster

108. Multimodal Imaging Studies in Youth: Identifying Trajectories and Sources of Variability

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 108.04

Topic: A.09. Adolescent Development

Support: NIA Grant R01 AG064247-04

Title: Measuring associations between physical activity and brain networks through functional connectivity analysis in periadolescent children: preliminary findings from the PRANK study

Authors: *A. M. HELLER[1], C. J. PHIPPS[1], M. K. RAMIREZ[1], J. N. SEXTON[1], L. BEHM[1], A. L. ZATKALIK[1], K. NICKOLAS[1], A. MAERLENDER[2], V. S. PHATAK[1], J. A. CRAMER[1], J. R. BLAIR[3], D. L. MURMAN[1], D. E. WARREN[1];
[1]Univ. of Nebraska Med. Ctr., Omaha, NE; [2]Univ. of Nebraska Lincoln, Lincoln, NE; [3]Boys Town Natl. Res. Hosp., Omaha, NE

Abstract: Periadolescence is a neurodevelopmental period characterized by expansive development of the brain's underlying functional networks. The frontoparietal (FPN), default mode (DMN), and dorsal attention (DAN) networks exhibit changes in functional connectivity associated with maturation of cognitive abilities. Understanding factors that may modify and strengthen these networks during development is an emerging field of scientific investigation. For example, recent evidence suggests that amount of physical activity and exercise may influence functional connectivity and cognition. Studies in populations of young and older adults that have participated in an exercise intervention found increased within-network connectivity and superior cognitive performance compared to control groups. While these findings have been replicated in younger children, the association between physical activity and brain network characteristics in periadolescence has yet to be fully elucidated. Specifically, the relationship between physical activity and developing brain networks, measured through resting state functional connectivity (rs-FC) analysis, is not well-understood in the periadolescent epoch. The current study tested the association between self-reported physical activity and rs-FC in a cohort of periadolescents aged 8-13 years (N=85, 43M, 42F). Participants completed a physical activity questionnaire reporting how many days per week they completed at least 60 minutes of moderate-to-vigorous physical activity, then completed an MRI study to evaluate rs-FC. MRI data were processed using the Human Connectome Project processing pipelines. Analysis of covariance between amount of self-reported exercise and rs-FC revealed patterns of focally increased within-network connectivity in the DMN, DAN, and (left) FPN associated with more days of exercise per week. Characterizing the influence of physical activity on development of brain networks that support cognition may provide key insights on strengthening such networks. Understanding these developmental trajectories, and targeted interventions to rescue them in cases of dysfunction, could potentially help to promote brain health and reduce the risk of neurological disease, including late-life disorders such as AD.

Disclosures: A.M. Heller: None. **C.J. Phipps:** None. **M.K. Ramirez:** None. **J.N. Sexton:** None. **L. Behm:** None. **A.L. Zatkalik:** None. **K. Nickolas:** None. **A. Maerlender:** None. **V.S. Phatak:** None. **J.A. Cramer:** None. **J.R. Blair:** None. **D.L. Murman:** None. **D.E. Warren:** None.

Poster

108. Multimodal Imaging Studies in Youth: Identifying Trajectories and Sources of Variability

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 108.05

Topic: A.09. Adolescent Development

Support: NIA Grant R01 AG064247

Title: Exploratory factor analysis of the neuropsychological battery from the PRANK study and factor covariance with hippocampal resting-state functional connectivity

Authors: *L. BEHM[1], J. N. SEXTON[1], A. M. HELLER[1], M. K. RAMIREZ[1], C. J. PHIPPS[1], A. L. ZATKALIK[1], K. NICKOLAS[1], A. C. MAERLENDER[2], V. S. PHATAK[1], J. A. CRAMER[1], J. BLAIR[3], D. L. MURMAN[1], D. E. WARREN[1];
[1]Univ. of Nebraska Med. Ctr., Omaha, NE; [2]Univ. of Nebraska Lincoln, Lincoln, NE; [3]Boys Town Natl. Res. Hosp., Omaha, NE

Abstract: In the periadolescent epoch, typically developing children exhibit improvements in many cognitive abilities (e.g., long-term memory, working memory, attention, and executive functions). During this period of development, functional brain networks also undergo significant reorganization, including networks associated with the hippocampus (Hc). However, the relationship between functional connectivity changes and improvements in cognitive ability are not well characterized. The Polygenic Risk of Alzheimer's Disease in Nebraska Kids (PRANK) study is an ongoing NIA-funded longitudinal study that aims to enhance understanding of how development of the periadolescent brain and cognitive abilities are affected by genetic risk for Alzheimer's disease (AD). Study participants, healthy periadolescent children ages 8-13 years, provide genetic and neuroimaging data, and they also complete an extensive neuropsychological battery which assesses cognitive development across many domains, with a strong emphasis on memory. Here, we assessed the variance structure of the cognitive assessments comprising the PRANK neuropsychological battery by conducting an exploratory factor analysis (EFA) of cross-sectional neuropsychological data (N=75; 38 male). We then assessed how individual differences in performance on each of the resulting factors covaried with hippocampal resting-state functional connectivity (Hc-RSFC). To do so, we utilized a seed-based approach with the bilateral hippocampus as the seed region of interest. The results of our EFA indicated that the PRANK neuropsychological battery primarily assessed four unique factors: long-term/relational memory, working memory, language, and attention/executive functions. Our neuroimaging data, in line with prior work, showed patterns of Hc-RSFC that overlap with ventral and lateral portions of the default mode network. In addition, we observed that individual differences in factor loading covaried regionally with Hc-RSFC. These preliminary results support the perspective that Hc-RSFC covaries regionally with children's performance on neuropsychological assessments of relational memory, working memory, language, and attention/executive functions. Future goals of the PRANK study include testing whether participants' AD polygenic risk scores are associated with individual differences in Hc-RSFC and cognitive abilities.

Disclosures: L. Behm: None. **J.N. Sexton:** None. **A.M. Heller:** None. **M.K. Ramirez:** None. **C.J. Phipps:** None. **A.L. Zatkalik:** None. **K. Nickolas:** None. **A.C. Maerlender:** None. **V.S. Phatak:** None. **J.A. Cramer:** None. **J. Blair:** None. **D.L. Murman:** None. **D.E. Warren:** None.

Poster

108. Multimodal Imaging Studies in Youth: Identifying Trajectories and Sources of Variability

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 108.06

Topic: A.09. Adolescent Development

Support: NIA Grant RO1 AG064247

Title: Quantifying age-related differences in brain activity related to subsequent memory in periadolescent children using task-based fMRI: preliminary data from the PRANK study

Authors: *M. RAMIREZ[1], J. N. SEXTON[1], C. J. PHIPPS[1], A. M. HELLER[1], L. BEHM[1], A. ZATKALIK[1], K. NICKOLAS[1], V. PHATAK[1], A. C. MAERLENDER[5], J. A. CRAMER[2], J. BLAIR[6], D. L. MURMAN[3], D. E. WARREN[4];
[1]Neurolog. Sci., [2]Radiology, [4]Neurosciences, [3]Univ. of Nebraska Med. Ctr., Omaha, NE; [5]Univ. of Nebraska at Lincoln, Lincoln, NE; [6]Boys Town Natl. Res. Hosp., Omaha, NE

Abstract: The brain undergoes considerable structural and functional changes during childhood development, including adolescence, and these changes are associated with cognitive development. One such change is the enhancement of relational memory abilities. The hippocampus is required for memory function as demonstrated by the hallmark memory deficits of neurological patients with hippocampal injuries, such as those associated with Alzheimer's disease (AD) and its concomitant hippocampal pathology. Childhood brain development may modify vulnerability to AD and other memory deficits later in life, and this motivates research into the brain's developmental trajectory and correlations with AD-vulnerable cognitive abilities like memory. Our ongoing NIA-funded study, the Polygenic Risk of Alzheimer’s disease in Nebraska Kids (PRANK) study, measures cognitive abilities as well as brain structure and function in periadolescent children (age 8-13 years). The PRANK study will test whether these variables are associated with genetic risk for AD (AD polygenic risk scores). Here, we report preliminary data measuring the relationship between age and hippocampal-dependent relational memory using a task-based fMRI to measure brain activity in a subsequent memory (SM) paradigm. A periadolescent sample from the PRANK study provided data for the current project (N = 86; 42 female, 44 male). A protocol adapted from the Human Connectome Project Development/Aging was used to collect MRI data. We used an SM task in which participants were asked to remember pairs of objects while fMRI-BOLD data were collected. This was followed by a memory test for the studied stimuli that included studied match pairs or non-studied mismatch pairs. Controlling for sex, we assessed the relationship between age and brain network activity associated with successful SM. There was preliminary evidence that age was negatively correlated with regions within the cingulo-opercular network during successful encoding of relational memories, such that there were regional decreases in activation within the cingulo-opercular network associated with increased age ($p<0.001$). Findings from this preliminary analysis suggest a relationship between age and network (de)activation during SM in periadolescent children. Future research will assess whether and how genetic risk for AD interacts with the observed SM-related brain activity.

Disclosures: **M. Ramirez:** None. **J.N. Sexton:** None. **C.J. Phipps:** None. **A.M. Heller:** None. **L. Behm:** None. **A. Zatkalik:** None. **K. Nickolas:** None. **V. Phatak:** None. **A.C.**

Maerlender: None. **J.A. Cramer:** None. **J. Blair:** None. **D.L. Murman:** None. **D.E. Warren:** None.

Poster

108. Multimodal Imaging Studies in Youth: Identifying Trajectories and Sources of Variability

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 108.07

Topic: A.09. Adolescent Development

Support: NICHD K01 HD083459-01A1

Title: White matter matters: Damage to thalamic radiations might mediate the relationship between pediatric TBI and rule-breaking behavior

Authors: E. GILLILAND[1], S. CROWELL[1], Y. KIM[1], W. CUNNINGHAM[2], K. VANNATTA[1], E. WILDE[3], *E. NELSON[4], K. YEATES[5], K. R. HOSKINSON[1];
[1]Ctr. for Biobehavioral Health, Abigail Wexner Res. Inst., Columbus, OH; [2]Dept. of Psychology, Univ. of Toronto, Toronto, ON, Canada; [3]Dept. of Neurol., Univ. of Utah Sch. of Med., Salt Lake City, UT; [4]Res. Inst. At Nationwide Children's Hospit, Columbus, OH; [5]Dept. of Psychology, Univ. of Calgary Col. of Med., Calgary, AB, Canada

Abstract: Objective: Traumatic brain injury (TBI) is a leading cause of death and disability in children. Many children with TBI also experience a collection of maladaptive behavioral outcomes, perhaps due to damage to white matter tracts post-injury. The thalamic radiations (TR) in particular have been associated with a range of behavioral outcomes including suicidality and externalizing. While many neuroimaging studies in pediatric TBI focus on cognitive deficits, there is a need to evaluate social and adaptive dysfunction after TBI given the persistence and associated impairment caused by these sequelae. Our aims are to 1) explore behavioral outcomes across TBI severity and 2) examine how white matter integrity of thalamic radiations (TR) may mediate these outcomes. Methods: Participants included 56 children with complicated-mild TBI (CMTBI; N=13, Mage=12.40, MTSI= 4.67 yr), moderate-severe TBI (MSTBI; N=19, Mage=11.46, MTSI= 3.61 yr) and orthopedic injury (OI; N=24, Mage=11.60 , MTSI=4.03 yr). Parents rated their child's behavior and adaptive function using the Child Behavior Checklist (CBCL) and Adaptive Behavior Assessment System 3rd Edition (ABAS-3). Children underwent diffusion weighted imaging on a Siemens 3T Prisma scanner. TR white matter microstructure was quantified using FSL's Tract Based Spatial Statistics (TBSS). Fractional anisotropy (FA) values were derived for each child for analysis in SPSS. Results: All three groups scored above the expected norms for CBCL and ABAS-3, indicating more aggressive and defiant behavior. Despite these cross-group elevations, there were nonetheless significantly greater aggressive and oppositional-defiant behavior. Parents also rated children with MSTBI as having worse practical, conceptual and social adaptive skills. Although there were strong correlations between adaptive function and FA in the TR, FA did not mediate the relationship between injury severity and

adaptive skills. The relationship between injury severity and rule-breaking behavior, however, was mediated by FA of the left and bilateral TR, with models accounting for 19.5% and 16.3% of variance, respectively. Conclusions: This study suggests that FA in the TR may meaningfully contribute to the links between injury severity and rule-breaking behavior. Notably, children with CMTBI, MSTBI, and OI all scored above the expected norms for externalizing and deficient adaptive skills, perhaps obscuring TBI-related impairment. Future studies should look at longitudinal development of key white matter tracts following injury and the relationships among injury severity, white matter integrity and behavioral and adaptive symptomology.

Disclosures: E. Gilliland: None. **S. Crowell:** None. **Y. Kim:** None. **W. Cunningham:** None. **K. Vannatta:** None. **E. Wilde:** None. **E. Nelson:** None. **K. Yeates:** None. **K.R. Hoskinson:** None.

Poster

108. Multimodal Imaging Studies in Youth: Identifying Trajectories and Sources of Variability

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 108.08

Topic: A.09. Adolescent Development

Support: NIH Grant R37MH101495

Title: Trajectories of Nucleus Accumbens and Anterior Insula Activity Across Adolescence

Authors: L. BORCHERS[1], **J. K. LEONG**[2], L. MORTAZAVI[1], I. H. GOTLIB[1];
[1]Psychology, Stanford Univ., Stanford, CA; [2]Univ. of Arkansas, Fayetteville, AR

Abstract: Adolescence is marked by increased risk taking. Naturalistic observations of increased risky driving, un-safe sex, and drug use in adolescents are borne out in longitudinal studies of adolescent brain development. During adolescence, nucleus accumbens (NAcc) activity in response to reward increases, whereas anterior insula (AIns) activity in response to loss decreases. Less is known about absolute levels of activation in these regions and prior work has focused primarily on outcomes. In this longitudinal study, we measured activity in the NAcc during the anticipation and receipt of gain, and activity in the AIns during the anticipation and receipt of loss, across adolescence. We measured brain activity with functional magnetic resonance imaging (fMRI) during a Monetary Incentive Delay task across 3 assessments. Participants were scanned at baseline (n=144; Mage=11.59, SD=1.05), 2 years later (n=122; Mage=13.47, SD=1.16), and 4 years later (n=101; Mage=15.53, SD=1.08). In addition, participants completed the Sensitivity to Punishment and Reward Questionnaire (SPSRQ) 6 years after their baseline session (n=53; Mage=17.50, SD=1.15). We preprocessed the fMRI data using fMRIPrep and extracted raw percent signal change in the bilateral AIns and NAcc. Spherical regions-of-interest (8 mm diameter) centered at the AIns (x=±37, y=−18, z=−5) and NAcc (x=±12, y=12, z=-7) were defined in pediatric MNI space. Trajectories of NAcc activation

during the anticipation and receipt of gain did not differ as a function of age or sex (all ps>.050). However, activation in the AIns decreased across adolescence during the anticipation (B=-0.21, p<.001) and receipt of loss (B=-0.21, p<.001). Follow-up analyses indicated that greater activity in the AIns during the receipt of loss at baseline was associated with lower punishment sensitivity six years later, measured by the SPSRQ (rs=-0.37, p=.007). Ample literature has documented that NAcc activation increases across adolescence; in our sample, however, we did not find age-related changes in NAcc activation, but did observe decreasing activation in the AIns with age. This may be one mechanism by which adolescents engage in more risk-taking - that is, increased risk-taking may be a compensatory response to lower activation in inhibitory regions. Further, baseline activity of the AIns predicted less sensitivity to punishment in late adolescence; therefore, future work should examine the relation between trajectories of AIns activation and changes in risk-taking across adolescence.

Disclosures: L. Borchers: None. **J.K. Leong:** None. **L. Mortazavi:** None. **I.H. Gotlib:** None.

Poster

108. Multimodal Imaging Studies in Youth: Identifying Trajectories and Sources of Variability

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 108.09

Topic: A.09. Adolescent Development

Support: NIH Grant MH124694
China Scholarship Council (201706990036)

Title: Latent structure in the genetic landscape of major psychiatric disorders underlies child psychopathology and implicates fetal cerebellar development

Authors: *D. E. HUGHES[1], K. KUNITOKI[1], S. ELYOUNSSI[1], M. LUO[2], O. M. BAZER[1], C. E. HOPKINSON[1], K. F. DOWLING[3], A. E. DOYLE[1], E. C. DUNN[1], H. ERYILMAZ[1], J. M. GILMAN[1], D. J. HOLT[1], E. M. VALERA[1], J. W. SMOLLER[1], C. A. M. CECIL[4], H. TIEMEIER[5], P. H. LEE[1], J. L. ROFFMAN[1];
[1]Massachusetts Gen. Hosp., Boston, MA; [2]Erasmus Univ., Rotterdam, Netherlands; [3]Univ. of Pittsburgh, Pittsburgh, PA; [4]Erasmus Univ. Med. Ctr., Rotterdam, Netherlands; [5]Harvard T. H. Chan Sch. of Publ. Hlth., Boston, MA

Abstract: Risk for psychiatric disorders arises early in life, reflecting in part the cumulative effects of thousands of common genetic variants. Polygenic risk score (PRS) analyses, which leverage data from large scale genome-wide association studies (GWAS), in conjunction with gene expression data have provided insight into the biological origins of psychiatric illness. Further, PRS analyses may one day provide a tool for early identification and treatment of psychiatric disorders. Complicating the application of PRS in children, GWAS are derived mainly from adult participants, and the genetics and symptomatology of psychiatric illnesses are

heterogeneous. Leveraging novel cross-disorder PRS (NDV), which culls shared genetic risk among four neurodevelopmental disorders, we sought to parse genomic risk for dimensional child psychopathology and to seek related neurodevelopmental mechanisms with gene expression and neuroimaging data. We compared the predictive ability of NDV PRS to 8 disorder-specific and 3 other cross-disorder PRS. We analyzed genomic and psychopathology data from non-related, non-Hispanic, male and female young adolescents (ages 9-13) of European descent from the Adolescent Brain Cognitive Development (ABCD; *n* = 4,459) and Generation R (*n* = 1,850) studies; gene expression data from GTEx V8 and BrainSpan; and neuroimaging data from a mixed-ancestry population of male and female young adolescents from ABCD (*n* = 8,658). Above all other PRS in both data sets (ABCD and Gen R), NDV most strongly predicted and accounted for the greatest variance in a broad range of dimensional psychopathology, spanning internalizing, externalizing, and psychosis spectrum symptoms. Analysis of spatiotemporal expression of NDV-associated genes showed that NDV genes show significant expression prenatally in the cerebellum ($p=8.68x10^{-08}$). Further, NDV PRS restricted to genes showing significantly greater prenatal than postnatal expression in the cerebellum predicted a range of psychopathology (p's $2.26x10^{-06}$ to 0.01, q&lt0.05). In neuroimaging analyses, total cerebellar gray volume associated with externalizing and psychosis spectrum symptoms (p's &lt 0.005, q&lt0.05). In follow-up analyses, left cerebellar lobules I-V and VIII showed strong associations with externalizing symptoms (p's &lt $1.88x10^{-04}$). These findings demonstrate that the genetic underpinnings of pediatric psychiatric symptoms are at least partially distinct from those of adult illness and implicate cerebellar developmental processes that originate in fetal life and endure through childhood.

Disclosures: **D.E. Hughes:** None. **K. Kunitoki:** None. **S. Elyounssi:** None. **M. Luo:** None. **O.M. Bazer:** None. **C.E. Hopkinson:** None. **K.F. Dowling:** None. **A.E. Doyle:** None. **E.C. Dunn:** None. **H. Eryilmaz:** None. **J.M. Gilman:** None. **D.J. Holt:** None. **E.M. Valera:** None. **J.W. Smoller:** None. **C.A.M. Cecil:** None. **H. Tiemeier:** None. **P.H. Lee:** None. **J.L. Roffman:** None.

Poster

108. Multimodal Imaging Studies in Youth: Identifying Trajectories and Sources of Variability

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 108.10

Topic: A.09. Adolescent Development

Support: R01MH124694 to J.L.R. and the Mass General Early Brain Development Initiative
The ABCD Study is funded by NIDA, NIAAA, and NCI, in partnership with the NICHD, NIMH, NIMHD, NINDS, and the NIH Office of Behavioral and Social Sciences Research

Title: Scan quality influences associations between structural MRI phenotypes and clinical variables in the Adolescent Brain Cognitive Development (ABCD) Study

Authors: *S. ELYOUNSSI, K. KUNITOKI, D. E. HUGHES, J. L. ROFFMAN; Psychiatry, Massachusetts Gen. Hosp. and Harvard Med. Sch., Boston, MA

Abstract: Background: Large prospective neurodevelopmental brain imaging studies such as the Adolescent Brain Cognitive Development Study enable well-powered associations between brain development and clinical variables, such as emergent psychopathology. However, MRI scans of youth participants are especially vulnerable to motion and other artifact. Here, we determined the extent to which structural MRI (sMRI) scan quality, as assessed through both manual and automated methods, influences relationships between sMRI and clinical indices. **Methods:** 11,263 minimally processed sMRI scans that passed initial automated QC were processed in Freesurfer and then rated from "1" (minimal artifacts) to "4" (substantial artifacts). We then assessed both (1) the well-established effects of age on cortical thickness, and (2) exploratory effects of cortical volumes on dimensional psychopathology (Child Behavior Checklist, CBCL) in a series of analyses that "built up" from including only "1"-rated scans (n=4,630) to including "1" through "4"-rated scans (n=10,304). All analyses were adjusted for sex and total intracranial volume (fixed) as well as site, scanner, and family ID (random)(ICV) and corrected for multiple comparisons (68 regions-of-interest) using the False Discovery Rate. **Results:** Quality ratings had minimal effects on relationships between age and cortical thickness. However, relaxing inclusion from "1" alone down to "1 to 4" scans resulted in substantial differences in volume-CBCL relationships; for example, the number of regions showing FDR-significant inverse relationships between cortical volume and CBCL Externalizing scores fell from 43 in the most inclusive analysis to 3 in the most stringent analysis. However, effect size comparisons suggest that some regions fell out of significance due to inadequate power. Further correction for scan quality using number of surface holes (Euler number) partially reduced the number of false positives that were driven by "3-" and "4"-rated scans. **Conclusions:** In large-scale neurodevelopmental cohorts that explore brain-behavior relationships, insufficient quality control of structural MRI images can result not just in error, but in bias. Improved QC methods are needed to minimize risk of both type I and type II error.

Disclosures: S. Elyounssi: None. **K. Kunitoki:** None. **D.E. Hughes:** None. **J.L. Roffman:** None.

Poster

108. Multimodal Imaging Studies in Youth: Identifying Trajectories and Sources of Variability

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 108.11

Topic: A.09. Adolescent Development

Support: NIA Grant RO1 AG064247

Title: Measuring the relationship between cognitive ability and modularity of intrinsic functional brain networks in a periadolescent sample: preliminary findings from the PRANK study

Authors: *C. PHIPPS[1], M. RAMIREZ[5], J. SEXTON[2], A. HELLER[3], L. BEHM[3], A. ZATKALIK[2], K. NICKOLAS[1], V. PHATAK[1], A. MAERLENDER[6], J. CRAMER[1], J. BLAIR[7], D. MURMAN[1], D. E. WARREN[4];
[2]Dept. of Neurolog. Sci., [3]Neurolog. Sci., [4]Neurosciences, [1]Univ. of Nebraska Med. Ctr., Omaha, NE; [5]Neurosci., Univ. of Nebraska Med. Ctr. Dept. of Pharmacol. and Exptl. Neurosci., Omaha, NE; [6]Univ. of Nebraska Lincoln, Lincoln, NE; [7]Boys Town Natl. Res. Hosp., Omaha, NE

Abstract: The periadolescent epoch is a period of significant development in the organization of the brain's intrinsic functional networks (IFNs). Differences in functional organization of the brain have been associated variability of cognitive abilities in young children and adults, but less is known about these associations during the periadolescent epoch. Here we discuss initial findings from our ongoing project, the Polygenic Risk of Alzheimer's disease in Nebraska Kids (PRANK) Study. The PRANK study seeks to assess the relationship between brain structure and function, cognition, and Alzheimer's disease polygenic risk scores (AD-PRS) from periadolescent children (age 8-13 years). Here, we report preliminary, cross-sectional findings from our analysis of the relationship between brain network measures and cognitive outcomes from the PRANK study. In the current study, we measured the relationship between organization of the IFNs of the brain and cognition using brain and cognitive measures from periadolescent children (N=87; 47F) enrolled in the PRANK study. Cognitive assessments included the NIH Toolbox cognitive battery; brain measures included structural and functional MRI data. The organization of the brain's IFNs was characterized using two measures: modularity of the whole-brain network; and mean participation coefficient across all nodes within each IFN. Both properties were derived from resting-state fMRI data by using the Human Connectome Project's Connectome Workbench tool. Our analysis identified statistically significant relationships between composite measures of cognition and IFN organization.. These composite measures included fluid cognition, early childhood cognition, and total cognition. The relationship between both hippocampal-dependent memory and organizational measures of the brain as well as age and organizational measures were also assessed. Our preliminary findings describe associations between brain network properties and cognitive measures in periadolescent children. Our analysis suggests a link between brain organization and cognitive performance, and we speculate that changes in global properties of brain organization during periadolescence may reflect, promote, or otherwise support cognitive development. Our ongoing PRANK study aims to examine how brain structure, brain function, and cognitive abilities are affected by AD-PRS, and our future goals will measure the influence of AD-PRS on brain network properties, cognitive abilities, and their association.

Disclosures: C. Phipps: None. **M. Ramirez:** None. **J. Sexton:** None. **A. Heller:** None. **L. Behm:** None. **A. Zatkalik:** None. **K. Nickolas:** None. **V. Phatak:** None. **A. Maerlender:** None. **J. Cramer:** None. **J. Blair:** None. **D. Murman:** None. **D.E. Warren:** None.

Poster

108. Multimodal Imaging Studies in Youth: Identifying Trajectories and Sources of Variability

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 108.12

Topic: A.09. Adolescent Development

Support: NIH Grant MH125479
NIH Grant EB008374

Title: Charting excitation-inhibition balance over the human lifespan

Authors: *G. LI, H. TAYLOR, Y. WU, S. AHMAD, K.-H. THUNG, Z. WU, G. LI, L. WANG, W. LIN, P.-T. YAP;
Univ. of North Carolina Chapel Hill, Chapel Hill, NC

Abstract: Excitation-inhibition (E-I) balance is a fundamental property of neuronal circuits and abnormal E-I balance has been hypothesized to be a key driver for multiple neurological and mental disorders. However, to date there are still no normative reference charts for E-I balance that can be used to benchmark individual growth trajectory and to predict aberrant E-I balance for early detection of diseases. To fill this important gap, we refined a recently developed Multiscale Neural Model Inversion (MNMI) framework that caters to large-scale networks and applied it to high quality resting-state functional MRI (rs-fMRI) datasets from the Lifespan Human Connectome Projects (HCP) to chart the trajectory of E-I balance over the human lifespan. Specifically, we modeled the whole-brain network dynamics with the biologically motivated Wilson-Cowan model and combined extended Kalman Filter with backpropagated filtering to estimate excitatory/inhibitory connection strengths among neural populations based on rs-fMRI. The regional E-I balance was defined as the ratio between the recurrent excitation and inhibition strengths. As a preliminary study, we included 100 subjects from the Baby Connectome Project (50 infancy: 0-1 years; 50 early childhood: 2-5 years), 100 subjects from the HCP Development (late childhood/adolescence: 5-21 years), 77 subjects from the HCP Young Adult (22-35 years), and 125 subjects from the HCP Aging (65 middle adulthood: 36-59 years; 60 late adulthood: 60-100 years) (male: 200; female: 202). Regional BOLD time series were extracted using the Desikan-Killiany atlas with 68 cortical regions grouped into six functional networks (visual, somatomotor, salience, limbic, frontoparietal control and default mode). We found that the overall E-I balance decreased significantly from infancy/early childhood to late childhood/adolescence ($p < 0.05$, FDR corrected) and remained relatively stable till middle adulthood followed by substantial increase in late adulthood ($p < 0.05$, uncorrected) (results were not significantly different between males and females). The E-I balance trajectory can be explained well by a quadratic polynomial with the lowest E-I ratio at around 19 years old. At the network level, we observed that higher-order networks (e.g., frontoparietal control) started at relatively high E-I balance and displayed more pronounced “U” shape development curves than lower-order networks (visual and somatomotor). Our study is the first attempt to chart the developmental E-I balance trajectory over the human lifespan, providing an important framework for both standardized assessment of individual growth and early detection of diseases.

Disclosures: **G. Li:** None. **H. Taylor:** None. **Y. Wu:** None. **S. Ahmad:** None. **K. Thung:** None. **Z. Wu:** None. **G. Li:** None. **L. Wang:** None. **W. Lin:** None. **P. Yap:** None.

Poster

108. Multimodal Imaging Studies in Youth: Identifying Trajectories and Sources of Variability

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 108.13

Topic: A.09. Adolescent Development

Support: Gruber Foundation
R01MH121095
R01AA027553
NIH/NIGMS T32GM007205
TL1 TR001864

Title: Multidimensional measures of handedness have distinct functional connectivity profiles in children

Authors: *L. TEJAVIBULYA[1], C. HORIEN[2], A. S. GREENE[2], M. L. WESTWATER[3], D. SCHEINOST[1];
[1]Yale Univ., New Haven, CT; [2]Yale Sch. of Med., New Haven, CT; [3]Natl. Inst. of Mental Hlth., NIH, McLean, VA

Abstract: IntroductionLeft-handed individuals (LH) comprise roughly 10% of the population. Previous studies have shown that differences in functional connectivity between left-handed (LH) and right-handed (RH) individuals span the whole brain beyond specific regions of interest, such as language and motor areas (1). Handedness has historically been determined on the basis of an individual's dominant hand for writing. Even so, as society moves away from writing and more towards typing, writing has become an outdated measure for handedness. This study uses functional magnetic resonance imaging (fMRI) to explore differences in the functional organization of the developing brain in relation to more specific measures of handedness, such as writing, throwing, spoon-use, and toothbrush-use.
MethodsResting-state fMRI scans from the baseline time point of the Adolescent Brain Cognitive Development (ABCD) study (2) (n = 6990, ages = 9-10 years) were parcellated using a 268-node functionally defined atlas (3). Pearson's r were then calculated between every pair of nodes to create a connectome for each participant. We used the Network-Based Statistic (NBS) (4) to identify differences in connectivity profiles between LH and RH for each specific measure of handedness. Permutation tests were used for significance testing to measure how large clusters are by chance.
ResultsBehavioral data for each handedness measure were correlated with one another (Fig. 1). While these correlations remain high, only the correlation between Writing and Spoon-use exhibited greater than 50% explained variance, indicating that different granular measures may

yield different results.Fig. 1
NBS was performed at thresholds of (component-determining threshold z = 1.96, 2-tailed, K = 5000 permutations) for every handedness measure, and results show that different handedness measures are associated with partially distinct connectivity profiles. While similar patterns emerge, such as more significant edges for LH in the frontal regions and more significant edges for RH in the motor regions, the patterns of connectivity across granular measures are not identical.
Fig. 2
ConclusionsWhile handedness has historically been defined by writing, our work demonstrates that different measures of handedness that extend beyond writing are related to different connectivity profiles in typically developing children. Future studies should consider the notion that handedness is dependent on a variety of other social factors and that footedness/sidedness could be important in understanding how sidedness differences can be controlled for in future fMRI studies.

Disclosures: L. Tejavibulya: None. **C. Horien:** None. **A.S. Greene:** None. **M.L. Westwater:** None. **D. Scheinost:** None.

Poster

108. Multimodal Imaging Studies in Youth: Identifying Trajectories and Sources of Variability

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 108.14

Topic: A.09. Adolescent Development

Support: NIH Grant 5K01MH116325
NIH Grant R01MH104479
NIH Grant R01MH107479-S1

Title: Associations between peer victimization and whole-brain neural activation during social evaluation in adolescent girls at risk for psychopathology

Authors: *M. REDIC[1], L. MACHLIN[1], M. SHERIDAN[1], K. K. PATEL[2], M. GILETTA[3], P. D. HASTINGS[4], M. K. NOCK[5], K. D. RUDOLPH[6], G. M. SLAVICH[7], M. J. PRINSTEIN[1], S. MARTIN[1], A. B. MILLER[1];
[1]Univ. of North Carolina Chapel Hill, Chapel Hill, NC; [2]Old Dominion Univ., Norfolk, VA; [3]Ghent Univ., Ghent, Belgium; [4]Univ. of California Davis, Davis, CA; [5]Harvard Univ., Cambridge, MA; [6]Univ. of Illinois Urbana-Champaign, Champaign, IL; [7]Univ. of California Los Angeles, Los Angeles, CA

Abstract: Peer victimization, a well-known risk factor for a variety of psychopathological outcomes including suicidality, is particularly potent during adolescence, especially among girls, due to increased sensitivity to social belongingness and inclusion (Sheppard, Giletta, & Prinstein,

2018). Peer-victimized adolescents exhibit heightened neural activation to social exclusion in emotional processing regions such as the amygdala (Rudolph et al., 2016). Moreover, greater neural activation in the left parahippocampal gyrus and fusiform gyrus have been associated with peer victimization in social exclusion tasks (Ke et al., 2022), yet few studies investigate neural effects of social evaluation in teens with suicidal ideation and behavior. The present study explores associations between peer victimization and neural activation during a social evaluation task in youth at risk for suicidal ideation and behavior. Participants were 122 biological females (9-17 years old, M = 12.68, SD = 1.96) with a history of suicidal ideation and behavior or depressive symptoms. During an fMRI scan, they completed a social evaluation task where they believed an unfamiliar peer was watching them (a blank screen indicated "Video On" or "System Off"). Neural activation during "Video On" was compared to baseline. Peer Victimization Questionnaire composite scores measured peer victimization. Threat composite scores used the Childhood Trauma Questionnaire (CTQ), Stress and Adversity Inventory for Adolescents (STRAIN), and Child Chronic Strain Questionnaire (CCSQ), excluding peer victimization items. Deprivation was measured by the CTQ, CCSQ, and STRAIN. Gender identity and medication information was collected at baseline. During Video On > baseline, adolescents showed greater activation in the middle temporal gyrus, superior and middle frontal gyrus, and supramarginal gyrus. Peer victimization was positively associated with activation in the lateral occipital cortex and precuneus and negatively associated with activation in the parahippocampal gyrus, frontal pole, and temporal fusiform cortex activation for this same contrast. Analyses controlled for gender identity, psychotropic medication, age, deprivation, and threat. Results show increased activation in the precuneus in girls who have experienced greater peer victimization, suggesting greater social cognitive processing of others and reduced activation in prefrontal regions associated with fluid reasoning, suggesting decreased cognitive processing during peer evaluation. This finding offers insight into cognitive biases in at-risk youth that may result from, and be specific to, peer victimization.

Disclosures: **M. Redic:** None. **L. Machlin:** None. **M. Sheridan:** None. **K.K. Patel:** None. **M. Giletta:** None. **P.D. Hastings:** None. **M.K. Nock:** None. **K.D. Rudolph:** None. **G.M. Slavich:** None. **M.J. Prinstein:** None. **S. Martin:** None. **A.B. Miller:** None.

Poster

108. Multimodal Imaging Studies in Youth: Identifying Trajectories and Sources of Variability

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 108.15

Topic: A.09. Adolescent Development

Support: NIMH P50MH096889

Title: Unpredictable sensory signals during early development and resting state connectivity of the paraventricular nucleus of the thalamus

Authors: *B. T. LEONARD[1], E. GORDI[2], S. L. SMALL[4], C. SANDMAN[5], H. STERN[3], T. Z. BARAM[6], L. GLYNN[7], M. A. YASSA[8], E. DAVIS[9];
[1]Neurobio. and Behavior, [3]Statistics, [2]Univ. of California, Irvine, Irvine, CA; [4]Sch. of Behavioral and Brain Sci., Univ. of Texas at Dallas Sch. of Behavioral and Brain Sci., Richardson, TX; [6]Anat. and Neurobio., [5]Univ. of California, Irvine, CA; [7]Psychology, Chapman Univ., Orange, CA; [8]Neurobio. and Behavior, Univ. of California Irvine, Irvine, CA; [9]Psychology, Univ. of Denver, Denver, CO

Abstract: *Rationale:* Emotional circuit maturation is shaped by sensory signals in the environment during early life. Unpredictable environmental sensory signals (UESS) during early life result in increased hippocampal synaptic pruning and enduring changes in emotional circuitry in rodents. In humans, deficits in memory and executive control during childhood and adolescence have been observed with exposure to elevated UESS during infancy. Maturation of emotional circuits requires top-down and bottom-up signal integration, and the paraventricular nucleus of the thalamus (PVT) is thought to play an important role in this process. There is a growing understanding that the PVT contributes to storing memories of salient experiences over long durations, as well as managing reward-seeking behavior under conditions of risk or uncertainty. Recently, we defined the functional connectivity (FC) patterns of the PVT in humans using resting state fMRI. We extend these results to investigate if UESS during early life impact PVT network connectivity during childhood. *Methods:* Maternal sensory signals during an interaction with her infant were coded during two video-recorded visits when the children were 6 and 12 months old. The predictability of these signals during the interaction with the infant was quantified by calculating the entropy rate (ER, based on state transition probabilities) and averaging across the two sessions. Imaging was conducted during childhood and early adolescence (8.3-11.3 years). Seed-to-voxel FC analysis was performed using the PVT as a seed region and controlling for other thalamic nuclei, using semipartial correlations. Participants were stratified by sex, and correlations with ER were examined within each sex: females (n = 38, median age 11.2 years) and males (n = 45, median age = 11.3 years.*Results:* In both sexes, we observed a positive (+) relationship between ER and PVT FC to voxels belonging to the precuneus and posterior cingulate cortex, and a negative (-) relationship for voxels in frontal pole and cerebellum. Females had a (+) relationship between ER and PVT FC to voxels of hippocampus, insula, striatum, fusiform cortex, and lingual gyrus, and a (-) relationship in occipital cortex, and superior parietal lobule. Males had a (+) relationship between ER and PVT FC to voxels of superior and middle frontal regions, anterior cingulate, and a (-) relationship in orbitofrontal cortex, and lingual gyrus. *Discussion:* The impact of UESS on PVT FC may be different across the sexes. Future work will include ROI-to-ROI analysis to investigate how ER influences PVT FC to key regions of the network including: the hippocampus, amygdala, and nucleus accumbens.

Disclosures: B.T. Leonard: None. **E. Gordi:** None. **S.L. Small:** None. **C. Sandman:** None. **H. Stern:** None. **T.Z. Baram:** None. **L. Glynn:** None. **M.A. Yassa:** None. **E. Davis:** None.

Poster

108. Multimodal Imaging Studies in Youth: Identifying Trajectories and Sources of Variability

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 108.16

Topic: A.09. Adolescent Development

Support: K01AA026889

Title: Impact of Light-to-Moderate Prenatal Tobacco and Alcohol Exposure on Brain Development in the ABCD Study © Cohort: Cortical Analysis

Authors: A. XIA, *K. UBAN;
Program in Publ. Hlth., Univ. of California Irvine, Irvine, CA

Abstract: Prenatal alcohol and tobacco exposure (PAE and PTE) are the most common teratogens. Past literature has examined developmental outcomes of PAE and PTE primarily among children known to be impacted or at high risk of being impacted. Little is known about how population patterns of PAE and PTE are associated with cortical development among neurotypical children. Structural MRI (sMRI) data from the Adolescent Brain and Cognitive Development (ABCD) study with 21 sites across the U.S. was used to examine population-level patterns of PAE and PTE and their cortical brain structure correlates in 9-10-year-olds. Complete baseline data (N = 5977) of children with processed sMRI data was used to examine 34 cortical regions of interest (ROIs). Predictor groupings leveraged retrospective parental reports of PTE [exposed (n = 744) and non-exposed as controls (n = 5233)], and PAE [early PAE (<12 weeks of gestation; n = 1449), extended PAE (> 12 weeks of gestation; n = 150), “don’t know” (n = 203) and no-PAE as controls (n = 4175)]. Processed T_1w acquisition was analyzed (Freesurfer v5.3) with generalized linear mixed effect models. Models were adjusted for age (months), sex at birth, race/ethnicity, hemisphere, household income, highest parental education, and preterm birth, with the study site as a random intercept. In the follow-up analysis, intracranial volume (ICV) was added in as a covariate. False discovery rate (FDR) correction was applied. Post FDR correction, PAE was associated with widespread increased volumes without adjustment for ICV (n= 21 ROIs within the frontal, temporal, and parietal cortices), and following adjustment for ICV (n=6 ROIs including cuneus, lateral occipital, middle orbitofrontal, middle temporal, postcentral, and superior parietal region volumes). Post FDR correction, PTE was not significantly associated with brain volumes without adjustment for ICV but was associated with reduced brain volumes following adjustment for ICV (n=2 ROIs, inferior parietal and precentral region volumes). These novel preliminary results show that population patterns of PAE and PTE, which appear to be more light-to-moderate exposures than historical research, are significantly associated with cortical brain outcomes at 9-10 years of age. PAE was associated with increased cortical volumes and increased proportions of cortical brain sizes relative to the total intracranial space. PTE was associated with reduced proportions of the brain attributed to cortical ROIs. In general, PAE was associated with more alterations in cortical ROIs compared to PTE. Future analyses will disentangle the opposing directionality of the effects of PAE and PTE on cortical outcomes.

Disclosures: A. Xia: None. **K. Uban:** None.

Poster

108. Multimodal Imaging Studies in Youth: Identifying Trajectories and Sources of Variability

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 108.17

Topic: A.09. Adolescent Development

Title: Distinct development of tissue microstructure across human thalamic nuclei

Authors: *O. SINGLETON, J. K. YAO, J. GOMEZ;
Princeton Neurosci. Inst., Princeton, NJ

Abstract: Structural and functional development of the human thalamus has been relatively neglected in the literature. Few studies exist that examine the fine-grained structural and functional development of the thalamic nuclei, especially using quantitative methods such as quantitative magnetic resonance imaging (qMRI), which is capable of reliably quantifying tissue composition. We used large datasets coupled with qMRI to examine whether thalamic nuclei display distinct tissue development. To that end, the present study investigated thalamic rate of development in each of 22 bilateral nuclei using the FreeSurfer automatic segmentation (Iglesias et al., 2018). Structural development of the thalamus was first assessed in a large dataset of 1377 subjects aged 5-100 (mean=38.6) using the ratio between T1-weighted and T2-weighted images, which is thought to be sensitive to myelin and dendrite density (Righart et al., 2017). Subjects were split into childhood and adulthood groups based on an age threshold of 17 years of age. While many thalamic nuclei experience protracted development across the lifespan, others remain relatively stable. For example, the medial ventral nucleus does not develop across the lifespan (n.s.) compared to the lateral dorsal and anteroventral nuclei which show significant development in their T1/T2 ratios (p's<0.0001), with tissue growth peaking around the age of 40. Overall, most thalamic nuclei follow a parabolic trajectory of development similar to what has been observed in white matter fasciculi. While the T1/T2 ratio is a useful measure of tissue development, it is still an open question if and what type of tissue is growing. Thus, we employed a developmental qMRI dataset to explicate these thalamic findings. In a cohort of 79 subjects aged 5-28 (mean=15.6), we validate that thalamic nuclei are undergoing tissue growth whereby relaxation time (T1), a measure sensitive to myelin content, is decreasing from childhood to a nadir around age 40 before degenerating. For example, T1 relaxation time in the lateral dorsal nucleus decreases by 73 ms from childhood to age 40 ($p<0.001$). Overall, our results indicated that the thalamus is developing from childhood to adulthood as well as throughout the adult lifespan. In addition, development deviates in surprising ways from what cortical findings would suggest. These unexpected developmental trajectories suggest further research to elucidate the developmental importance of these nuclei is warranted.

Disclosures: O. Singleton: None. **J.K. Yao:** None. **J. Gomez:** None.

Poster

108. Multimodal Imaging Studies in Youth: Identifying Trajectories and Sources of Variability

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 108.18

Topic: A.09. Adolescent Development

Support: NSF Career Grant 1848004
Hellman Fellows Fund
UCLA Academic Senate fund

Title: Quantifying neural spatial variability as an index of adolescent inhibitory control specialization

Authors: *W. MEREDITH, J. GUASSI MOREIRA, A. MÉNDEZ LEAL, N. SARAGOSA-HARRIS, Y. WAIZMAN, E. NINOVA, E. GAINES, J. SILVERS;
UCLA, Los Angeles, CA

Abstract: Abstract: Adolescence is a period of heightened experience-dependent specialization, where some cognitive strategies are behaviorally and neurally reinforced, and other suboptimal strategies are pruned over time. Dimensions of adolescent cognitive control, including inhibitory control, demonstrate heterogenous developmental profiles when assessed across different biobehavioral measures. While behavioral performance on inhibitory control tasks stabilizes and appears adult-like by mid-adolescence, trajectories of neural development underpinning inhibitory control are less clear. Neural specialization is speculated to undergird adolescent cognition, although quantifying such specialization is difficult with popular univariate neuroimaging methods. The present study uses a novel approach to characterize adolescent inhibitory control specialization by measuring multivariate spatial variability, which quantifies relative contributions of smaller neural subclusters to task-related cortical activity in larger regions of interest (ROI). Using a sample of 49 adolescents aged 9-22 years (mean =15.3 years, SD = 3.7 years; 49% female) from an ongoing longitudinal study, we replicated condition-induced behavioral differences in reaction time and accuracy alongside non-linear, age-related behavioral stabilization around mid-adolescence. Neural spatial variability was modeled for the incongruent-congruent fMRI contrast in regions of DLPFC, cingulate, insula, and parietal cortex, identified from a Neurosynth association map. Leveraging the Gini coefficient, spatial variability was measured within whole ROIs as well as nested subspherical ROIs (4mm radius) “packed” inside each whole ROI starting at the center of gravity. Over and above non-linear age relationships, individuals with greater neural specialization (lower spatial variability) in regions of parietal cortex demonstrated higher behavioral performance scores across whole ROI and nested subspherical ROI analyses. Individuals with greater subspherical neural specialization in DLPFC additionally demonstrated greater behavioral performance scores after controlling for non-linear age relationships. Together, these results demonstrate that cortical spatial variability is an important developmental feature of adolescent inhibitory control that uniquely explains behavioral markers of successful inhibitory control performance divorced from chronological age.

Disclosures: **W. Meredith:** None. **J. Guassi Moreira:** None. **A. Méndez Leal:** None. **N. Saragosa-Harris:** None. **Y. Waizman:** None. **E. Ninova:** None. **E. Gaines:** None. **J. Silvers:** None.

Poster

108. Multimodal Imaging Studies in Youth: Identifying Trajectories and Sources of Variability

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 108.19

Topic: A.09. Adolescent Development

Support: NSF Grant 1940094
NSF Grant 2116707
NSF Grant 1649865

Title: Multi-domain Effects of the Adolescent Environment on Empathetic Behaviors and their Neural Substrates

Authors: *C. SMITH[1], S. BROOKS[1], C. STAMOULIS[2];
[1]Pediatrics, Boston Children's Hosp., Boston, MA; [2]Med., Boston Children's Hospital/Harvard Univ., Boston, MA

Abstract: Adolescence is a period of profound brain maturation during which neural circuits supporting high-level cognitive processes, including Theory of Mind and broadly social cognition, are significantly re-organized and optimized. During this period, environmental factors can have a significant impact on these processes. Given the complexity of environmental domains (including family, school, neighborhood, culture), their aggregate impact on developing neural circuits, particularly those supporting social cognition, remains elusive. In this study, longitudinal neuroimaging, demographic and survey data from the Adolescent Brain Cognitive Development Study were investigated to identify domains impacting both social outcomes associated with empathy and functional brain circuits. Empathetic behaviors included being considerate of others' feelings, being helpful when others are hurt, upset, or feeling ill, offering to help others, and not feeling guilty after misbehaving, and were extracted from the Strength and Difficulties Questionnaire and the Child Behavior Checklist. Topological properties measuring efficiency of information processing, community organization, regional connectedness, and network resilience were estimated for social, limbic, reward, control, and default mode networks. A total of n = 5200 youth at baseline [median age (interquartile range (IQR)) =120 (13.0) months, 2464 (47.4%) female], and n = 3302 at the two year follow-up [median age (IQR) =144 (13.0) months, 1653 (50.0%) female] were analyzed. At baseline, increased family closeness and parent-child communication were associated with increased empathetic behaviors ($p<0.04$). These parameters were also correlated with increased efficiency, community structure, median connectivity, resilience, local connectedness, and regional importance of elements of the social, reward, control, and default networks ($p<0.05$). Increased

family conflict and parental belief in working hard because it reflects on the family were negatively associated with behavioral and brain outcomes ($p<0.05$). Anxiety, depression, and anhedonia were inversely correlated with behavioral but not network properties ($p<0.04$). At the 2-year follow-up, increased family closeness and parent-child communication were positively associated, while increased family conflict and anhedonia were negatively associated with empathetic behaviors ($p<0.05$), but not with topological network properties. These results suggest that various environmental factors impact empathetic behaviors and functional networks broadly supporting social cognition in pre and early adolescence.

Disclosures: **C. Smith:** None. **S. Brooks:** None. **C. Stamoulis:** None.

Poster

108. Multimodal Imaging Studies in Youth: Identifying Trajectories and Sources of Variability

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 108.20

Topic: A.09. Adolescent Development

Support: АП 08856595 "EEG/MRI study of brain development, emotional-cognitive functions, and genetic markers in different age groups", PI A.Kustubayeva

Title: Brain Morphometry Changes during Development

Authors: O. KABENOVA[1], R. SIUGZDAITE[2], I. BRAK[3], B. KERIMKULOV[4], ***A. KUSTUBAYEVA**[1];
[1]Al Farabi Kazakh Natl. Univ., Almaty, Kazakhstan; [2]2MRC Cognition and Brain Sci. Unit, Univ. of Cambridge, Cambridge, United Kingdom; [3]Natl. Ctr. for Neurosurg., Nur-Sultan, Kazakhstan; [4]Suncar Med. Centre, Almaty, Kazakhstan

Abstract: Abstract There is growing evidence of the studies on normative brain development, especially with regard to regional age and sex differences in brain morphology. However, there are a lot of inconsistencies regarding the developmental trajectories. Brain morphometry study was conducted in 86 typically developing volunteers from 12 to 20 years old (mean: 16.1, SD=2.7 years, 43 females) from Almaty city area. Structural MRI data were acquired by using 3T GE Signa Architect MR Scanner scan and preprocessed by using FreeSurfer 7.2.0. Indices of surface area, thickness and volume of cortical and subcortical structures were correlated with age and analyzed in sex groups. Results revealed significant negative correlations between age and cortical gray matter (GM) volume ($r=-0.337$; $p=0.001$) and significant positive correlations with central ($r=0.350$; $p=0.001$) and middle anterior corpus callosum ($r=0.307$; $p=0.004$). Significant thinning across the four major cortical regions bilaterally was observed across the age span. Moreover, only left entorhinal cortex showed significant increase in thickness ($r=0.294$; $p=0.006$). Four cortical regions (parahippocampal, pericalcarine, precentral and temporal pole cortices) bilaterally showed no significant associations with age. Only a few unilateral

associations of cortical area with age were observed: left inferior parietal (r=-0.264; p=0.014), posterior cingulate (r= -0.236; p=0.029), right precuneus (r=-0.243; p=0.024) and supramarginal (r=-0.257; p=0.017) cortex areas correlate negatively with age. The analyses confirmed significant differences in GM brain volume between genders. We also found sex differences in cortical thickness: bilaterally medial orbitofrontal (F= 4.550; p=0.036, F= 5.083; p=0.027), posterior cingulate (F= 5.354; p= 0.023, F= 6.446, p=0.013) and right hemispheric rostral middle frontal (F= 6.072; p=0.016) cortices tend to be thicker in males. Area of all brain regions tend to be significantly higher in males. This study provides the first brain morphology dataset in young local population. The main developmental patterns were apparent in cortical grey matter. Sexual dimorphism in the developmental course of the cortical maturation was expressed in 11 % higher total brain volume in males than in females, and higher total cortex volume due to its larger area, but not to thickness.

Disclosures: O. Kabenova: None. **R. Siugzdaite:** None. **I. Brak:** None. **B. Kerimkulov:** None. **A. Kustubayeva:** None.

Poster

108. Multimodal Imaging Studies in Youth: Identifying Trajectories and Sources of Variability

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 108.21

Topic: A.09. Adolescent Development

Title: Gradients of myelination covariance in adolescents

Authors: *Y. LI[1], C. J. HUMPHRIES[1], J. BERO[1], A. KUMAR[1], S. NAG[1], H. LEE[1], D. LEE[2,1]; [1]Neurogazer, Inc., Towson, MD; [2]Neurosci., Johns Hopkins Univ., Baltimore, MD

Abstract: Structural covariance in the cerebral cortex is assumed to reflect multiple micro-structral factors, such as synaptogenesis based on functional synchronous firing, direct synaptic connection, or common gene expression in synapses development. However, organizational dimensions underly the pattern of structural covariance remains poorly understood. In this study, we sought to identify the principal modes of spatial variation in myelination covariance (MC) of adolescents (N=443, 10~15 years) by leveraging T1w/T2w-based cortical myelin mapping and nonlinear manifold learning technique, and examined their relationship with the patterns derived from macrostructure, functional connectivity (FC) and gene expression. Derived from diffusion map embedding method, the principal gradient of MC ($G1_{MC}$) accounted for 34% of the spatial variance and showed an anterior-posterior organizational axis from frontal cortex to occipital regions. The second gradient ($G2_{MC}$) showed a dorsal-ventral/lateral-medial pattern, explaining 16% of variance. By randomly splitting the samples, we showed that these organizational patterns of MC were highly reproducible (r=0.94 and 0.90 for $G1_{MC}$ and $G2_{MC}$, respectively). When compared to low-dimensional embeddings of resting-state FC, the $G1_{MC}$ correlated significantly with $G2_{FC}$ in adolescents (r=0.49; spatial autocorrelation-preserving spin test,

p_{spin}=0.001) which represents the macroscale functional hierarchy spanning from unimodal to association cortical regions. This similarity suggests that the major organizational dimension of myelination covariance may be reinforced through the long-range temporal correlation in neural activity. Gradients of macrostructural cortical thickness covariance (TC) also showed significant correlation with gradients of MC yet in a shifted manner, with r=0.74 for $G1_{TC}$ versus $G2_{MC}$ (p_{spin}<0.001), and 0.62 for $G2_{TC}$ versus $G1_{MC}$ (p_{spin}=0.005), which indicates the major organizational dimensions align well between the two structural measures but display different rankings in variation of covariance patterns. To assess how the organizational features of myelination covariance might be genetically regulated, we performed the gradient decomposition on correlation matrix of regional gene expression data from the Allen Human Brain Atlas and observed a significant correlation between the first gradient of gene expression and $G1_{MC}$ (r=0.57, p_{spin}=0.002). In sum, we identified two major organizational gradients of MC in a cohort of adolescents and found various levels of concordance with gradients from macrostructural, functional, and molecular features.

Disclosures: **Y. Li:** A. Employment/Salary (full or part-time):; Neurogazer USA Inc. **C.J. Humphries:** A. Employment/Salary (full or part-time):; Neurogazer USA Inc. **J. Bero:** A. Employment/Salary (full or part-time):; Neurogazer USA Inc. **A. Kumar:** A. Employment/Salary (full or part-time):; Neurogazer USA Inc. **S. Nag:** A. Employment/Salary (full or part-time):; Neurogazer USA Inc. **H. Lee:** A. Employment/Salary (full or part-time):; Neurogazer USA Inc. **D. Lee:** A. Employment/Salary (full or part-time):; Neurogazer Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neurogazer Inc..

Poster

108. Multimodal Imaging Studies in Youth: Identifying Trajectories and Sources of Variability

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 108.22

Topic: A.09. Adolescent Development

Support: NIMH F32MH122057
R01MH116147

Title: Age effects on white matter microstructure during development, assessed with advanced diffusion-weighted brain MRI

Authors: *K. E. LAWRENCE[1], S. M. BENAVIDEZ[1], E. LALTOO[1], J. T. MCCRACKEN[2], P. M. THOMPSON[1];
[1]Imaging Genet. Center, Mark and Mary Stevens Neuroimaging & Informatics Inst., USC, Los Angeles, CA; [2]Univ. of California Los Angeles, Los Angeles, CA

Abstract: White matter develops substantially during childhood and adolescence. Previous diffusion-weighted MRI work quantifying developmental changes in white matter microstructure have primarily used the conventional single-shell reconstruction model, diffusion tensor imaging (DTI). However, DTI has well-established limitations in its ability to model crossing fibers. The advanced single-shell model, the tensor distribution function (TDF), addresses these limitations by using a continuous mixture of tensors to capture multiple underlying fiber populations. We recently demonstrated that TDF captures age effects on white matter microstructure more sensitively in adulthood than DTI. Here we assessed the utility of TDF for capturing age effects during development. We analyzed cross-sectional dMRI scans from 143 neurotypical youth (5-21 years old; 28.7% female) from the NIMH Data Archive and the Autism Brain Imaging Data Exchange. Metrics derived from DTI included fractional anisotropy (FA^{DTI}), and mean, axial, and radial diffusivity (MD, AD, RD). TDF was used to derive an advanced measure of fractional anisotropy (FA^{TDF}). Diffusion-weighted MRI indices were projected to a standard white matter skeleton using publicly available ENIGMA protocols and mean whole-skeleton diffusivity values were then extracted for each metric. The advanced statistical approach ComBat was used to harmonize across scanners. We found that both FA^{DTI} and FA^{TDF} increased over the course of development in our cross-sectional sample (both p's<0.001). MD, AD, and RD decreased with age in our developmental sample (all p's<0.001). Contrasting with our findings in adulthood, TDF exhibited a similar or reduced sensitivity to age effects in development compared with DTI (FA^{DTI}: R^2=0.28; MD: R^2=0.31; AD: R^2=0.13; RD: R^2=0.39; FA^{TDF}: R^2=0.13). The relative sensitivity of our FA^{DTI} and FA^{TDF} metrics suggests that white matter changes during development may be driven in part by changes in crossing fibers, contrasting with previous developmental work in smaller multi-shell samples. Future large-scale work using multiple advanced reconstruction models and longitudinal data is warranted to better understand the neurobiology underlying developmental changes in white matter microstructure.

Disclosures: K.E. Lawrence: None. **S.M. Benavidez:** None. **E. Laltoo:** None. **J.T. McCracken:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Roche, Octapharma, and GW Pharmaceuticals for research unrelated to this abstract.. F. Consulting Fees (e.g., advisory boards); Roche, TRIS Pharmaceuticals, Octapharma, and GW Pharmaceuticals for research unrelated to this abstract. **P.M. Thompson:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Biogen, Inc. for research unrelated to this abstract..

Poster

108. Multimodal Imaging Studies in Youth: Identifying Trajectories and Sources of Variability

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 108.23

Topic: A.09. Adolescent Development

Title: Regional variation and developmental changes in spatial and temporal autocorrelations of resting-state BOLD signals

Authors: *J. BERO[1], Y. LI[1], C. HUMPHRIES[1], A. KUMAR[1], S. NAG[1], H. LEE[1], M. SHINN[2], J. D. MURRAY[3], D. LEE[1,4];
[1]Neurogazer USA Inc., Towson, MD; [2]Univ. Col. London, London, United Kingdom;
[3]Psychiatry, Yale Univ., New Haven, CT; [4]Neurosci., Johns Hopkins Univ., Baltimore, MD

Abstract: Blood-oxygen-level-dependent (BOLD) signals measured from the human brain at rest are both spatially and temporally correlated, but their underlying mechanisms and the nature of individual variability remain incompletely understood. Nevertheless, it has been found that both spatial and temporal autocorrelations are highly robust and capture a meaningful amount of the topological information in the BOLD signals. Furthermore, spatial and temporal autocorrelations in the resting-state BOLD signals are reflected in many popular graph theoretic measures, and also give rise to the topology of the well-known resting state networks. Therefore, characterizing the patterns of autocorrelation in BOLD signals is an important task in order to fully account for the functional connectivity (FC). In addition, although changes in FC are thought to correspond to behavioral changes between youth and adulthood, autocorrelations in the BOLD signals have been investigated mostly in adult populations. Therefore, in the present study, we quantified and compared spatial and temporal autocorrelations in the resting-state fMRI data collected from adolescent population (N=443; age range = 10 to 15) to those taken from adults in the Human Connectome Project (HCP) 1200 subject dataset. The adult data were preprocessed with the HCP minimal preprocessing pipeline, while the data from adolescent subjects were processed with an in-house pipeline modified to match the spatial and temporal processing of the HCP. Comparison of temporal and spatial scales from the corresponding autocorrelation functions showed that the pattern of variation across the brain is highly consistent for adolescent and adult populations(r=0.91 and 0.93 for temporal and spatial autocorrelations). We also examined the autocorrelations in subgroups of adolescent populations divided by age and found that the changes in spatial and temporal autocorrelations during adolescence followed the same trend observed from adolescents to adults. These findings suggest that age-related changes in spatial and temporal autocorrelations in BOLD signals are coupled to brain development, and that this might underlie changes in the functional connectivity between adolescence and adulthood.

Disclosures: **J. Bero:** A. Employment/Salary (full or part-time):; Neurogazer USA Inc. **Y. Li:** A. Employment/Salary (full or part-time):; Neurogazer USA Inc. **C. Humphries:** A. Employment/Salary (full or part-time):; Neurogazer USA Inc. **A. Kumar:** A. Employment/Salary (full or part-time):; Neurogazer USA Inc. **S. Nag:** A. Employment/Salary (full or part-time):; Neurogazer USA Inc. **H. Lee:** A. Employment/Salary (full or part-time):; Neurogazer USA Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neurogazer USA Inc.. **M. Shinn:** None. **J.D. Murray:** None. **D. Lee:** A. Employment/Salary (full or part-time):; Neurogazer Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neurogazer Inc..

Poster

108. Multimodal Imaging Studies in Youth: Identifying Trajectories and Sources of Variability

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 108.24

Topic: A.09. Adolescent Development

Support: P01 HD103133

Title: Relationship between brain structural network integrity and emotional and behavioral symptoms in youth living with perinatally-acquired HIV

Authors: *K. A. SCAMBRAY[1], G. A. CACERES[1], K. MALEE[2], R. SMITH[3], P. L. WILLIAMS[4], L. M. JENKINS[5], L. WANG[6];
[1]Psychiatry and Behavioral Sci., Northwestern Univ., Chicago, IL; [2]Ann & Robert H. Lurie Children's Hosp. of Chicago, Chicago, IL; [3]Pediatrics, Univ. of Illinois, Chicago, IL; [4]T.H. Chan Sch. of Publ. Hlth., Harvard Univ., Boston, MA; [5]Psychiatry and Behavioral Sci., Northwestern, Chicago, IL; [6]Ohio State Univ. Wexner Med. Ctr., The Ohio State Univ. Neurosci. Grad. Program, Columbus, OH

Abstract: Emotional development is sometimes compromised among youth living with perinatal HIV (YLPHIV) and may be complicated by social determinants of health that increase risk. Less is known about brain changes associated with acute or persistent symptoms. This study assessed the relationship between structural brain network integrity, using morphometric similarity networks (MSNs), and emotional symptoms in YLPHIV.
We included 40 YLPHIV from the PHACS network Adolescent Master Protocol (AMP) and 214 PHIV unexposed youth from the PING study as a control group. The Emotional Symptoms Inventory (ESI), from the Behavioral Assessment System for Children- Second Edition (BASC-2), was administered only to the YLPHIV group to assess internalizing problems. Elevated ESI scores signaled serious emotional difficulties. T1-weighted structural scans were processed in FreeSurfer, and parcellated for 360 cortical regions. Pearson’s correlation coefficients were calculated using seven statistical measures of grey matter across all regions, for each individual. To account for spurious weak connections, we utilized a threshold to maintain a range of 5-40% of the strongest connections, resulting in a 360x360 MSN matrix for each threshold. For each MSN matrix, graph-theoretic measures of transitivity, assortativity, and global efficiency were calculated for the Default Mode Network (DMN), Salience Network (SN), Cognitive Control Network (CCN), and the whole-brain. To assess group differences in each structural network measure, a repeated measures ANCOVA accounting for sex, age, and race was conducted with threshold as the within-subject repeated factor. Linear regressions were used to assess relationships between ESI score, the outcome, and structural network measures at fixed thresholds.
The control group had significantly higher assortativity in the DMN (Mean Difference (MD)=.02, p= .02) and whole-brain (MD= .04, p< .001) compared to YLPHIV group. The control group also demonstrated higher global efficiency in the SN (MD= .007, p<.001), DMN (MD= .004, p= .03), and whole-brain (MD= .002, p< .001). Among YLPHIV, higher ESI scores

(worse functioning) were associated with lower global efficiency in the DMN (β= -464.8, p= .01) and higher global efficiency in the SN (β = 230.0, p=.02).
YLPHIV demonstrated decreased structural integrity in the SN, DMN, and whole-brain, suggesting the potential contribution of PHIV on the developing brain. Our findings also demonstrate worsening function is related to lower global efficiency in the SN and higher in the DMN. This may be reflective of a potential disconnect between SN and DMN in YLPHIV, thus warranting further investigation.

Disclosures: K.A. Scambray: None. **G.A. Caceres:** None. **K. Malee:** None. **R. Smith:** None. **P.L. Williams:** None. **L.M. Jenkins:** None. **L. Wang:** None.

Poster

108. Multimodal Imaging Studies in Youth: Identifying Trajectories and Sources of Variability

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 108.25

Topic: A.09. Adolescent Development

Support: NIH R01 ES031074
NIH U01DA041048
NIH U01DA050989
NIH U01DA051016
NIH U01DA041022
NIH U01DA051018
NIH U01DA051037

Title: Effects of Social & Environmental Stressors on Resting-State Functional Connectivity in the ABCD Study

Authors: *A. OMARY[1,2], C. CARDENAS-INIGUEZ[1], D. COTTER[1], K. SUKUMARAN[1], M. HERTING[1];
[1]Population and Publ. Hlth. Sci., USC, Los Angeles, CA; [2]Psychology, Harvard Univ., Cambridge, MA

Abstract: Features of the social environment (e.g., neighborhood disadvantage; Hackman et al., 2021) and the built environment (e.g., air pollution; Herting et al., 2019) have been shown to significantly impact brain development and cognitive function in children and adolescents. Moreover, it has been shown in the Adolescent Brain Cognitive Development℠ Study (ABCD Study®) that indicators of neighborhood socioeconomic status are predictive of resting-state functional connectivity (rsFC) in children (Rakesh et al., 2021). The present study aims to replicate and expand on these findings, in order to further disentangle the effects of family and neighborhood-level social and built environmental stressors on rsFC development. Using a sample of 8336 children (50.6% male, aged 9-10 years) from the ABCD Study, we aimed to

predict rsFC in the salience (SN), frontoparietal (FPN), and default mode networks (DMN) of the brain using sociodemographic data, neighborhood disadvantage measures from the Area Deprivation Index, estimates of annual average outdoor ambient air pollution (i.e., O3, PM2.5, and NO2 levels), and physical environmental stressors from the Child Opportunity Index 2.0. All analyses were conducted using linear mixed-effects modeling, while controlling for age, sex, handedness, MRI scanner type, and head motion, with family and study site as random factors. We found DMN rsFC was negatively associated with neighborhood high school graduation rates ($b = -0.0002$, $p = .022$). Additionally, lower DMN rsFC was seen in children from households reporting a total household income of less than $50,000 as compared to children from households reporting income between $50,000 and $100,000 ($b = -0.0042$, $p = .028$). In contrast, SN rsFC was positively associated with neighborhood average income ($b = 0.018$, $p = .017$) and chemical toxicant exposure levels ($b = 0.0017$, $p = .042$). Finally, we found that FPN rsFC was positively associated with neighborhood home ownership rates ($b = 0.0001$, $p = .008$) and high-skill employment rates ($b = 0.0002$, $p = .009$), as well as negatively associated with neighborhood unemployment ($b = -0.0036$, $p = .042$) and high school graduation rates ($b = -0.0004$, $p = .001$). FPN rsFC was also negatively related to extreme heat exposure ($b = -0.0017$, $p = .010$). Together, these results show that both social and built environmental stressors have unique relationships on rsFC development in late childhood and early adolescence.

Disclosures: **A. Omary:** None. **C. Cardenas-Iniguez:** None. **D. Cotter:** None. **K. Sukumaran:** None. **M. Herting:** None.

Poster

108. Multimodal Imaging Studies in Youth: Identifying Trajectories and Sources of Variability

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 108.26

Topic: A.09. Adolescent Development

Support: NIH U01DA041022
NIH U01DA041028
NIH U01DA041048
NIH U01DA041089
NIH U01DA041106
NIH U01DA041117
NIH U01DA041120

Title: Associations between reading for pleasure and cortical surface area in the ABCD Study

Authors: *D. M. SMITH, A. M. DALE, T. L. JERNIGAN;
Univ. of California San Diego, La Jolla, CA

Abstract: Objective: Reading skill is influenced by many genetic and environmental factors. Time spent reading for pleasure has recently been found to be associated with reading skill, even after accounting for sociodemographic covariates. However, to our knowledge there have been no large-scale studies assessing the relationship between pleasure reading and brain structure. In this study, we aimed to investigate the relationship between self-reported pleasure reading and vertex-wise cortical thickness and surface area in the Adolescent Brain and Cognitive Development (ABCD) Study.
Methods: Using baseline data from ABCD study release 4.0 (n = 6,861, age 9-10), we used linear mixed effects models to estimate the effect of parent-reported pleasure reading on cortical surface area (n = 6,861) and cortical thickness (n = 6,274) at each vertex. We first ran "reduced" models that included only age, sex, scanner ID, and MRI software as fixed covariates. In subsequent models we added self-reported race, parental education, parental income, and reading skill as additional fixed effects. All models included a random effect of family.
Results: In the reduced models of cortical surface area, pleasure reading was significantly associated with cortical surface area in the right lateral temporal cortex (maximum z-statistic 5.65). After adding race, parental income, and parental education as fixed covariates, this relationship remained significant at the vertex-wise level (maximum z-statistic 5.48). Adding reading skill to the model led to a decrease in the observed associations (maximum z-statistic = 4.15), though visual inspection of cortical plots revealed a pattern of association in the same region of the right lateral temporal cortex. Models for cortical thickness did not achieve vertex-wide significance (all z-statistics < 4.0).
Conclusions: Pleasure reading was independently associated with cortical surface area in the right lateral temporal cortex. Associations held even after accounting for sociodemographic variables known to be related to reading, such as race and socioeconomic status. Despite the shared variance with reading skill, results indicate that pleasure reading is a robust factor associated with variance in cortical morphology in youth.

Disclosures: D.M. Smith: None. **A.M. Dale:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; General Electric Healthcare. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); CorTechs Labs, Inc.. F. Consulting Fees (e.g., advisory boards); CorTechs Labs, Inc., Human Longevity, Inc.. **T.L. Jernigan:** None.

Poster

108. Multimodal Imaging Studies in Youth: Identifying Trajectories and Sources of Variability

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 108.27

Topic: A.09. Adolescent Development

Support: NIH Grant K22-MH109558

Title: Cortical thickness alterations in the default mode network predict aggression scores

Authors: *J. BASHFORD-LARGO[1], K. BLAIR[1], M. DOBBERTIN[2], J. R. BLAIR[3], J. ELOWSKY[1], A. MATHUR[1], A. DOMINGUEZ[1], S. BAJAJ[1];
[1]Multimodal Clin. Neuroimaging Lab., [2]Child and Adolescent Psychiatric Inpatient Ctr., Boys Town Natl. Res. Hosp., Boys Town, NE; [3]Child and Adolescent Mental Hlth. Ctr., Copenhagen, Denmark

Abstract: Aggression has significant costs to society. Previous literature has related aggression to structural alterations in regions including ventromedial prefrontal cortex (PFC) and anterior cingulate cortex. Notably, though, this literature has primarily used a region-based rather than a network-based approach. Network-based approaches in conjunction with regional analysis can give us a more detailed picture of neural findings. This study will fill the scientific gap of what networks associate with aggression severity within adolescents. Structural MRI data was collected from 340 adolescents (125 F/215 M) with a mean age of 16.29 (SD=1.20, 14-18 years), and IQ of 103.91 (SD=10.73). Aggression symptomology was indexed via Reactive Proactive Questionnaire (RPQ). The brain was parcellated via Yeo's atlas into seven spatially distributed networks. Freesurfer was used to estimate Cortical Thickness (CT) from both networks and regions within networks. Because of the heterogeneity of the sample within psychiatric diagnosis and medications, follow-up regression was used including six common psychiatric diagnoses and the use of antipsychotic, stimulant, and SSRI medications. Our network-based regression analysis was significant (R^2=0.089; F(18,321)=1.76, p=0.032). Specifically, CT of the right Default Mode Network (DMN) had a significant negative regression weight, indicating those with lower CT in the right DMN had higher RPQ scores, (standardized B= -0.275; p=0.032). None of the other networks significantly contributed to the model. Our regression analysis of regions within the right DMN revealed a significant equation R^2=0.065, F(10,329)=2.30, p=0.013. Within these regions, CT of a cluster comprising superior frontal, medial orbitofrontal, and rostral and caudal anterior cingulate cortices had a significant negative regression weight, indicating those with lower CT within these regions had higher RPQ scores (standardized B= -0.124; p=0.039). When this analysis was repeated using the reactive aggression subscale scores, similar results were obtained. However, this was not the case if proactive scores were used. Follow-up regression analysis with psychiatric diagnoses and medications mirrored results of the main analysis, indicating that these variables did not significantly change the main results. This study expands our knowledge on the neurobiology of adolescent aggression such that increasing aggression levels are associated with CT alterations in the right DMN. This provides evidence for network morphometry differences in aggression severity and can be valuable in translating to therapeutic techniques.

Disclosures: J. Bashford-Largo: None. **K. Blair:** None. **M. Dobbertin:** None. **J.R. Blair:** None. **J. Elowsky:** None. **A. Mathur:** None. **A. Dominguez:** None. **S. Bajaj:** None.

Poster

108. Multimodal Imaging Studies in Youth: Identifying Trajectories and Sources of Variability

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 108.28

Topic: A.09. Adolescent Development

Support: Aston University
Encephalitis Society

Title: Magnetoencephalography and magnetic resonance imaging cortical thickness as multimodal markers of cognitive functioning in paediatric autoimmune encephalitis

Authors: *C. BILLAUD[1], A. G. WOOD[1,2], D. GRIFFITHS-KING[1], K. KESSLER[1,3], E. WASSMER[1,4], S. WRIGHT[1,4], E. FOLEY[1];
[1]Inst. of Hlth. and Neurodevelopment, Aston Univ., Birmingham, United Kingdom; [2]Clin. Sci., Murdoch Children's Res. Inst., Melbourne, Australia; [3]Sch. of Psychology, Univ. Col. Dublin, Dublin, Ireland; [4]Dept. of Neurol., Birmingham Children's Hosp., Birmingham, United Kingdom

Abstract: Background
Paediatric autoimmune encephalitis (PAE) is an inflammatory brain disease that causes cognitive deficits, psychiatric symptoms, seizures, magnetic resonance imaging (MRI) and electroencephalography (EEG) abnormalities. Patients can experience residual cognitive difficulties months to years after acute illness. Neuroimaging analyses combining magnetoencephalography (MEG) and MRI measures of cortical thickness have never been done in PAE. In other populations, multimodal approaches have shown evoked responses and cortical thickness to be statistically associated, and together predicting cognitive performance. Both techniques can examine neural changes in absence of remarkable MRI abnormalities, and thus may be more sensitive to predicting cognitive performance. In light of research linking P300 brain responses to cortical thickness and cognition, we predicted that MEG-measured P300 (M300) and cortical thickness would correlate with each other and with processing speed and working memory in PAE.
Methods
Children diagnosed with AE were recruited from Birmingham Children's Hospital, UK, at least 18 months after diagnostic imaging. They completed MEG recordings during an auditory oddball task; T1w structural MRI; and cognitive evaluation using the WISC-V. MEG recordings were preprocessed and epochs time-locked to target stimuli. Brainstorm was used for coregistration with MRI scans and source modelling. Cortical thickness was estimated with Freesurfer. M300 amplitude, latency, and grey matter thickness of bilateral auditory cortices were computed and correlated with processing speed and working memory scores. Whole-brain cortical thickness was also investigated for cluster-wise corrected correlation with M300 amplitude and latency.
Results
To date, eight children with AE (aged 11.18±3.8y, 5F and 3M) have participated. No measure of M300 or cortical thickness was significantly associated with working memory or processing speed. Cluster-wise cortical thickness in the bilateral lateral occipital/lingual/fusiform areas (R r=-0.8, L r=-0.8; p=<.05) and the right pars triangularis/middle frontal areas (r=-0.78, p=.039) negatively corrected with M300 amplitude.
Discussion
M300 amplitude may reflect underlying anatomical structures of areas previously linked to P300.

It remains unclear whether M300 and cortical thickness are indicators of cognitive functioning in PAE, and both measures may differ from previous findings in typically developing populations. Larger cohorts are needed to reliably explore imaging markers and the present results may change as more cases and healthy controls are included.

Disclosures: C. Billaud: None. **A.G. Wood:** None. **D. Griffiths-King:** None. **K. Kessler:** None. **E. Wassmer:** None. **S. Wright:** None. **E. Foley:** None.

Poster

108. Multimodal Imaging Studies in Youth: Identifying Trajectories and Sources of Variability

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 108.29

Topic: A.09. Adolescent Development

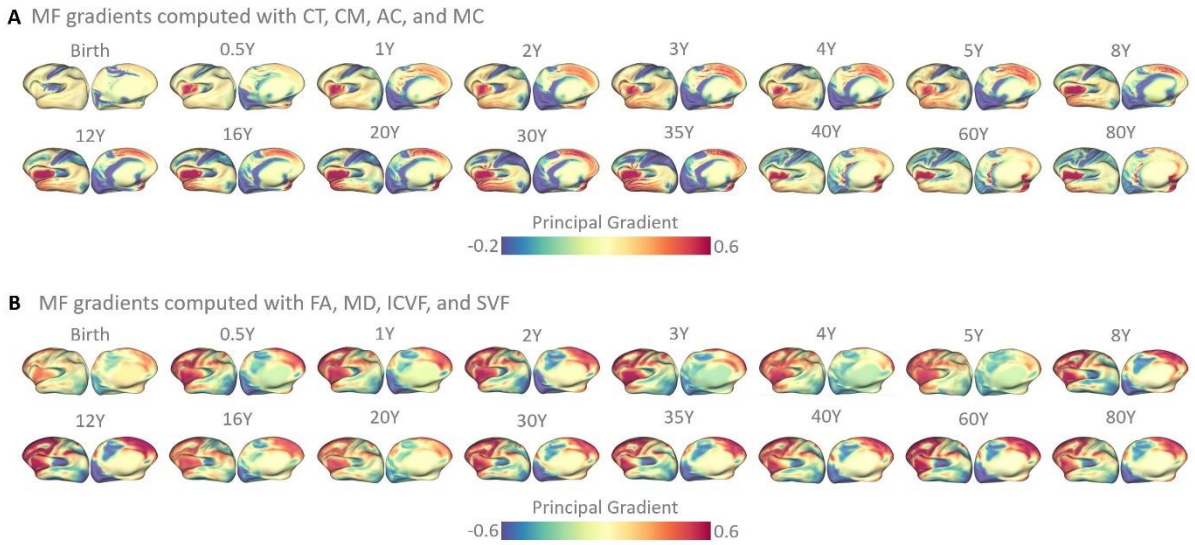
Support: NIH Grant EB008374
NIH Grant MH125479

Title: Multimodal feature gradients of the cerebral cortex across the human lifespan

Authors: *S. AHMAD, K. HUYNH, H. TAYLOR, Y. WU, Z. WU, W. LIN, L. WANG, G. LI, P.-T. YAP;
The Univ. of North Carolina at Chapel Hill, Chapel Hill, NC

Abstract: Advances in neuroimaging and analysis help investigate topological organization of the cerebral cortex that establishes the foundation to constrain brain function and cognition. In vivo MRI facilitate analysis of hierarchical axes, called gradients, reflecting the systematic variations in brain structural features and cognitive functions. However, the hierarchical organization of macrostructural and microstructural brain features along the principal organizing axis across the lifespan is still unexplored. Here, we map for the first time multimodal feature (MF) gradients over the cerebral cortex, revealing topological organization of the macro- and microstructural features from birth to late adulthood. To study the patterns of MF gradients, we constructed the vertex-level MF connectome by estimating the cortical macrostructural (cortical thickness - CT, average convexity - AC, and mean curvature - MC) and microstructural (cortical myelin - CM, fractional anisotropy - FA, mean diffusivity - MD, intracellular volume fraction - ICVF, and soma volume fraction - SVF) features from MRI data of subjects recruited as part of the lifespan human connectome projects. Then, we mapped the hierarchical organization of MF gradients using diffusion map embedding technique, depicting the gradual transition of multimodal features over the entire cerebral cortex. We obtained two sets of gradients by segregating features into two groups: (i) MF gradients computed with CT, CM, AC, and MC; and (ii) MF gradients computed with FA, MD, ICVF, and SVF. For the first feature group, the principal gradient is anchored at one end by sensorimotor and visual cortices and the other end by association cortices (Fig. A). For the second feature group, the principal gradient varies along

the posterior-anterior axis from visual cortex to the frontal association cortex (Fig. B). We also observed that these MF gradients evolve during early infancy and then stabilize through the rest of the life course. Collectively, our findings reveal two organizational axes for multimodal features measured across the lifespan.



Disclosures: **S. Ahmad:** None. **K. Huynh:** None. **H. Taylor:** None. **Y. Wu:** None. **Z. Wu:** None. **W. Lin:** None. **L. Wang:** None. **G. Li:** None. **P. Yap:** None.

Poster

108. Multimodal Imaging Studies in Youth: Identifying Trajectories and Sources of Variability

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 108.30

Topic: A.09. Adolescent Development

Support: NSF Grant 1940094
NSF Grant 1649865
NSF Grant 2116707

Title: Impact of the Adolescent Environment and Brain Connectome on Emotional Health Outcomes During the COVID-19 Pandemic

Authors: S. BROOKS[1], C. SMITH[1], *C. STAMOULIS[2];
[1]Pediatrics, Boston Children's Hosp., Boston, MA; [2]Boston Children's Hospital/Harvard Univ., Boston, MA

Abstract: The COVID-19 pandemic has had unprecedented but incompletely understood effects on youth mental health. A complex set of factors likely played a critical role in youth responses

to pandemic-related stressors. However, the role of the underlying brain circuitry on mental resilience remains unknown. This study investigated the impact of environmental factors and organization of functional brain circuits on emotion, stress, and coping during the pandemic. Resting-state fMRI data collected mostly before the pandemic from n = 1384 adolescents [at the 2-year follow-up, 52.67% female; median age (interquartile range (IQR)) = 144 (13) months] in the Adolescent Brain Cognitive Development study were analyzed. Sleep, physical activity, history of depression and anxiety, demographics, and COVID-19 questionnaire data (collected on average 20 months after the fMRI) were also analyzed. Emotions (lonely, sad, unhappy, angry), ability to cope with personal issues, and overall mental health scores were examined. Linear regression models assessed relationships between brain network properties and these outcomes, as well as the latter's correlations with environmental and other parameters. LASSO regression identified a parsimonious set of independent variables for each outcome. Mediating effects of network topology on relationships between environment and emotional outcomes were also assessed. Parent-child conflict, being more fearful than friends, and difficulty falling asleep correlated with higher emotional distress ($p<0.02$). Stronger parental belief on allowing growing children to make their own decisions was associated with lower negative emotions ($p=0.04$). Efficiency, community organization and topological resilience of the bilateral reward network were positively associated with confidence in handling personal problems. The same properties in the right limbic network were correlated with less frequent loneliness and sadness, difficulty having fun, feeling like life went wrong, and feeling they couldn't do anything right ($p<0.05$). Median intra- and inter-network connectivity of the thalamus was inversely related with frequency of feeling angry ($p<0.03$). The right limbic network topology mediated feelings of loneliness, difficulty having fun, feeling that life went wrong, and feeling they couldn't do anything right. Thalamic connectivity mediated feelings of anger ($p<0.05$). These results suggest that the organization of brain networks supporting reward and emotion processing and multiple environmental factors may have played an important role in emotional health and mental resilience in adolescents during the COVID-19 pandemic.

Disclosures: S. Brooks: None. **C. Smith:** None. **C. Stamoulis:** None.

Poster

108. Multimodal Imaging Studies in Youth: Identifying Trajectories and Sources of Variability

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 108.31

Topic: A.09. Adolescent Development

Support: NIH Grant MH121868

Title: Deep learning for analysis of diffusion-MRI based white matter tractometry

Authors: J. QIAO[1], J. D. YEATMAN[2], ***A. ROKEM**[1], A. RICHIE-HALFORD[2];
[1]Univ. of Washington, Seattle, WA; [2]Stanford, Stanford, CA

Abstract: Tractometry uses diffusion-weighted MRI (dMRI) to delineate the tissue properties of brain white matter connections. Using anatomical landmarks, it finds the locations of major white matter pathways in the brain of each individual and extracts summary statistics of the diffusion along the length of each major pathway. However, inferences from the tractometry tract profiles are complicated due to residual individual variability in the extraction of tissue properties, and due to complex non-linear relationships between brain tissue properties and phenotypes of interest, such as: individual differences in cognitive abilities, progress towards developmental mile-stones or brain health. Deep learning methods use regularities in large datasets to learn complex, non-linear functions relating different aspects of the data. We implemented open-source software that applied deep learning methods, originally designed for time series analysis, to the analysis of tractometry data within an existing toolbox for statistical analysis of tractometry data (https://richiehalford.org/AFQ-Insight/). In analysis of dMRI data from 1,817 participants in the Healthy Brain Network study, we found that deep learning algorithms can accurately learn the relationship between tractometry data and biological age, deriving dMRI-based estimates of "brain age" (Franke and Gaser, 2019). These estimates achieve accuracy that exceeds the previous state-of-the-art brain age prediction with dMRI data (Richie-Halford et al. 2021; PLoS Comp Biol), with a median absolute error of under 1.3 years. Moreover, while previous work required introducing a non-linear link function between age and white matter properties, the neural networks learns this non-linearity directly from the data. These results demonstrate the potential that deep learning methods have to uncover complex and non-linear relationships between dMRI data and a range of phenotypes.

Disclosures: J. Qiao: None. **J.D. Yeatman:** None. **A. Rokem:** None. **A. Richie-Halford:** None.

Poster

108. Multimodal Imaging Studies in Youth: Identifying Trajectories and Sources of Variability

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 108.32

Topic: A.09. Adolescent Development

Support: NIH Grant MH121868
NIH Grant 5R01HD095861-03

Title: Early life adversity and white matter development

Authors: *A. RICHIE-HALFORD[1], E. ROY[1], J. KRUPER[2], J. YEATMAN[1], A. S. ROKEM[2]; [1]Stanford Univ., Stanford, CA; [2]Psychology, Univ. of Washington, Seattle, WA

Abstract: The link between exposure to early life adversity (ELA) and psychopathology, cognition, and brain structure are widely acknowledged and reported. In particular, childhood adversity has been associated with depression, post-traumatic stress disorder, low educational

attainment, and deficits in language development and executive functioning (Guloksuz et al. 2018). Most studies use structural or functional MRI to link changes in brain structure to childhood adversity. However, there is a burgeoning body of research observing changes in tissue properties of the brain's white matter connections, assessed in diffusion MRI (dMRI). In particular, children exposed to adversity exhibit differences in the uncinate fasciculus, cingulum, and superior longitudinal fasciculus (Gur et al. 2019). We sought to test these findings in an analysis of dMRI data from 1,817 participants in the Healthy Brain Network study, a large, heterogeneous dataset. ELA was estimated in the negative life events scale (NLES), a self-reported cumulative list stress assessment. We also measured the threat dimension of childhood adversity (McLaughlin et al. 2014) using the child perception of interparental conflict's threat (CPIC-threat) subscale, and Alabama parenting questionnaire (APQ) corporal punishment subscale. Direct comparisons between each of the ELA strata in the three tracts of interest find no significant differences, and statistical matching on age, sex, and socioeconomic status reduced nominal differences further. To detect complex and non-linear relationships between tissue properties and ELA, we fit a series of gradient boosted random tree models (XGBoost) to predict adversity measures. Models that included white matter tissue properties as predictors demonstrated no additional predictive skill over demographic-only models. In summary, we found no associations between the three adversity measures and white matter integrity as measured by FA in 24 major white matter tracts.

Disclosures: A. Richie-Halford: None. **E. Roy:** None. **J. Kruper:** None. **J. Yeatman:** None. **A.S. Rokem:** None.

Poster

108. Multimodal Imaging Studies in Youth: Identifying Trajectories and Sources of Variability

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 108.33

Topic: A.09. Adolescent Development

Title: Cortical thinning variation through brain development and aging is influenced by cortical layer composition and thickness values in childhood

Authors: *T. C. MARCAL, C. E. G. SALMON;
Univ. of São Paulo, Ribeirão Preto, Brazil

Abstract: Cortical thinning occurs throughout life at varying rates and is related to geometric factors, pruning, brain plasticity, neurodegenerative diseases, and cognitive functions of specialized structures. However, the neurobiological substrates at the different scales are poorly understood - mesoscale cortical layering, macroscopic cortical thickness, and, ultimately, functional neuroanatomy. We have processed anatomical magnetic resonance images of 871 participants (8-83 y.o.) in FreeSurfer software. The database came from Nathan Kline Institute and comprised participants without a history of neurological diseases. From a polynomial model

of the cortical thickness throughout the lifespan, we obtained the thickness variation rates of the cortex segmented in the 44 Von Economo structures. We modeled the thinning rates considering demographic variables and structural properties of the cortex using the Light Gradient Boosting Machine method. The cortical layer composition was included and was based on the BigBrain database. For explainability, we calculated the SHAP values, a technique that utilizes game theory to determine the contribution of each feature to individual model output. No region showed a constant value of cortical thinning during life. The thinning curve presented a behavior of a parabola with symmetry between 20 to 85 years, with a minimum thinning around 50 years and a maximum thinning between 10-20 years. As expected, age was the variable most relevant to the model, followed by the portion of cortical layers 1, 4, and 5, estimation of thickness at ten years, and the specific lobe. The contributions of age to thinning had the form of a parabola with higher contributions before 30 years and after 75 years. The contribution of layer 1 to thinning was proportional to its portion at a young age and inversely proportional to old age. On the other hand, the contributions of layers 4 and 5 had an inverse behavior. The parietal and temporal lobes had a greater contribution to thinning than the other lobes after 50 years. There was a positive linear relationship between thickness estimated at ten years and its contribution to thinning; the slope was inversely proportional to age, i.e., higher slopes during adolescence. The best model explained up to 87% variation of cortical thinning among cortical structures and ages. Six anatomical spread structures were not well fitted to the tested models. Our findings point to the relevance of different scale variables for the understanding of cortical thinning in brain development and aging. It suggests the role of each scale in a different mechanism of thinning.

Disclosures: **T.C. Marcal:** None. **C.E.G. Salmon:** None.

Poster

108. Multimodal Imaging Studies in Youth: Identifying Trajectories and Sources of Variability

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 108.34

Topic: A.09. Adolescent Development

Support: European Research Council (ERC) Grant No. 694786

Title: Cortical tracking and phase amplitude coupling to sung speech and how they predict language performance; longitudinal data from infants and adults.

Authors: *A. ATTAHERI[1], Á. NÍ CHOISDEALBHA[1], G. M. DI LIBERTO[2], S. ROCHA[1], P. BRUSINI[3], N. MEAD[1], H. OLAWOLE-SCOTT[1], P. BOUTRIS[1], S. GIBBON[1], I. WILLIAMS[1], C. GREY[1], S. FLANAGAN[1], D. PANAYIOTOU[1], A. PHILLIPS[1], M. ALFARO E OLIVEIRA[1], C. BROUGH[1], U. GOSWAMI[1];
[1]Ctr. for Neurosci. in Educ., Univ. of Cambridge, Cambridge, United Kingdom; [2]SCSS, École Normale Supérieure, Dublin, Ireland; [3]Univ. of Liverpool, Liverpool, United Kingdom

Abstract: Speech contains important temporal information in its low frequencies and the synchronisation or “cortical tracking” of low frequency neural oscillations to the envelope of speech assists in encoding the signal. In adults, neurophysiological signals in the delta and theta bands are known to track the envelope of speech, and the phase of these low frequency oscillations also temporally organise the amplitude of high frequency oscillations in a process called phase amplitude coupling (PAC). However, the relative contribution of different cortical frequency bands in infants remains unexplored.
The alignment of cortical neural signals to specific stimulus parameters of speech has been shown to play a key role in adult language processing, yet this comparison to early language measures is unexplored in infants.
Here we report longitudinal EEG data from 112 infants (Cambridge BabyRhythm study), aged 4-, 7- and 11- months, as they listened to nursery rhymes. After establishing the presence of stimulus-related neural signals (PSD), multivariate temporal response function (mTRF) analyses measured the strength and maturation of cortical speech tracking, whilst a normalised modulation index (nMI) assessed PAC. We replicated this experiment with 21 adult participants, to see whether delta and theta cortical oscillatory networks differ when tracking speech in the infant and adult brain.
We recorded language data assessing semantics, gesture, phonology, timing and grammar, in both the adults and infants, to see if individual differences in language performance could be predicted from our EEG results.
Peaks in stimulus-related spectral power (PSD) were different in the two populations. In Infants, PSD peaks were observed in the delta and theta ranges with a developmental maturation of the theta peaks. Whilst stimulus-related increases in PSD power were present in the adult data at these frequencies, PSD peaked at different points.
Both infants and adults showed significant cortical tracking of the sung speech in both delta and theta bands but not in the alpha band. Furthermore, delta band values were significantly greater than values in the theta band in both populations.
PAC was stronger for theta- versus delta- driven coupling in adults but was equal for delta- versus theta-driven coupling in infants. Finally, we describe which of our battery of language outcome measures were predicted by each of the above EEG measures.
These data suggest that cortical speech tracking mechanisms are present early in infancy but undergo developmental changes into adulthood. Furthermore, cortical oscillation measures can predict certain elements of infant language performance.

Disclosures: **A. Attaheri:** None. **Á. Ní Choisdealbha:** None. **G.M. Di Liberto:** None. **S. Rocha:** None. **P. Brusini:** None. **N. Mead:** None. **H. Olawole-Scott:** None. **P. Boutris:** None. **S. Gibbon:** None. **I. Williams:** None. **C. Grey:** None. **S. Flanagan:** None. **D. Panayiotou:** None. **A. Phillips:** None. **M. Alfaro e Oliveira:** None. **C. Brough:** None. **U. Goswami:** None.

Poster

108. Multimodal Imaging Studies in Youth: Identifying Trajectories and Sources of Variability

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 108.35

Title: WITHDRAWN

Poster

109. Aminergic Transmission: Function, Regulation, and Techniques

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 109.01

Topic: B.01. Transmitters, Transporters, and Other Signaling Molecules

Support: NIH Grant MH086530
NARSAD Young Investigator Grant #28731
Max Kade Fellowship
NIH Grant MH107132

Title: Detection and pharmacological normalization of context-dependent repetitive and compulsive behaviors in mice expressing the psychiatric disease-associated DAT Val559 variant

Authors: *A. STEWART[1,2], G. L. DAVIS[1], F. P. MAYER[1], L. B. AREAL[1], M. J. RABIL[1], R. D. BLAKELY[1,2];
[1]Biomed. Sci., [2]Stiles-Nicholson Brain Inst., Florida Atlantic Univ., Jupiter, FL

Abstract: We previously reported that the dopamine (DA) transporter (DAT) substitution DAT Ala559Val, identified in male subjects with autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD), triggers non-vesicular, anomalous DA efflux (ADE) in transfected cells and in DAT Val559 mice *in vivo*. Moreover, we have found that DAT Val559 KI mice display schedule- and context-dependent impulsivity and enhanced reward motivation. DAT Val559 mice also acquire cocaine conditioned place preference (CPP) at WT levels but display delayed extinction to the drug-context association, suggesting altered behavioral flexibility and increased habit formation. To test this hypothesis, we utilized a within-subject, lever-pressing paradigm with distinct nose-poke pressing schedules to bias male WT and DAT Val559 mice toward the formation of goal-directed (random ratio, RR) or habitual (random interval, RI) behavior, probing response rate sensitivity to reward devaluation. DAT Val559 mice were able to modulate nose-poke behavior appropriately following reward devaluation, but demonstrated perseverative checking behavior regardless of training schedule, returning to the reward dispenser (checking) despite satiation prior to task initiation. Indeed, whereas DAT Val559 mice display normal cognitive flexibility as monitored by re-learning a visual pairwise discrimination task, devaluation of reward consistently evoked habitual checking, regardless of reinforcement schedule. In the absence of reward motivation in the Y Maze, male DAT Val559 mice also displayed perseverative behavior compared to controls, demonstrating decreased spontaneous alternation and an increase in direct revisits into the same arm of the maze that could be normalized by i.p. administration of either the D2-type receptor antagonist sulpiride or the κ opioid receptor (KOR) antagonist nor-BNI. Experiments are underway to determine

whether the impact of nor-BNI on DAT Val559 phenotypes extends to conditioned behaviors and what DA circuits drive these altered behaviors. Given prior work indicating a selective penetrance of DAT Val559 at the level of D2-type autoreceptor modulation of transporter phosphorylation, surface trafficking and DA clearance in male dorsal striatum (DS), we propose that aberrant DS DA signaling leads to retention of habitual behavior. In support of this idea, we observe altered spine density of DS medium spiny neurons in DAT Val559 males versus WT animals. From a clinical perspective, our work suggests that targeting dynorphin signaling may relieve perseverative and compulsive behaviors arising from tonic elevations in extracellular DA.

Disclosures: A. Stewart: None. **G.L. Davis:** None. **F.P. Mayer:** None. **L.B. Areal:** None. **M.J. Rabil:** None. **R.D. Blakely:** None.

Poster

109. Aminergic Transmission: Function, Regulation, and Techniques

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 109.02

Topic: B.01. Transmitters, Transporters, and Other Signaling Molecules

Support: HEO-CLT, PSC/CUNY

Title: Muscarinic M5 receptor modulates DAT through G protein βϒ subunits

Authors: *L. GONZALEZ REYES, A. WALLS, A. H. KOTTMANN, G. E. TORRES; City Col. of New York, New York, NY

Abstract: We have previously shown that Gβϒ subunits of G proteins interact with the dopamine transporter (DAT) to promote dopamine (DA) efflux. However, the G protein-coupled receptor (GPCR) that may be directly involved in activating Gβϒ subunits and modulating DAT function has not yet been identified. Since both dopaminergic and cholinergic fibers have been shown to simultaneously innervate forebrain areas, we investigate the possible interaction between DAT and muscarinic receptors using immunohistochemistry (IHC). We found that among the muscarinic acetylcholine receptors (mAChR), the M5 receptor (M5R) showed high colocalization and interaction through proximity ligation assay (PLA) with DAT in several brain areas including the dorsal striatum, prefrontal cortex, septum, and hippocampus. Histological studies also showed that colocalization of these proteins takes place on dopamine terminals innervating the wall of blood vessels including arterioles and capillaries across the brain areas where such colocalization was identified. Studies on the M5R knockout mice confirmed that these animals undergo blood vessel degeneration accompanied with DAT upregulation. To explore the functional interaction between M5R and DAT on extracellular dopamine we used fiber photometry and in vivo microdialysis. The M5R negative regulator ML 375 prevented oxotremorine-induced-DA release in the dorsal striatum suggesting an interaction in which M5R mediates acetylcholine induced-dopamine DA release in striatal terminals. Similar experiments

in the M5R KO mice are in progress. Collectively, these results suggest that M5R is expressed in the terminal of dopamine fibers and may interact with the DAT through Gβϒ subunits.

Disclosures: L. Gonzalez Reyes: None. **A. Walls:** None. **A.H. Kottmann:** None. **G.E. Torres:** None.

Poster

109. Aminergic Transmission: Function, Regulation, and Techniques

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 109.03

Topic: B.01. Transmitters, Transporters, and Other Signaling Molecules

Support: ANID Schoolarship 21201333
ANID Interniship 21201333
RFCUNY

Title: New interaction between Gβγ protein the human norepinephrine transporter (hNET), insights from in silico studies.

Authors: ***L. DINAMARCA VILLARROEL**[1], G. E. TORRES[2], A. FIERRO[1];
[1]Organic Chem., Pontificia Univ. Catolica de Chile, Santiago, Chile; [2]Molecular, Cell. and Biomed. science, The City Col. of New York, New York, NY

Abstract: The human Norepinephrine Transporter (hNET) play a crucial role in the reuptake of norepinephrine (NE) and epinephrine (EP), terminating the action of these neurotransmitters. Different drugs approved for treating neuropsychiatric conditions including depression and attentional deficit disorders, interact with NET, blocking the reuptake, increasing the extracellular concentration of NE, or even producing efflux through the transporter. Monoamine transporter are highly regulated through signaling mechanisms and protein-protein interactions. We have discovered a new interaction between the dopamine transporter DAT and Gβγ subunits of G proteins. Our data indicate that the binding of Gβγ to the carboxy terminus of DAT promotes DA efflux. Here, we investigated whether the related NET presents a similar Gβγ regulation. Using *in silico* simulations, we identified a binding site between NET and Gβγ, which produces conformational changes that might support NE efflux in a physiological state. The molecular model also suggests that the interaction between NET and Gβγ alter the NE binding site within the transporter. We are now experimentally testing the predictions from the model. Our data support a novel mechanism by which NET is regulated by G proteins.

Disclosures: L. Dinamarca Villarroel: None. **G.E. Torres:** None. **A. Fierro:** None.

Poster

109. Aminergic Transmission: Function, Regulation, and Techniques

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 109.04

Topic: B.01. Transmitters, Transporters, and Other Signaling Molecules

Support: NIMH - MH121453
PA Dept of Health - CURE

Title: Bidirectional ERK1/2 modulation in dopaminergic neurons regulates DAT trafficking and function

Authors: *C. BESADA[1], S. LEWANDOWSKI[1], O. V. MORTENSEN[2];
[1]Drexel Univ. Col. of Med., Philadelphia, PA; [2]Dept of Pharmacol. & Physiol., Drexel Univ., Philadelphia, PA

Abstract: Dopamine (DA) is a neurotransmitter that plays a critical role in motivation, reward, and learning. The dopamine transporter (DAT) is responsible for the reuptake of released DA, making it a central regulator of DA neurotransmission. DAT is a target for psychostimulants such as cocaine, giving DAT a key role in psychostimulant-use disorders. Two signaling pathways that contribute to DAT regulation and trafficking to and from the plasma membrane involve the protein kinase C (PKC) and the mitogen activated protein kinase (MAPK) ERK1/2. ERK1/2 is inactivated by the MAPK phosphatase MKP3, which specifically dephosphorylates ERK1/2. Prior *in vitro* data demonstrated that activation of PKC by phorbol 12-myristate 13-acetate (PMA) results in decreased DAT surface-expression; MKP3 overexpression attenuates this effect. Furthermore, related studies have shown that ERK1/2 activation may lead to phosphorylation of DAT on threonine 53 (Thr53), however, the significance of this phosphorylation is not completely understood, but it is thought to play a significant role in DAT function and trafficking. *In vivo* data from our lab shows exogenous overexpression of MKP3 and resulting ERK1/2 inactivation increases DAT surface-expression, but interestingly reduces DAT transcript levels. This suggests that post-transcriptional regulation of DAT, such as proteasomal degradation, may be affected by ERK1/2. Additionally, MKP3 overexpression reduced Thr53 phosphorylation levels despite the overall increase of DAT surface-expression. To further characterize the contributions of ERK1/2 to DAT regulation and trafficking *in vivo*, we will use two viral constructs: AAV9-FLEX-MKP3-R (MKP3) and AAV9-FLEX-OptoSOS-R (OptoSOS). OptoSOS is an optogenetic tool that enables blue-light activation of ERK1/2. Both constructs enable cre recombinase-dependent expression in DA neurons of the VTA, allowing for spatiotemporal inactivation or activation of ERK1/2. We have confirmed that ERK1/2 is activated by blue-light in a cre-dependent manner, and similar to our results with MKP3 overexpression, ERK1/2 activation results in changes in DAT surface-expression and phosphorylation. We will utilize these constructs to better understand the role of ERK1/2 signaling in regulation of DAT phosphorylation and membrane trafficking. Taken together, our results indicate that ERK1/2 serves a critical physiological role in DAT regulation, and these studies will provide important information regarding the mechanistic relationship between DAT trafficking, phosphorylation, and activity. These tools could help to reveal novel therapeutic strategies for psychostimulant-use disorders.

Disclosures: C. Besada: None. **S. Lewandowski:** None. **O.V. Mortensen:** None.

Poster

109. Aminergic Transmission: Function, Regulation, and Techniques

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 109.05

Topic: I.08. Methods to Modulate Neural Activity

Title: Simultaneous recording of neuromodulator and calcium spatiotemporal activity reveals differences between dopaminergic, noradrenergic and serotonergic cortical activity

Authors: *M. J. DESFORGES[1], P. FLOTHO[2], B. KUHN[1], K. DOYA[1];
[1]Okinawa Inst. of Sci. and Technol., Okinawa, Japan; [2]Univ. des Saarlandes, Saarbrücken, Germany

Abstract: Do neuromodulators provide a homogenous global signal across the cortex or diverse heterogeneous signals to spatially-restricted targets? Answering this fundamental question is essential for understanding the role of neuromodulation. Here we used recently developed genetically-encoded fluorescent biosensors and calcium indicator (jRGECO1a) to compare the precise spatiotemporal release of dopamine (dLight1.2), noradrenaline (GRAB_NE1m) and serotonin (GRAB_5-HT3.5). Dual-channel two-photon microscopy allowed for simultaneously recording of both extracellular neuromodulator and intracellular calcium concentrations in the motor cortex of mice. We assessed mean pixel correlations as a function of distance, at 25μ;;m intervals at 6Hz sampling rate. We found a consistently sharp drop in correlated neuromodulator activity between 0 and 25μ;;m, from 1.0 to 0.4, suggesting a similarly limited spread for each system. However, comparing calcium and neuromodulator activity between imaging channels, we found distinct differences. At the same location, distance 0, calcium activity was more highly correlated with serotonin (0.41), than noradrenaline (0.38) or dopamine (0.35); the subsequent decrease as a function of distance was similar between systems. Together, this suggests heterogeneity in cortical neuromodulation both spatially and between neuromodulator systems. Simultaneous two-photon calcium and neuromodulator recordings promise to improve our understanding of the underlying computation performed by neuromodulation in the cortex. This method allows for quantification of the spatiotemporal heterogeneity of neuromodulator release and effects on neuronal activity.

Disclosures: **M.J. Desforges:** None. **P. Flotho:** None. **B. Kuhn:** None. **K. Doya:** None.

Poster

109. Aminergic Transmission: Function, Regulation, and Techniques

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 109.06

Topic: B.01. Transmitters, Transporters, and Other Signaling Molecules

Support: MH121453

Title: Allosteric dopaminetransportermodulator inhibits cocaine-induced behaviors

Authors: *Y. XU[1], S. LEWANDOWSKI[3], C. BESADA[2], O. V. MORTENSEN[4];
[1]Drexel Univ., Drexel Univ. Col. of Med., Philadelphia, PA; [2]Drexel Univ. Col. of Med., Drexel Univ. Col. of Med., Phila, PA; [3]Col. of Med., [4]Drexel Univ. Col. of Med., Drexel Univ., Philadelphia, PA

Abstract: The neurotransmitter dopamine (DA) is involved in motivation, reward mechanisms, and many central nervous system diseases. DA is transported into the presynaptic neurons by a protein called dopamine transporter (DAT). The psychostimulant cocaine is an inhibitor of DAT. When DAT is inhibited by cocaine, the DA in the synaptic cleft increases and this leads to amplified downstream dopaminergic signaling primarily in the mesolimbic pathway. This increase in cocaine elicited DA signaling is responsible for its addictive properties. Because DAT is the primary target of cocaine, compounds acting on the DAT in novel ways could potentially treat cocaine use disorders. We previously found a novel compound—KM822 and characterized it as an allosteric modulator of DAT function that significantly decreases cocaine-induced locomotive response in planarians. To test if KM822 has similar effects in mammals, we administered KM822 and cocaine through intracranial infusions into Long Evans rats' nucleus accumbens (NAc) and measured locomotion. We targeted the NAc as it is a part of the brain that plays a crucial role in the mesolimbic dopaminergic pathway and has been recognized by its high density of DAT. Our results showed that KM822 significantly decreased hyper-locomotion induced by cocaine and notably did not cause any increase in locomotion by itself. We also examined KM822's ability to interfere with cocaine's rewarding effect using the conditioned place preference (CPP) assay. In this assay, animals are tested for their preference for a cocaine-associated environment as a model of cocaine seeking. Unlike the locomotion assay, this assay is more relevant to behaviors associated with cocaine addiction and therefore has a higher translational value. c-Fos expression is frequently utilized as a functional marker to investigate neuronal processes in response to a stimulus. To determine how KM822 affects neuronal activity in the NAc, c-Fos staining was conducted, and the expression of c-Fos was compared between animals treated with KM822 and those treated with the vehicle before cocaine infusion. In the future, we plan to further assess the abuse liability of KM822 as well as evaluate the impact of KM822 on extinction and relapse. Overall, these studies demonstrate the ability of KM822 to block DAT inhibitor-induced behaviors in rats and provide strong evidence that the novel allosteric DAT modulator KM822 has significant potential for treating cocaine addiction.

Disclosures: **Y. Xu:** None. **S. Lewandowski:** None. **C. Besada:** None. **O.V. Mortensen:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); US patent 9616065.

Poster

109. Aminergic Transmission: Function, Regulation, and Techniques

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 109.07

Topic: B.01. Transmitters, Transporters, and Other Signaling Molecules

Support: The Lundbeck Foundation
The Independent Research Fund Denmark

Title: Investigating the role of K^+ in the transport mechanism of neurotransmitter:sodium symporters

Authors: *S. G. SCHMIDT[1], M. G. MALLE[2], A. NIELSEN[1], A. NYGAARD[1], C. F. PUGH[1], S. S. R. BOHR[2], J. C. NIELSEN[1], I. H. POULSEN[1], K. D. RAND[3], N. S. HATZAKIS[2], C. J. LOLAND[1];
[1]Dept. of Neurosci., [2]Dept. of Chem., [3]Dept. of Pharm., Univ. of Copenhagen, Copenhagen, Denmark

Abstract: The neurotransmitter:sodium symporters (NSSs) are secondary active transporters that couple the reuptake of neurotransmitters from the extracellular space to the symport of Na^+. The family includes transporters of dopamine, serotonin, norepinephrine, and GABA. The serotonin transporter (SERT) is known to also couple substrate uptake to antiport of K^+. The bacterial Leucine Transporter (LeuT) is a classical structural model for the NSSs. LeuT can also bind K^+ (Billesbølle et al., Nat. Commun., 2016), but investigations of K^+-coupled transport in other NSSs have been sparse, and the K^+ ion-binding site is unknown. Here we used human dopamine transporter (DAT) expressed in Expi293F cells and *Drosophila*(d) DAT expressed and purified from Expi293F cells to measure the dependence of ions on radiolabeled ligand binding. We reconstituted dDAT into liposomes containing buffers with varying cations to measure how this affected uptake of dopamine, and into liposomes containing fluorescent Na^+- and K^+ indicators to measure fluxes of Na^+ and K^+. To map the similarities between the effect of K^+ in LeuT, SERT, and DAT, we expressed and purified LeuT to measure K^+ dependence on ligand binding, conformational changes, and substrate uptake. We mutated all coordinating residues in the sodium binding site Na1 and examined the effects to identify residues involved in K^+ binding in LeuT. We show that Na^+-dependent ligand binding to dDAT and human DAT is inhibited by K^+. We find that K^+ inside the proteoliposomes increases the dopamine uptake capacity and maximum uptake velocity for dDAT. We find that the rates of K^+ efflux are increased under dopamine uptake conditions and the rates of Na^+ influx are increased by dopamine and intra-proteoliposomal K^+ in combination. Based on these results, we suggest that K^+ can bind to and be antiported by DAT and that this increases the rate of the dopamine transport cycle. For LeuT, we find that K^+ concentration dependently increases the uptake rate of alanine, but unlike dDAT, extra-vesicular K^+ does not affect substrate uptake. We find that the affinity of Na^+ and K^+ is affected simultaneously by mutations in the Na1 site, this suggests that the Na1 site is highly sensitive to the interaction between K^+ and LeuT. Our results expand on the fundamentals of dopamine transport and prompt a reevaluation of the impact of K^+ on other NSSs in this pharmacologically important family. The effect of K^+ in LeuT resembles a range of findings from SERT and DAT, hence the Na1 site mutations examined could serve as a starting point for future attempts to locate the K^+ binding site in SERT and DAT.

Disclosures: **S.G. Schmidt:** None. **M.G. Malle:** None. **A. Nielsen:** None. **A. Nygaard:** None. **C.F. Pugh:** None. **S.S.R. Bohr:** None. **J.C. Nielsen:** None. **I.H. Poulsen:** None. **K.D. Rand:** None. **N.S. Hatzakis:** None. **C.J. Loland:** None.

Poster

109. Aminergic Transmission: Function, Regulation, and Techniques

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 109.08

Topic: B.01. Transmitters, Transporters, and Other Signaling Molecules

Support: NIH Grant 5R01NS112176-02
NRF 2021R1A2B5B02002437

Title: Optimization of N-MCSWV waveform to mitigate fouling for chronic serotonin recordings

Authors: ***J. BARNETT**[1], A. GOYAL[2], A. RUSHEEN[2], J. YUEN[3], C. D. BLAHA[2], K. E. BENNET[4], Y. OH[2], D. JANG[7], J. D. FRYER[5], K. H. LEE[2], H. SHIN[6];
[1]Mayo Clin., Scottsdale, AZ; [3]Dept. of Neurologic Surgery, [4]Chair, Div. of Engin., [2]Mayo Clin., Rochester, MN; [5]Neurosci., Mayo Clin., Scottsdale, AZ; [6]Neurologic Surgery, Mayo Clin., Rochester, MN; [7]Biomed. Engin., Hanyang Univ., Seoul-City, Korea, Republic of

Abstract: Serotonin is a neurotransmitter integral to emotion, motivation, appetite, social instincts, and sleep. Understanding serotonergic neurotransmission in the brain is particularly important within the context of disordered psychiatric systems, including depression, post-traumatic stress disorder, substance use and eating disorders. Despite recent advances in our understanding of phasic (acute) serotonergic signaling, the regulation of tonic (chronic) serotonin levels remains relatively unexplored. The therapeutic efficacy of selective serotonin reuptake inhibitors (SSRIs) is thought to be due to changes in tonic serotonin signaling. Contemporary *in vivo* recording technologies, such as microdialysis and fast-scan cyclic voltammetry (FSCV) are unable to reliably measure tonic changes in serotonin release due to biofouling— a well-documented phenomenon in which the surface of a carbon fiber microelectrode (CFM) becomes saturated. Without salvaging the surface of the saturated electrode, CFMs measuring neurotransmission in the synapse have a half-life on the order of hours to days— incompatible with chronic recording. Attempts have been made to reduce biofouling, yet despite modifications to the waveform and use of different CFM coatings, no reliable method has been reported. Here we present the results of a novel approach for N-Multiple Cyclic Square Wave Voltammetry (N-MCSWV) to reduce signal fouling and enhance the longevity of the electrode *in vivo*. Through repeated modifications to the N-MCSWV waveform, it was found that utilization of a higher switching potential consistently mobilized the plated compounds into their daughter ions, effectively cleaning the working area of the CFM and enabling repeated use. We found that a +1.3 V switching potential is sufficient to clear oxidative byproducts from the electrode surface, enabling continued measurement of the electroactive neurotransmitters in the synapse. Thus, this

novel and relatively simple approach is intended to enhance the usable lifespan of the CFM and enable *in vivo* recording in patients with a need for chronic Deep Brain Stimulation. These results demonstrate that N-MCSWV is capable of measuring tonic levels of serotonin *in vivo*, paving the way for a deeper mechanistic understanding of the role of serotonin neurotransmission in both normal and disordered psychiatric systems.

Disclosures: **J. Barnett:** None. **A. Goyal:** None. **A. Rusheen:** None. **J. Yuen:** None. **C.D. Blaha:** None. **K.E. Bennet:** None. **Y. Oh:** None. **D. Jang:** None. **J.D. Fryer:** None. **K.H. Lee:** None. **H. Shin:** None.

Poster

109. Aminergic Transmission: Function, Regulation, and Techniques

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 109.09

Topic: B.01. Transmitters, Transporters, and Other Signaling Molecules

Support: NIH U01NS1208020

Title: Imaging dopamine signaling during aversion with an improved genetically encoded dopamine indicator

Authors: ***A. PAL**[1], J. ROSHGADOL[1], J. SUN[1], J. A. CHOUINARD[2], J. R. WICKENS[3], L. TIAN[1];
[1]Univ. of California, Davis, Davis, CA; [2]Neurobio. Res. Unit, Okinawa Inst. of Sci. and Technol., Onna-Son, Japan; [3]Neurobio. Res. Unit, OKINAWA INSTITUTE OF SCIENCE AND TECHNOLOGY, Onna-son, Japan

Abstract: The mammalian brain quickly adjusts its functional state in response to environment changes via the action of neuromodulators across spatiotemporal scales. Dopamine (DA) is one of the most important neuromodulators and are essential for survival, foraging, motivation and reward. Current research suggests, that during unexpected aversive stimuli and cues that predict them, DA terminals in the Nucleus accumbens are significantly excited. Furthermore, studies indicate that medial pre-frontal cortex receives DA inputs during said aversive experiences. We employed a large scale protein engineering strategy to optimize and tune the sensitivity of dLigth1.4, a dopamine sensor based on inert DRD4 receptors. The improved variant, dLight2.1, can robustly detect sparse, physiological relevant DA release across different brain regions with various imaging modality including confocal microscopy, two-photon microscopy and fiber photometry in awake behaving animals. Using fiber-photometry, we observed distinct dopamine dynamics with improved sensitivity that are brain region specific in response to fear-learning.

Disclosures: **A. Pal:** None. **J. Roshgadol:** None. **J. Sun:** None. **J.A. Chouinard:** None. **J.R. Wickens:** None. **L. Tian:** None.

Poster

109. Aminergic Transmission: Function, Regulation, and Techniques

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 109.10

Topic: B.01. Transmitters, Transporters, and Other Signaling Molecules

Support: NIH Grant DA035714
NIH Grant DA041932
SC INBRE SIRP Grant

Title: Mutational effects of the human norepinephrine transporter on basal and Tat-induced inhibition of dopamine transport

Authors: *D. PORTER[1], S. E. DAVIS[1], M. J. STRAUSS[1], Y. YUAN[2], S. LIN[1], P. MCQUILLEN[1], H. DAVENPORT[1], C.-G. ZHAN[2], J. ZHU[1];
[1]Drug Discovery and Biomed. Sci., Univ. of South Carolina, Columbia, SC; [2]Univ. of Kentucky, Lexington, KY

Abstract: The HIV regulatory protein, transactivator of transcription (Tat)-induced dysregulation of dopaminergic transmission has been implicated as a central factor in the development of HIV-1 associated neurocognitive disorders (HAND). Our recent report revealed that dopamine transport through the norepinephrine transporter (NET) is reduced in the prefrontal cortex of inducible Tat transgenic mice. The prefrontal cortex is an important brain region for higher cognitive function, where the NET plays a critical role in the reuptake of dopamine and norepinephrine. Our recently developed three-dimensional computational model of Tat-human NET (hNET) showed that Tat-hNET binding is highly dynamic and that Tat preferentially binds to hNET in its outward-open state. HIV-1 Tat forms hydrogen bond interactions with side chain hNET residues Y467, N184, E223, N198, T186, Y205, and E212. Based on the Tat-hNET model, this study examined the mutational effects of these hNET residues on basal and Tat-induced inhibition of dopamine uptake through hNET. Compared to wild-type hNET, neither of Y467H or Y467F altered B_{max} and K_d values of [^{3}H]WIN35,428 binding, whereas Y467H but not Y467F decreased the B_{max} of [^{3}H]nisoxetine binding without changes in K_d. Y467H also increased the affinity of nisoxetine for inhibiting [^{3}H]dopamine uptake relative to wild-type hNET. Recombinant Tat_{1-86} (140 nM) induced a significant reduction of [^{3}H]dopamine uptake in wild-type hNET, which was attenuated in both Y467H and Y467F. Compared to wild-type hNET, neither Y467H or Y467F altered [^{3}H]dopamine efflux in CHO cells expressing WT hNET and mutants, whereas Y467F but not Y467H decreased [^{3}H]MPP^+ efflux. Additionally, compared to WT hNET, the specific [^{3}H]dopamine uptake was reduced in T186A, N198A, E212A and E223A, and unchanged in N184A and Y205F, in which only N198A attenuated the Tat-induced decrease in dopamine uptake observed in WT hNET. These results demonstrate Y467 and N198 as functional recognition residues in hNET for Tat-induced of dopamine transport and provide a novel insight into the molecular basis for developing selective compounds for Tat-NET interaction in the context of HAND.

Disclosures: **D. Porter:** None. **S.E. Davis:** None. **M.J. Strauss:** None. **Y. Yuan:** None. **S. Lin:** None. **P. McQuillen:** None. **H. Davenport:** None. **C. Zhan:** None. **J. Zhu:** None.

Poster

109. Aminergic Transmission: Function, Regulation, and Techniques

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 109.11

Topic: B.01. Transmitters, Transporters, and Other Signaling Molecules

Support: SPARC Grant to SD from University of South Carolina
NIH Grant DA035714 to JZ
NIH Grant DA041932 to JZ

Title: Hiv-1 tat protein alters synaptic dopamine release in a region-specific manner in inducible tat transgenic mice using fast scan cyclic voltammetry

Authors: *S. DAVIS[1], M. J. FERRIS[2], J. ZHU[3];
[1]Univ. of South Carolina, Columbia, SC; [2]Physiol. and Pharmacol., Wake Forest Sch. of Med., Winston Salem, NC; [3]Drug Discovery and Biomed. Sci., Col. of Pharmacy, Univ. of South Carolina, Columbia, SC

Abstract: Dysregulation of dopamine homeostasis by the HIV-1 protein transactivator of transcription (Tat) has been implicated as a mediating factor of HIV-1 associated neurocognitive disorders (HAND). To determine whether Tat expression alters the real-time changes in extracellular dopamine levels in inducible Tat transgenic (iTat-tg) mice, we used fast scan cyclic voltammetry (FSCV) to measure phasic-stimulated dopamine release in brain slices. Following 7- or 14-day doxycycline (Dox)-induced Tat expression in iTat-tg and G-tg (Tat null) mice, we found that baseline phasic dopamine release was increased in the caudate putamen (CPu) by ~100% compared to saline-treated iTat-tg mice. However, 14- or 21-day Dox-induced Tat expression induced a 45% reduction in the baseline phasic DA release in the nucleus accumbens core (NAc) in iTat-tg mice. Previous reports from our laboratory have demonstrated that Tat protein dysregulates dopamine homeostasis via inhibition of both dopamine transporter (DAT) and vesicular monoamine transporter2 (VMAT2). To determine the mechanisms of the Tat-induced alteration of extracellular dopamine in iTat-tg mice, we further determined Tat-induced alteration of extracellular dopamine levels in response to nomifensine, a DAT inhibitor, and Ro 4-1284, a VMAT2 inhibitor that can inhibit vesicular packaging dopamine into synaptic vesicles. We found that both saline- and Dox-treated iTat-tg mice displayed enhanced phasic dopamine release in the CPu in response to nomifensine in a concentration-dependent manner (1 nM-10 μM), in which the nomifensine-increased dopamine level was about 50-70% greater in Dox-treated mice than that observed in control mice. Repeated phasic stimulation of dopamine release in the CPu and NAc was examined by bath-application of Ro 4-1284 (500 nM) until no dopamine was detected. We found no difference in Ro 4-1284-induced depletion of dopamine between iTat-tg and G-tg mice following 14-day Dox-induced Tat expression. The current

findings suggest that inducible Tat expression alters synaptic dopamine release in iTat-tg mice, which may potentially increase vulnerability to substance abuse in HIV-infected individuals. Thus, the findings from the current study highlight a potential mechanism for addressing Tat-induced dysregulation of dopaminergic transmission and its associated cognitive deficits observed in HIV-1 infected patients.

Disclosures: **S. Davis:** None. **M.J. Ferris:** None. **J. Zhu:** None.

Poster

109. Aminergic Transmission: Function, Regulation, and Techniques

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 109.12

Topic: B.01. Transmitters, Transporters, and Other Signaling Molecules

Support: NIH Grant DA035714
NIH Grant DA041932
NIH Grant DA041932

Title: HIV-1 Tat protein-induced inhibition of [^{3}H]dopamine uptake in the prefrontal cortex of inducible Tat transgenic mice is attenuated in dopamine transporter Y88F knock-in mice harbored with the Tat transgenic mice

Authors: *J. ZHU[1], M. M. STRAUSS[2], A. C. JIMÉNEZ TORRES[3], S. E. DAVIS[4], K. PORTER[3], J. P. MCLAUGHLIN[5], C.-G. ZHAN[6];
[1]Col. of Pharmacy, Univ. of South Carolina, Col. of Pharmacy, Univ. of South Carolina, Columbia, SC; [2]Children's Natl. Med. Ctr., Children's Natl. Med. Ctr., Washington, DC; [3]Drug Discovery and Biomed. Sci., Univ. of South carolina, Columbia, SC; [4]Univ. of South Carolina, Univ. of South Carolina, Columbia, SC; [5]Univ. of Florida, Univ. of Florida, Gainesville, FL; [6]Pharmaceut. Sci., Univ. of Kentucky, Lexington, KY

Abstract: Dysregulation of dopamine (DA) neurotransmission has been linked to the development of HIV-associated neurocognitive disorders (HAND), which are highly prevalent in the era of combination antiretroviral therapies. We have reported that the human DA transporter (hDAT) tyrosine88 residue can form a hydrogen bond with the HIV-1 Tat residue lysine19, which plays a key role in the Tat-DAT interaction. Mutation of the tyrosine88 residue (Y88F) retained basal DAT-mediated DA uptake and attenuated *in vitro* Tat-induced inhibition of DA uptake in WT hDAT, whereas mutation of Tat lysine19 to alanine (K19A) also attenuated Tat-inhibited DA uptake. Furthermore, we have demonstrated that the HIV-1 Tat protein decreases DAT-mediated DA uptake in the prefrontal cortex of inducible Tat transgenic (iTat-tg) mice. This study validated whether the *in vitro* attenuation of Tat-induced inhibition of DAT activity by the DAT Y88F mutant can be replicated *in vivo* in iTat-tg mice. First, we generated a novel DAT Y88F$^{+/+}$ knock-in mouse model, which showed no difference in the V_{max}/K_m values of [^{3}H]DA uptake and B_{max}/K_d values of [^{3}H]WIN35,428 binding, suggesting that the mutation of

DAT at Y88 does not alter basal DAT function and DAT binding sites. In addition, no significant difference in 60-min assessment of total locomotor activity was observed between $Y88F^{+/+}$ and C57BL/6J mice, suggesting that Y88F knock-in mice retain normal DAT function/expression and its associated motivation. We then generated a novel hybrid Y88F knock-in/iTat-tg harbored with iTat-tg mice. Following 7- or 14-day administration of doxycycline (Dox)-induced Tat expression, the V_{max} of [^{3}H]DA uptake in the prefrontal cortex was decreased in iTat-tg mice compared to saline-treated iTat-tg mice, which was significantly attenuated in the Y88F/iTat-tg mice. In addition, Dox-treated iTat-tg mice displayed a deficit in novel object recognition, which was alleviated in $Y88F^{+/+}$/iTat-tg mice following Dox administration. This study has a significant impact of DAT Y88F mutant in Tat-induced inhibition of DAT function in the prefrontal cortex, which may be attributed to the cognitive deficit observed in iTat-tg mice. Determining the genetic basis underlying the interaction between Tat and DAT may reveal novel therapeutic possibilities for preventing the development of HAND. Thus, these findings demonstrate that developing allosteric modulatory molecules that through the Tat-DAT interaction attenuate Tat binding to DAT are of great scientific and clinical potential.

Disclosures: J. Zhu: None. **M.M. Strauss:** None. **A.C. Jiménez Torres:** None. **S.E. Davis:** None. **K. Porter:** None. **J.P. McLaughlin:** None. **C. Zhan:** None.

Poster

109. Aminergic Transmission: Function, Regulation, and Techniques

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 109.13

Title: WITHDRAWN

Poster

109. Aminergic Transmission: Function, Regulation, and Techniques

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 109.14

Topic: B.01. Transmitters, Transporters, and Other Signaling Molecules

Support: NIH Grant DA035714
NIH Grant DA041932

Title: Identification of pyrimidine structure-based compounds as allosteric ligands of the dopamine transporter as therapeutic agents for NeuroHIV

Authors: *A. C. JIMENEZ-TORRES[1], A. HASTIE[1], S. E. DAVIS[1], K. D. PORTER[1], S. T. NESTOR[2], O. MOUKHA-CHAFIQ[2], T. H. NGUYEN[2], S. ANANTHAN[2], C. E. AUGELLI-

SZAFRAN[2], J. ZHU[1];
[1]Dept. of Drug Discovery and Biomed. Sci., Univ. of South Carolina, Columbia, SC; [2]Dept. of Chemistry, Scientific Platforms Div., Southern Res. Inst., Birmingham, AL

Abstract: Despite the widespread use of combination antiretroviral therapies (cART) to control peripheral HIV infection and improve the life of HIV patients, persistent expression of HIV proteins within the CNS may play a central role in the development of HIV-associated neurocognitive disorders (HAND). HIV-1 Transactivator of transcription (Tat) protein-induced dysregulation of dopamine (DA) transmission has been implicated as a major pathogenic factor for HAND, however, the current therapeutics are insufficient for treating HAND. We have demonstrated that SRI-32743, a novel allosteric modulator, attenuates Tat-induced inhibition of DA transporter (DAT)-mediated DA uptake in cells expressing wild type human DAT (WT hDAT) and in Tat transgenic mice. In addition, SRI-32743 ameliorates Tat-induced recognition deficits and potentiation of cocaine reward in iTat transgenic mice (iTat-tg). Through structure activity relationship studies of SRI-32743, 163 pyrimidine analogs were synthesized and evaluated for the ability to modulate DAT function allosterically and interact with Tat binding sites on DAT. Results show that these compounds partially inhibited [^{3}H]DA uptake (IC_{50} values, 0.96-10.64 µM) and [^{3}H]WIN35,428 binding (IC_{50} values, 1.29-13.18 µM) in CHO cells expressing WT hDAT. Compared to the classic DAT inhibitors, GBR12909 and cocaine, these compounds were characterized as atypical ligands by their submaximal inhibition profile (E_{max}, in general, <75%) of DA reuptake. In addition, we found that IC_{50} values of SRI-46564, SRI-46562, SRI-45949 and SRI-32743 for inhibiting DA uptake in WT hDAT were 7- to 262-fold greater than their affinities of DA uptake in mouse striatal synaptosomes, respectively. SRI-46286, with a quinazoline core and SRI-46564, with a pyrrolopyrimidine core, were selected for further characterization of their allosteric modulatory profiles. Compared to their respective vehicle controls, SRI-46286 inhibited DA uptake by 14% at 50 nM and 34% at 1500 nM with a significant reduction of K_m, whereas SRI-46564 inhibited DA uptake by 47% at 50 nM and 72% at 1500 nM. The addition of SRI-46286 or SRI-46564 following cocaine slowed the cocaine-induced dissociation rate of [^{3}H]WIN35,428 binding in WT hDAT relative to cocaine alone. These findings suggest that the pyrimidine series of compounds have potential for therapeutic application in preventing Tat-induced dysregulation of the DA system observed in HAND patients through allosteric modulation of DAT.

Disclosures: A.C. Jimenez-Torres: None. **A. Hastie:** None. **S.E. Davis:** None. **K.D. Porter:** None. **S.T. Nestor:** None. **O. Moukha-Chafiq:** None. **T.H. Nguyen:** None. **S. Ananthan:** None. **C.E. Augelli-Szafran:** None. **J. Zhu:** None.

Poster

110. Dopamine Neuron Regulation

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 110.01

Topic: C.03. Parkinson’s Disease

Support: NIH R01 NS115809

Title: Characterizing the combined neuroprotective effects of estrogen and cytisine in a 6-OHDA mouse model of Parkinson's disease

Authors: *S. M. ZARATE[1], I. SHIRVAIKAR[2], S. RAHMAN[2], G. PANDEY[3], R. SRINIVASAN[4];
[1]Texas A&M Col. of Med., College Station, TX; [2]Texas A&M Univ. Col. of Med., College Station, TX; [3]Texas A&M Univ. Col. of Med., Bryan, TX; [4]Dept. of Neurosci. and Exptl. Therapeut., Texas A&M Univ. Col. of Med., College Station, TX

Abstract: Parkinson's disease (PD) is a movement disorder characterized the by the progressive loss of dopaminergic neurons in the substantia nigra. The two greatest risk factors for PD are advanced age and male sex such that as age increases the prevalence of PD increases at a 2-fold higher rate in men than women. Current treatments for men and women are symptomatic, cause severe side effects, and lose efficacy over time. Interestingly, chronic tobacco use has been shown to reduce the risk of PD by 50% and our studies have shown that low doses of nicotine (100 nM) attenuate apoptotic endoplasmic reticulum (ER) stress in DA neurons. Thus, we rationalized that nicotine and nicotinic agonists could reduce ER stress. Using a 6-OHDA model of PD we found that alternate day i.p. injections of 0.2 mg/kg cytisine, a partial nicotinic acetylcholine receptor agonist, was sufficient to reduce parkinsonian motor deficits and decrease 6-OHDA induced neurodegeneration of DA neurons only in female mice. In contrast, cytisine treated male mice showed no change in motor deficits or DA neuron loss but rather showed a pathological increase in nuclear expression of the apoptotic ER stress protein CHOP. To test whether cytisine and estrogen could work in combination to exert neuroprotection in female mice, we exposed primary DA cultures to 10 nM 17-β-estradiol, 200 nM cytisine, or 17-β-estradiol and 200 nM cytisine. We found that 17-β-estradiol alone reduced expression of CHOP and that 200 nM cytisine reduced two additional ER stress proteins, ATF6 and XBP1. To further characterize the effects of cytisine and 17-β-estradiol in a 6-OHDA mouse model of PD we used four groups of 2-3-month-old female mice which included: 1) sham operated female mice treated with cytisine 2) ovariectomized (OVX) female mice treated cytisine 3) sham operated female mice treated with saline, and 4) OVX female mice treated with saline. PD related behaviors were assessed using apomorphine rotations and forced walking via the Digigait system. Consistent with our previous work, intact cytisine treated females had significantly less apomorphine induced rotations than intact saline treated females; however, there was no difference in the average number of rotations between intact cytisine females and OVX cytisine female mice. Using the Digigait system we found that intact saline treated female mice showed abnormalities in paw angle and gait symmetry but not intact cytisine or OVX cytisine females. These data suggest sex specific mechanisms in cytisine pharmacology and a potential role for local brain derived 17-β-estradiol in the neuroprotective effect of cytisine in female mice.

Disclosures: S.M. Zarate: None. **I. Shirvaikar:** None. **S. Rahman:** None. **G. Pandey:** None. **R. Srinivasan:** None.

Poster

110. Dopamine Neuron Regulation

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 110.02

Topic: C.03. Parkinson's Disease

Support: NIH R91 NS115809

Title: Sex Differences in Novel Transgenic Mice with Constitutively Upregulated Acetylcholine Receptors, Implications for Parkinson's Disease

Authors: *G. PANDEY[1], S. ZARATE[2];
[1]Texas A&M Univ. Neurosci. Inst. For Neurosci., Bryan, TX; [2]Neurosci. and Exptl. Therapeut., Texas A&M Col. of Med., Bryan, TX

Abstract: Sex Differences in Novel Transgenic Mice with Constitutively Upregulated Acetylcholine Receptors: Implications for Parkinson's Disease
Gauri Pandey[1,2*], Sara M. Zarate[2], and Rahul Srinivasan[21]Texas A&M Institute for Neuroscience, Texas A&M University, College Station, TX, USA[2]Department of Neuroscience and Experimental Therapeutics, Texas A&M College of Medicine, Bryan, TX, USA
Parkinson's disease (PD) incidence rates predict a worldwide pandemic that will affect over 12 million people by 2040, underscoring an urgent need for neuroprotective drugs. Unfortunately, no neuroprotective drugs are currently available, and most proposed neuroprotective drugs failed clinical trials because PD is produced by a range of insults not replicated in any one animal model. For this reason, we focus on hyperactivated endoplasmic reticulum (ER) stress, a convergent apoptotic mechanism for multiple PD-related toxicities. Nicotine reduces PD risk, however, nicotine concentrations in tobacco users cannot activate neuronal nicotinic acetylcholine receptors (nAChRs), making this an unlikely mechanism for neuroprotection of dopaminergic (DA) neurons. We have previously shown that nanomolar concentrations of nicotinic ligand, cytisine, rapidly chaperone β2-subunit-containing (β2*) nAChRs out of the ER. This directly reduces the ER stress response, which is critical for neuroprotection. To test this hypothesis, we created a novel transgenic mouse line named β2-mutant, with enhanced ER export of β2* nAChRs. Surprisingly, β2-mutant mice demonstrate significant increases in Sec24D ER exit sites (ERES) within substantia nigra pars compacta (SNc) DA neurons of only female, but not male mice. We also induced parkinsonism in mice by unilateral injection of 6-OHDA in the dorsolateral striatum. Interestingly the β2-mutantions reduced apomorphine rotations only in female mice. Our data suggests the β2-mutations exert neuroprotection in female mice only.

Disclosures: G. Pandey: None. **S. Zarate:** None.

Poster

110. Dopamine Neuron Regulation

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 110.03

Topic: C.03. Parkinson's Disease

Support: NIH Grant R21 AG063007

Title: Alphalisa-based hts for the identification of small-molecules that reduce intracellular alpha-synuclein levels

Authors: *M. YOUNG, C. ZHU, L. FAROOQI, J. CAMPAGNA, V. JOHN;
UCLA, Los Angeles, CA

Abstract: Alpha-synuclein (αsyn) is the primary protein implicated in Parkinson's Disease, and is involved in the progression of other neurodegenerative diseases including Dementia with Lewy Bodies, Multiple Systems Atrophy, and Alzheimer's Disease. Pathology in these disease states is associated with higher levels of αsyn expression, and the accumulation of αsyn into toxic oligomeric species. Reducing the expression of αsyn has been shown to reverse pathology and memory deficits in mice. Thus, identifying small-molecules that reduce cellular αsyn levels is a promising therapeutic approach for treating these diseases. In the current work, we have utilized AlphaLISA technology to establish a high-throughput screening (HTS) platform for the detection of compounds which lower intracellular αsyn levels. We have also setup a BiFC assay to evaluate hits for their effects on αsyn oligomerization. Riluzole, a small-molecule previously shown to lower αsyn mRNA levels, is used as a positive control to validate the HTS assay, and for the evaluation of its effects on αsyn oligomerization in the BiFC assay. We will present data on this molecule from our in vitro and in vivo testing along with the screening platform we are using to identify hits from the UCLA library of 300,000 small-molecules. Hits will be validated in downstream assays and evaluated for potency, and the best drug-like properties. The top hits with good brain permeability will then be tested in human iPSC-derived neurons and *ex-vivo* organotypic slice cultures for final characterization/validation.

Disclosures: M. Young: None. **C. Zhu:** None. **L. Farooqi:** None. **J. Campagna:** None. **V. John:** None.

Poster

110. Dopamine Neuron Regulation

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 110.04

Topic: C.03. Parkinson's Disease

Title: Modulation of dopamine neuron activity by a novel enzyme catalyzing synuclein nitration

Authors: E. VERTUDES[1], S. BOUDOUKHA[1], I. GRISWOLD-PRENNER[1], R. ESANOV[2], ***V. DANG**[1];
[1]Nitrase Therapeut., BRISBANE, CA; [2]GSK, San Francisco, CA

Abstract: Post translational modifications, including nitration, of alpha-synuclein have been implicated in dopamine neuron pathologies in Parkinson's disease (PD). Nitrated alpha-synuclein has been detected in PD patients and injection of nitrated synuclein into rodent causes dopamine neurons pathology. We have identified a novel enzyme, Synuclein Nitrase, that catalyzes synuclein nitration. To understand the role of Synuclein Nitrase in neurons, we have examined the effect of Synuclein Nitrase knockout on the electrical activity of differentiated dopaminergic neurons (iDAs) derived from human iPSC lines from both non-PD and fPD patients. Multielectrode array analysis of cultured iDAs derived from fPD and non-PD individuals revealed distinct activity patterns for the two cell types: fPD iDAs have a higher weighted mean firing rate and a higher network burst frequency than non-PD iDAs. In addition, analysis of the network bursts synchrony index shows that fPD iDAs have reduced synchrony compared to non-PD iDAs. Knocking out Synuclein Nitrase in familial iDAs reduced the weighted mean firing rate and network burst frequency to levels comparable to that of non-PD iDAs. Interestingly, Synuclein Nitrase KO increased the network synchrony index for both fPD and non-PD iDAs. These results strongly suggest that Synuclein Nitrase influences the electrical activity pattern of iDAs. Studies are ongoing to evaluate Synuclein Nitrase modulation of the function and viability of fPD and non-PD iDAs over time under basal conditions and in response to stressful stimuli. These studies demonstrate important electrophysiologicial deficits in fPD iDA neurons and show that modification of Synuclein Nitrase activity reduces these defects. Our results provide a functional rationale for the development of small molecule inhibitors of Synuclein Nitrases as potential novel disease-modifying therapeutics for PD patients.

Disclosures: E. Vertudes: A. Employment/Salary (full or part-time):; Nitrase Therapeutics. **S. Boudoukha:** A. Employment/Salary (full or part-time):; Nitrase Therapeutics. **I. Griswold-Prenner:** A. Employment/Salary (full or part-time):; Nitrase Therapeutics. **R. Esanov:** Other; Former Employee with Nitrase Therapeutics. **V. Dang:** A. Employment/Salary (full or part-time):; Nitrase Therapeutics.

Poster

110. Dopamine Neuron Regulation

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 110.05

Topic: C.03. Parkinson's Disease

Title: Identification of novel TMEM175 modulators using a high-throughput automated electrophysiology platform

Authors: *D. DALRYMPLE, L. HUTCHISON, C. BROWN, L. GERRARD, I. MCPHEE, D. PAU;
SB Drug Discovery, SB Drug Discovery, Glasgow, United Kingdom

Abstract: TMEM175 is a novel, constitutively active lysosomal potassium channel involved in regulating lysosomal pH and autophagy. Mutations in this gene have been shown to impair

normal lysosomal and mitochondrial function, and as a result, increase aggregation of insoluble proteins such as phosphorylated α-synuclein, a hallmark of Parkinson's Disease. Such protein aggregation can lead to cell toxicity and death, resulting in the degenerative physical and cognitive symptoms typical of PD. Consequently, there is significant potential for TMEM175 to play a key role in the treatment of Parkinson's disease. By increasing the activity of this potassium channel it may be possible to enhance the efficiency of the cellular recycling process, leading to increased breakdown of toxic aggregates such as α-synuclein. However, the lack of specific pharmacological tools has hampered further investigation into the exact role of TMEM175 in normal lysosomal function and its role in such pathological processes.
Advancements in high throughput screening technologies have allowed rapid assessment of large numbers of compounds against ion channel drug targets using patch-clamp electrophysiology. We have successfully developed recombinant cell lines expressing wild-type TMEM175 as well as gain of function (Q65P) and loss of function (M393T) mutants using stably transfected HEK cells. Characterization of these cell lines was performed with ease using high-throughput automated electrophysiology and reproducible concentration response curves were achieved with the potassium channel inhibitor 4-aminopyridine (4-AP).
A rapid and robust automated, high-throughput electrophysiology screening assay was subsequently developed to enable identification of both activators and inhibitors of TMEM175. This enabled execution of a high-throughput screen against wild-type TMEM175 yielding an average success rate of 82% positive wells per chip and an average z-prime of 0.77 .The screening campaign successfully identified a number of active compounds with the ability to modulate TMEM175 in a concentration-dependent manner with XC_{50} values in the low micromolar range, confirming the successful development of a TMEM175 electrophysiology assay capable of identifying novel pharmacological tools with which to further investigate the role of this exciting target in normal physiology and in disease.

Disclosures: D. Dalrymple: None. **L. Hutchison:** None. **C. Brown:** None. **L. Gerrard:** None. **I. McPhee:** None. **D. Pau:** None.

Poster

110. Dopamine Neuron Regulation

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 110.06

Topic: C.03. Parkinson's Disease

Title: Generation of co-culture system between highly pure midbrain dopaminergic neurons and astrocytes from human iPSCs

Authors: A. MANOLE, A. RHEE, C. GAO, ***N. LIN**;
iXCells Biotechnologies, San Diego, CA

Abstract: Dopamine (DA) neurons in the midbrain are essential for directing fundamental brain functions such as voluntary movement, reward processing, and working memory. The substantia

nigra (SN) and ventral tegmental area (VTA) have the most DA neurons in the midbrain. Neurodegenerative disorders such as Parkinson's disease (PD) are characterized by the degeneration of DA neurons in the pars compacta region of the SN. Loss of DA neurons is not the only neuropathological alteration in PD; an increase in astroglial cells in post-mortem brain tissue from PD patients has also been reported. Consequently, a co-culturing system between DA neurons and astrocytes derived from normal or patient-induced pluripotent stem cells (iPSCs) can enable the generation of cell models with features relevant to human physiology, making it a valuable tool for biochemical analysis, disease modeling, and a wide range of clinical applications. Using proprietary protocols, highly pure, fully differentiated and functional human iPSC-derived DA neurons were derived. These cells displayed typical neuronal morphology and expressed characteristic transcription factors and markers of midbrain DA neurons such as EN1, FoxA2, and tyrosine hydroxylase as shown by immunofluorescence analysis and flow cytometry measurements. Moreover, using another in-house protocol, fully mature astrocytes were derived from the same donor iPSCs. These displayed mature astrocytic markers including, CD44 antigen, S100 calcium-binding protein (S100β), and glial fibrillary acidic protein (GFAP). Astrocytes are immunocompetent cells that participate in neuroinflammation by secreting cytokines and chemokines, which may have protective or detrimental consequences for neuronal survival. Using human cytokine blot arrays, we observed key downstream cytokine targets such as IL-6 and IL-8 being released post-inflammatory stimulation, demonstrating functional consequences on the DA neurons. Furthermore, co-culturing these two cell types lead to iPSC-derived DA neurons exhibiting mature synapse formation. Future studies will develop more robust, new multicellular culture models to better understand the influence of cellular crosstalk on neuroinflammation and would harness this knowledge for therapeutic development.

Disclosures: **A. Manole:** None. **A. Rhee:** None. **C. Gao:** None. **N. Lin:** None.

Poster

110. Dopamine Neuron Regulation

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 110.07

Topic: C.03. Parkinson’s Disease

Support: IN213719 PAPIIT, UNAM
272815 CONACYT

Title: Semaphorin 3C guides human dopaminergic axons in rat organotypic slices normalizing parkinsonian.related alterations in striatal networks

Authors: B. URRIETA-CHAVEZ[1], O. A. CARBALLO-MOLINA[1], V. CALDERÓN-ORTIZ[1], V. A. CÁCERES-CHÁVEZ[1], J. LÓPEZ-NIÑO[1], J. BARGAS[2], ***I. VELASCO**[3];
[1]Inst. de Fisiología Celular – Neurociencias, Univ. Nacional Autónoma de México., México, Mexico; [2]Neurociencia Cognitiva, Inst. de Fisiologia Celular, UNAM, Mexico City, Mexico; [3]IFC, UNAM, Mexico, Mexico

Abstract: Parkinson disease (PD) is caused by the degeneration of the axons connecting the substantia nigra (SN) and the striatum, with the consequent decrease of dopamine release in the latter, causing the appearance of motor symptoms in patients. Being the second most common neurodegenerative disease of the elderly, PD has been one of the targets of regenerative medicine, in which the use of human embryonic stem cells (hESCs) differentiated to DaN has been proposed as a potential treatment. However, the path that the axons have to travel after grafting DaN in the SN to reach the striatum is long, and the adult brain is an adverse environment for axonal growth. Recently, the use of biocompatible materials has been of interest for the gradual release of soluble factors such as recombinant proteins. The ability of PuraMatrix hydrogel for the release of Sema3C and the stimulation of growth and targeting of human DaN has been reported by our group. Here, a PD model of organotypic culture was used to combine the release of Sema3C by this hydrogel, with the deposition of GFP-expressing DaN on the SN, to assess attraction of dopamine axons towards the striatum. We found a preferential growth towards Sema3C release. Additionally, electrophysiological recordings of GFP-expressing cells in the organotypic cultures allowed to establish that human neurons need to reach 50 days in vitro to show signs of electical maturity. By using calcium imaging to study the striatal circuits, we observed that the alterations caused by dopamine denervation in the rat brain slice were modified by grafted human DaN. These results support the notion that this model is useful to observe axonal development, as well as electrophysiological parameters indicative of maturation and modification of striatal circuits after transplantation of human DaN.

Disclosures: B. Urrieta-Chavez: None. **O.A. Carballo-Molina:** None. **V. Calderón-Ortiz:** None. **V.A. Cáceres-Chávez:** None. **J. López-Niño:** None. **J. Bargas:** None. **I. Velasco:** None.

Poster

110. Dopamine Neuron Regulation

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 110.08

Topic: C.03. Parkinson's Disease

Support: Swedish Research Council
Knut and Alice Wallenberg Foundation

Title: Direct reprogramming of human glia into neurons in a three-dimensional culture system

Authors: *J. GIACOMONI, A. BRUZELIUS, M. HABEKOST, D. RYLANDER OTTOSSON, A. FIORENZANO, P. STORM, M. PARMAR;
Lund Univ., Lund, Sweden

Abstract: Parkinson's disease (PD), one of the most common neurodegenerative disorders, is primarily characterized by progressive loss of dopamine (DA) neurons in the ventral midbrain. The relatively focal degeneration in PD makes it a good candidate for cell replacement therapies, and efforts are on their way to use stem cell derived-DA neurons in clinical trials. An emerging

alternative approach to cell transplantation is *in vivo* reprogramming, where resident glia is converted into neurons directly inside the brain. Proof-of-concept that in *vivo* conversion can be a viable option has been provided in rodent studies but relevant pre-clinical models where human cells are converted are lacking. We have previously established a renewable and reproducible stem cell-based system of human glial progenitor cells for direct neural conversion and identified optimal combinations of fate determinants for the generation of functional DA neurons *in vitro*. We have now developed a 3D culture model for direct conversion with the idea that better recapitulation of the complexity of a 3D space more closely mimics conversion *in vivo*. We show that cells converted in the 3D system develop into functionally mature DA neurons at a higher efficiency and faster pace than neurons converted in 2D. We use single-nucleus transcriptomics to map glia heterogeneity, explore neuronal lineage diversity after direct cell conversion and to further understand the reprogramming competence of different subtypes of glial progenitors. Our data show that reprogramming in 3D increases conversion efficiency, accelerates the reprogramming process and generates mature and functional DA neurons within 2 weeks, making it a valuable model for direct conversion of human glia.

Disclosures: J. Giacomoni: None. **A. Bruzelius:** None. **M. Habekost:** None. **D. Rylander Ottosson:** None. **A. Fiorenzano:** None. **P. Storm:** None. **M. Parmar:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Parmar Cells AB. F. Consulting Fees (e.g., advisory boards); Paid Consultancy, steering group member and commissioned research for Novo Nordisk AS Cell Therapy Research and Development unit, SAB/ Paid Consultancy of Arbor Bio. Other; U.S. patent 15/093,927; EP17181588; PCT/EP2018/062261, Academic research collaborations with Novo Nordisk AS.

Poster

110. Dopamine Neuron Regulation

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 110.09

Topic: C.03. Parkinson’s Disease

Title: Functional Characterization of GBA Mutation in iPSC-derived Midbrain Dopaminergic Neuron

Authors: *D. TASTAD[1], A. ZHANG[1], J. DRUCKS[1], L. ZEBROWSKI[2], A. BRATT-LEAL[1], X. ZHANG[3];
[1]Aspen Neurosci., San Diego, CA; [2]Aspen Neurosci., Aspen Neuroscience, United Kingdom; [3]Aspen Neurosci., Aspen Neuroscience, CA

Abstract: Parkinson’s disease (PD), a progressive neurodegenerative disorder that primarily affects dopaminergic neurons of the substantia nigra, is currently the second most common neurodegenerative disorder, affecting more than 10 million people worldwide. While most PD cases are currently considered to be idiopathic, recent findings have linked multiple alterations in

genes to an increased likelihood for developing PD. Mutations in the glucosylceramidase beta 1 (GBA1) gene have recently been shown to confer a 20- to 30-fold increased risk for developing PD and 7-10% of all PD patients have a mutation in GBA1 (GBA1-PD). Currently, there are no rodent models that accurately recapitulate the pathophysiology of GBA1-PD, making it difficult to properly model this debilitating disease. In this study, we sought to model GBA1-PD by using iPSC-derived dopaminergic neurons (DANs) from patient lines with GBA1 mutations. Here, we report successfully differentiating E326K (n=2) and N370S (n=2) GBA1 variant-carrying induced pluripotent cells (iPSCs) into DANs and provide a thorough phenotypic characterization of lysosomal function, mitochondrial function, alpha-synuclein uptake, and alpha-synuclein degradation. We found that in mature DANs, lysosomal function was impaired but mitochondrial function was not affected. Additionally, we found an increase in the uptake of alpha-synuclein preformed fibrils and a decrease in their lysosomal degradation. Next, we examined whether gene correction can restore GCase function. To test this, we performed an *in vitro* GCase activity assay, found that GCase activity levels were restored in the gene corrected GBA1-PD donor lines (n=2) when compared to their isogenic pairs (n=2). After gene correction, we found that both lysosomal function and the ability to degrade alpha-synuclein fibrils were also restored. Our ability to use iPSC-derived DANs provides a novel way to model GBA1-PD and further our understanding of the molecular mechanisms underlying this disease.

Disclosures: **D. Tastad:** A. Employment/Salary (full or part-time):; Aspen Neuroscience. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Aspen Neuroscience. **A. Zhang:** A. Employment/Salary (full or part-time):; Aspen Neuroscience. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Aspen Neuroscience. **J. Drucks:** A. Employment/Salary (full or part-time):; Apsen Neuroscience. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Aspen Neuroscience. **L. Zebrowski:** A. Employment/Salary (full or part-time):; Aspen Neuroscience. **A. Bratt-leal:** A. Employment/Salary (full or part-time):; Aspen Neuroscience. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Aspen Neuroscience. **X. Zhang:** A. Employment/Salary (full or part-time):; Aspen Neuroscience. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Aspen Neuroscience.

Poster

110. Dopamine Neuron Regulation

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 110.10

Topic: C.03. Parkinson’s Disease

Title: Novel beta-Glucocerebrosidase Chaperone Compounds Identified from Cell-based Screening Reduce Pathologically Accumulated Glucosylsphingosine in iPS-derived Dopaminergic Neurons

Authors: *Y. NAITO, T. KOJIMA, M. HOMMA, M. TANAKA, H. MATSUI;
Neurosci. Drug Discovery Unit, Takeda Pharmaceut. Co. Limited., Fujisawa Kanagawa, Japan

Abstract: Beta-glucocerebrosidase (GBA1) gene encodes the lysosomal beta-glucocerebrosidase (GCase) that metabolizes the lipids, glucosylceramide (GlcCer) and glucosylsphingosine (GlcSph). Loss-of-function mutations in GBA1 such as L444P cause Gaucher's disease (GD) in biallelic carriers and significantly increase a risk for Parkinson's disease (PD) and dementia with Lewy bodies (DLBs) in monoallelic carriers. Thus, boosting GCase activity in the central nervous system has been considered as an attractive therapeutic approach for neurological symptoms of GD and PD/DLBs. Given that recombinant GCase protein cannot cross the blood-brain barrier due to its high molecular weight, it is invaluable to develop a brain-penetrant small molecule GCase activator or pharmacological chaperone as a viable therapeutic strategy. Despite considerable efforts to screen potent GCase activators/chaperones, cell-free assays using recombinant GCase protein have only yielded compounds with marginal efficacy and micromolar EC50 that would not have sufficient clinical efficacy and safety margin. Therefore, we utilized fluorescence-labeled GCase suicide inhibitor, MDW933, to directly monitor lysosomal GCase activity and performed cell-based screening in fibroblast from a GD patient with homozygotic L444P mutations.
Here, we identified novel compounds that increase fluorescence signal from labeled GCase with L444P mutation in dose dependent manner. Secondary assays using an artificial cell-permeable lysosomal GCase substrate also support that identified compounds augment lysosomal GCase L444P in the fibroblast. Moreover, those compounds increase total GCase L444P protein, suggesting the pharmacological chaperone-like mechanism of action. To further elucidate the effect of the compounds on endogenous GCase substrate, GlcSph, we generated iPSC-derived dopaminergic neurons with GBA1 L444P mutations that exhibit GlcSph accumulation *in vitro*. Importantly, the identified compounds reduce GlcSph in iPSC-derived dopaminergic neurons with GBA1 L444P mutation, indicating the increase in lysosomal GCase by the compounds could lead to the clearance of pathologically accumulated GlcSph. Together, our findings pave the way to develop a potent and efficacious GCase chaperon compound as a potential therapeutic approach for GD and PD/DLB patients with GBA1 mutation or decreased GCase activity.

Disclosures: **Y. Naito:** A. Employment/Salary (full or part-time):; Takeda Pharmaceutical Company Limited. **T. Kojima:** A. Employment/Salary (full or part-time):; Takeda Pharmaceutical Company Limited. **M. Homma:** A. Employment/Salary (full or part-time):; Takeda Pharmaceutical Company Limited. **M. Tanaka:** A. Employment/Salary (full or part-time):; Takeda Pharmaceutical Company Limited. **H. Matsui:** A. Employment/Salary (full or part-time):; Takeda Pharmaceutical Company Limited..

Poster

110. Dopamine Neuron Regulation

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 110.11

Topic: C.03. Parkinson's Disease

Support: Farmer Family Foundation's Parkinson's Research Initiative
NIH R01 NS104324-01A1
Ellison Foundation

Title: 4-octyl itaconate attenuates toxins-induced neuronal cell death via activation of the glial nrf2 pathway in the cellular model of parkinson's disease

Authors: *N. XIA, A. ALBALAKHI, S. LIN, Y. XU, M. SCHWARZSCHILD, R. BAKSHI; Mass Gen. Hosp., Charlestown, MA

Abstract: Chronic neuroinflammation plays an important role in Parkinson's disease (PD) pathogenesis, one of the most common age-related neurodegenerative diseases. Pro-inflammatory toxins like lipopolysaccharide (LPS) can induce dopaminergic neuronal death either alone or in combination with other PD toxins that reinforce the involvement of inflammation in the development or the progression of the disease. Nuclear factor-erythroid factor 2-related factor 2 (Nrf2) is a transcription factor that plays a crucial role in cellular defense against oxidative stress and neuroinflammation in CNS. In MPTP mice models, Nrf2 modulates microglial dynamics and control's microglial function. Activators of Nrf2 pathways, such as the recently identified endogenous metabolite itaconate, can function as a regulatory mediator of the inflammatory response. Itaconate is a tricarboxylic acid cycle metabolite produced by immune-responsive gene 1 in response to inflammatory stimulus. In this study, we aim to investigate the neuroprotective potential of Itaconate and its cell-permeable derivate 4-octyl itaconate (OI) in LPS-stimulated BV2 microglial cells as a cellular model to mimic the activated microglia pathology in PD. We observed that OI suppressed the LPS-induced up-regulation of pro-inflammatory cascades of inducible nitric oxide synthase, cyclooxygenase-2, and cytokines release in BV2 microglial cells. We also found that OI up-regulated the p62/Nrf2/HO-1/NF-κB axis pathway in the presence of LPS treatment. To determine the impact of itaconate on neurons, we treated N2a neuronal cells with a conditioned medium (CM) from LPS with or without OI-treated BV2 cells. We found that CM derived from OI-treated BV2 cells showed significant protective effects against Rotenone/MPP^+ induced neurotoxicity. However, the direct treatment of OI on N2a cells did not impact Rotenone or MPP^+ toxicity. Our present study provides compelling evidence that OI exerts a dramatic anti-inflammatory effect on microglia, resulting in neuron survival against toxin-induced cell death in vitro. Our results of OI's ability to curb neuronal degeneration via microglia cells call for future research to pursue itaconate and its derivatives as a therapeutic strategy against PD.

Disclosures: N. Xia: None. **A. Albalakhi:** None. **S. Lin:** None. **Y. Xu:** None. **M. Schwarzschild:** None. **R. Bakshi:** None.

Poster

110. Dopamine Neuron Regulation

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 110.12

Topic: C.03. Parkinson's Disease

Support: National Research Foundation of Korea (NRF-2021R1I1A3060435)
National Research Foundation of Korea (NRF-2020R1I1A3070388)
National Research Foundation of Korea (NRF-2020R1F1A1076616)
Chonnam National University Hospital Biomedical Research Institute (BCRI21039)
Jeollanam-do Science and Technology R&D Project (Development of Stem Cell-Derived New Drug)

Title: Treatment of neural-induced human adipose tissue-derived stem cell-conditioned medium regulates mitochondria, ER, and their tethering proteins in rotenone-induced toxicity on SH-SY5Y cells

Authors: *M. RAMALINGAM[1], J. HWANG[1], J. YOO[1], D. KIM[1], J. CHOI[1], E. JANG[1,2], K. K. SONI[1], H.-H. CHO[3], B. C. KIM[4], E. KIM[2], S. JANG[1], H.-S. JEONG[1];
[1]Dept. of Physiol., Chonnam Natl. Univ. Med. Sch., Hwasun-gun,, Korea, Republic of;
[2]Biopharmaceutical Res. Ctr., Jeonnam Bioindustry Fndn., Hwasun-gun, Korea, Republic of;
[3]Dept. of Otolaryngology-Head and Neck Surgery, [4]Dept. of Neurol., Chonnam Natl. Univ. Med. Sch. and Hosp., Gwangju, Korea, Republic of

Abstract: Parkinson's disease (PD) is a progressive neurodegenerative disorder. Mitochondrial deficit associated with PD impairs intracellular trafficking which trigger protein aggregation and neurodegeneration. Exposure of rotenone (ROT), a mitochondrial complex I inhibitor, leads to PD-specific neurodegeneration by increased reactive oxygen species, aggregation of α-synuclein (α-syn), and ubiquitin (Ub). Mitophagy, mitochondrial fission, fusion, transport, biogenesis, and degradation plays a critical role in PD. In addition, accumulation of α-syn protein misfolding and aggregation results endoplasmic reticulum (ER) stress in neurons. Moreover, mitochondria and the ER communication through the mitochondria-associated membranes (MAM) also play a role in the pathogenesis of PD. In this present study, we examined the neurogenic differentiation of human adipose tissue-derived stem cells (NI-hADSCs)-conditioned medium (NI-hADSC-CM) against ROT-induced toxicity in SH-SY5Y cells on mitochondria, ER, and MAM tethering. For experiments, SH-SY5Y cells were incubated in the absence or presence of ROT (0.5 μM) for 48 h and treated with NI-hADSC-CM (at 50% dilution) during last 24 h. In results, ROT toxicity for 48 h significantly increased leucine rich repeat kinase 2 (LRRK2) and insoluble Ub levels along with phospho (p)-DRP1 Ser616/total (t)-DRP1. ROT decreased PINK1, parkin, DJ-1, TOM20, p-DRP1 Ser637/t-DRP1, mitofusion-1 (MFN1), -2 (MFN2), and OPA1. In ER pathway, ROT increased BiP (GRP78), IRE1α, p-PERK Thr981, ATF4, and CHOP, but decreased p-PERK Thr980 and p-/t-eIF2α. ROT toxicity increased VDAC and GRP75 and decreased p-IP3R Ser1756/t-IP3R1. However, NI-hADSC-CM treatment decreased the LRRK2, insoluble Ub, p-DRP1 Ser616, IRE1α, p-PERK Thr981, ATF4, CHOP, VDAC, and GRP75. In addition, NI-hADSC-CM treatment restored the levels of parkin, DJ-1, TOM20, p-DRP1 Ser637, MFN1, MFN2, OPA1, p-PERK Thr980, p/t-eIF2α, and p-IP3R Ser1756. These data suggested that NI-hADSC-CM treatment decreased ROT-induced toxicity by modifying LRRK2 and ubiquitin involved mitophagy, downregulate the mitochondrial fission by increased mitochondrial fusion, relieve the ER stress subsequently resulting in stabilized IP3R-GRP75-VDAC tethering. Taken together, our results show that NI-hADSC-CM treatment regulating signaling pathways of

mitochondria-ER interaction could facilitate the beneficial effects in PD and other neurodegenerative disorders.

Disclosures: **M. Ramalingam:** None. **J. Hwang:** None. **J. Yoo:** None. **D. Kim:** None. **J. Choi:** None. **E. Jang:** None. **K.K. Soni:** None. **H. Cho:** None. **B.C. Kim:** None. **E. Kim:** None. **S. Jang:** None. **H. Jeong:** None.

Poster

110. Dopamine Neuron Regulation

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 110.13

Topic: C.03. Parkinson's Disease

Support: JSPS KAKENHI (grant numbers JP 17K08444 and 20K07154)

Title: Mir-101 regulates neuronal cell death by targeting suppressor/enhancer lin-12-like (SEL1L) in a cellular model of Parkinson's disease using 6-hydorxydopamine

Authors: *T. OMURA[1,2], L. NOMURA[2], H. NISHIGUCHI[1], K. YAMAMOTO[1], S. IMAI[2], S. NAKAGAWA[2], K. ITOHARA[2], A. YONEZAWA[2], T. NAKAGAWA[2], I. YANO[1], K. MATSUBARA[2,3];
[1]Dept. of Pharm., Kobe Univ. Hosp., Kobe, Japan; [2]Dept. of Clin. Pharmacol. and Therapeut., Kyoto Univ. Hosp., Kyoto, Japan; [3]Dept. of Pharm., Wakayama Med. Univ. Hosp., Wakayama, Japan

Abstract: Endoplasmic reticulum (ER) stress is a cause of Parkinson's disease (PD). We have proved that the ubiquitin ligase HMG-CoA reductase degradation 1 (HRD1) and its stabilizer suppressor/enhancer lin-12-like (SEL1L) participate in ER stress. Our recent study demonstrated that the suppression of SEL1L promotes neuronal cell death in a cellular PD model. This finding suggests that SEL1L is also one of the key targets for PD therapy. Therefore, it should be worthwhile to investigate whether microRNAs (miRNAs) regulate SEL1L expression in neurons, since relationships between miRNAs and the development of neurological disease, such as PD, have been recently indicated. Here, based on miRNA databases and previously published reports, we searched for miRNAs that could regulate SEL1L expression and examined the effects of this regulation on cell death in PD models produced by 6-hydroxydopamine (6-OHDA). We first identified five candidate miRNAs that could regulate SEL1L expression. Among them, the expression of miR-101 was inversely correlated with that of SEL1L in 6-OHDA-treated SH-SY5Y cells. We selected miR-101 as a candidate miRNA for SEL1L regulation. We confirmed that miR-101 directly targeted the 3'-untranslated region of SEL1L, and miR-101 suppressed SEL1L expression and consequently promoted cell death in PD models. These results suggest that miR-101 regulates SEL1L expression and could serve as a new PD therapeutic target.

Disclosures: **T. Omura:** None. **L. Nomura:** None. **H. Nishiguchi:** None. **K. Yamamoto:** None. **S. Imai:** None. **S. Nakagawa:** None. **K. Itohara:** None. **A. Yonezawa:** None. **T. Nakagawa:** None. **I. Yano:** None. **K. Matsubara:** None.

Poster

110. Dopamine Neuron Regulation

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 110.14

Topic: C.03. Parkinson's Disease

Support: MOST 109-2320-B-077-005-MY3
MOHW110-NRICM-B-325-112104

Title: Sirt1 activator srt1720 alleviates paraquat-induced cell death

Authors: *N.-K. HUANG[1], C. CHAO[2], C. HUANG[3], J. CHENG[4], I. LEE[5], Y. YANG[6], C. YEI[4], P. LIN[4], J. CHEN[7];
[1]Nat Res. Inst. Chin Med., Natl. Res. Inst. of Chinese Medicine, Ministry of Hlth. and Welfare, Taipei, Taiwan; [2]Inst. of Neuroscience, Natl. Chengchi Univ., Taipei, Taiwan; [3]Med. Res. Center, Cardinal Tien Hosp., New Taipei City, Taiwan; [4]Natl. Res. Inst. of Chinese Med., Taipei, Taiwan; [5]Herbal Med. Department, Yokohama Univ. of Pharm., Yokohama, Japan; [6]Dept. of Biotech. and Animal Science, Natl. Ilan Univ., Ilan, Taiwan; [7]Sch. of Pharmaceut. Sciences, Natl. Yang-Ming Chiao TungUniversity, Taipei, Taiwan

Abstract: Paraquat (1,1'-dimethyl-4,4'-bipyridinium, PQ) has been used as an herbicide worldwide for more than 50 years. Epidemiological studies have indicated a strong correlation between Parkinson's disease (PD). Currently, paraquat has been known to induce PD-like syndromes. Thus, PQ has widely been accepted as a PD mimetic. On the other hand, several studies have shown that the impaired activity of sirtuin 1 (SIRT1) may correlate with the etiology of PD. Although resveratrol is a famous SIRT1 activator that alleviates toxicities in PD models, the protective mechanisms remain elusive for its unspecific effects. Therefore, a more specific agonist for SIRT1, SRT1720, was used to investigate the mechanisms of SIRT1 in preventing PQ-induced cytotoxicity. This study used PQ-treated human neuroblastoma SH-SY5Y cells and mice as PD models to examine the protection of SRT1720. The neutral red assay was used to measure cell viability. Fluorescent stainings, such as CellRox, were used to measure oxidative stress, mitochondrial membrane potential, and free radicals. Western blot analysis, immunocytochemistry, immunohistochemistry, and gene silence were used to examine the expression and protection of SIRT1 and/or its downstream targets, such as PGC-1α and antioxidative enzymes. Besides, antioxidative enzyme activities were also measured after PQ and SRT1720 treatments. SRT1720 was found to alleviate PQ-induced toxicity in cell and animal models. Genetic silence and pharmacological inhibition of SIRT1 attenuated SRT1720's protection against PQ-induced toxicity. Besides, SRT1720 not only attenuated PQ-induced increased oxidative stress and mitochondrial free radical formations but also decreased PGC-1α

level and mitochondrial membrane potential and biogenesis. Further, *PGC-1α* silencing attenuated SRT1720's protection against PQ-induced toxicity. In summary, the protection of SRT1720 may regulate through SIRT1 and its signalings, such as PGC-1α, to prevent PQ-induced toxicity. Therefore, SRT1720 might have therapeutic potential in treating PD.

Disclosures: **N. Huang:** None. **C. Chao:** None. **C. Huang:** None. **J. Cheng:** None. **I. Lee:** None. **Y. Yang:** None. **C. Yei:** None. **P. Lin:** None. **J. Chen:** None.

Poster

110. Dopamine Neuron Regulation

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 110.15

Topic: C.03. Parkinson's Disease

Support: DGAPA-UNAM
SIP-IPN
CONACYT # 302799

Title: Sio_2 nano-matrices increase dopaminergic markers expression in differentiated or undifferentiated sh-sy5y human neurons

Authors: *A. J. ESPADAS-ALVAREZ[1], P. VERGARA-ARAGON[3], L. P. TEXCO-MARTINEZ[3], H. G. ESPADAS-ALVAREZ[4], R. GARCIA-VILLEGAS[5], E. GONZALEZ-GOMEZ[2];
[1]Biociencias e Ingeniería, [2]Biociencias e Ingenieria, Inst. Politécnico Nacional, Ciudad de México, Mexico; [3]Fisiología, Univ. Nacional Autónoma de México, Ciudad de México, Mexico; [4]Ctr. de Investigación sobre Enfermedades Infecciosas, Inst. Nacional de Salud Pública, Cuernavaca, Morelos, Mexico; [5]Fisiología, Ctr. de Investigación y de Estudios Avanzados del IPN, Ciudad de México, Mexico

Abstract: We are interested in developing new and better biotechnological strategies for the treatment of diseases of the central nervous system. In previous studies we build and evaluate silicon dioxide nanomatrices (SiO_2-NMs) that releasing dopamine to treat Parkinson's disease in animal model and the results was encouraging. In this new study, we build SiO_2-NMs empty or dopamine-containing and evaluate the morphologic response and the dopaminergic markers expression in differentiated or undifferentiated SH-SY5Y human neurons. Interestingly, both SiO_2-NMs enhances dopaminergic markers and the levels expression of tyrosine hydroxylase of SH-SY5Y neurons are likes dopaminergic neurons *in vivo*. These results suggest that SiO_2-NMs are good candidate for used how agent for restore the dopaminergic system.

Disclosures: **A.J. Espadas-Alvarez:** None. **P. Vergara-Aragon:** None. **L.P. Texco-Martinez:** None. **H.G. Espadas-Alvarez:** None. **R. Garcia-Villegas:** None. **E. Gonzalez-Gomez:** None.

Poster

110. Dopamine Neuron Regulation

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 110.16

Topic: C.03. Parkinson's Disease

Support: NINDS R01NS112203

Title: Changes in 14-3-3θ phosphorylation within neurons following exposure to trichloroethylene.

Authors: *W. J. STONE[1], T. A. YACOUBIAN[1], B. R. DE MIRANDA[2], A. KAMATH[1]; [1]Dept Neurol., Univ. of Alabama at Birmingham, Birmingham, AL; [2]Neurol., Univ. of Alabama, Birmingham, Birmingham, AL

Abstract: Parkinson's Disease (PD) is the most common neurodegenerative movement disorder in the world and its prevalence is projected to continue increasing. PD is pathologically characterized by degeneration of dopaminergic neurons (DA) within the substantia nigra pars compacta (SNc), accompanied by neuroinflammation and aggregation of misfolded alpha-synuclein (α-syn) into Lewy bodies and neurites. In addition to α-syn, these pathologic aggregates display immunoreactivity with 14-3-3 proteins. 14-3-3s are a group of highly conserved, multifunctional molecular hub proteins that have been repeatedly implicated in several neurodegenerative diseases and are key regulators of neuronal function and cell death. Our lab has previously shown that 14-3-3 overexpression, particularly of the 14-3-3θ isoform, is protective in neurotoxin, α-syn, and LRRK2 models while 14-3-3 inhibition accelerates toxicity. We also showed that insoluble levels of 14-3-3θ, one of seven mammalian isoforms, phosphorylated at serine residue 232 (pS232), are increased in PD and Dementia with Lewy Bodies (DLB) and positively correlate with clinical and pathological severity. ***However, what promotes 14-3-3 dysfunction in disease is unclear***. Our preliminary data suggests that the environmental toxicant, trichloroethylene (TCE), induces 14-3-3θ phosphorylation at S232. TCE is an industrial solvent associated with a 6-fold increase in PD risk and the most frequently reported volatile organic chemical within US groundwater. Rodents exposed to TCE display selective neurodegeneration of the dopaminergic neurons within the SNc. We treated M17 neuroblastoma cells with TCE for 6, 12, 24, and 48 hours and cell lysates and measured levels of pS232 and total 14-3-3θ by Western blot. Levels of pS232 were found significantly increased at 24 hours post-TCE treatment, supporting a potential role for 14-3-3θ phosphorylation in mediating TCE neurotoxicity. We also observed elevated levels of pS232 14-3-3θ in the brain following TCE exposure *in vivo*. Striatal tissue from rats administered a daily oral gavage of vehicle (olive oil) or 50, 100, 200, or 400 mg/kg TCE for 3 weeks were analyzed for pS232 and total 14-3-3θ by Western blot. Dosages of TCE at or above 100 mg/kg resulted in a significant increase in pS232 levels compared to vehicle. Together, these findings demonstrate a consistent trend of increased 14-3-3θ phosphorylation following TCE exposure in neuronal populations. We therefore intend to test whether blockade of phosphorylation at S232 can attenuate the neurotoxicity induced by TCE exposure.

Disclosures: **W.J. Stone:** None. **T.A. Yacoubian:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Dr. Yacoubian has a U.S. Patent No. 7,919,262 on the use of 14-3-3s in neurodegeneration.. **B.R. De Miranda:** None. **A. Kamath:** None.

Poster

110. Dopamine Neuron Regulation

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 110.17

Topic: C.03. Parkinson's Disease

Support: NINDS Grant R56NS115767
NINDS Grant RF1NS115767
NIGMS Grant T32GM135028

Title: Role of Rab27 and its effectors in Alpha-Synuclein handling

Authors: *K. J. SCHOLZ, T. A. YACOUBIAN;
Dept Neurol., Univ. of Alabama At Birmingham, Birmingham, AL

Abstract: Alpha-synuclein (asyn) is the key protein implicated in Parkinson's Disease (PD) and Dementia with Lewy Bodies (DLB), two common neurodegenerative disorders which lack therapies to slow neurodegeneration. Asyn is hypothesized to promote neurodegeneration by prion-like spread from cell to cell throughout the brain, yet little is known about the mechanism of propagation or the factors that influence it. Rab proteins are small GTPases that play critical roles in vesicular trafficking and have been implicated in synucleinopathies. We have previously shown that the Rab27b GTPase is increased in human PD and DLB and that knockdown of Rab27b reduces autophagic clearance of asyn in cellular models. In this study, we aimed to expand our studies on the effects of overexpressing Rab27b and additionally to investigate Rab27b effector proteins that may mediate Rab27b's effects. We previously created a doxycycline-inducible neuroblastoma line that, upon doxycycline treatment, induces asyn overexpression and consequent secretion of asyn that is toxic when transferred to separately cultured cells. These asyn cells were transfected with GFP-tagged Rab27b or GFP as control. We found that Rab27b overexpression (OE) reduces the secretion of asyn into the culture media relative to a GFP-expressing control line. We further demonstrated that Rab27b OE results in increased autophagic flux, as Rab27b-OE cells display more robust LC3II buildup than GFP-control cells when treated with the autophagosome-lysosome fusion inhibitor chloroquine. Preliminary results also show that Rab27b overexpression reduces asyn paracrine toxicity. Like other GTPases, Rab27b interacts with its targets through effector proteins, and we have identified Coronin1C and Synaptotagmin-like Protein 5 (SLP5) as potential players in asyn handling. These proteins are expressed in our asyn cell model and colocalize with Rab27b and with autophagic and lysosomal markers LAMP1, LC3II, and P62. Additionally, we have determined via western blot that Coronin1C is elevated in temporal cortical lysates from human

PD subjects compared to age-matched controls. We recently generated knockdown cell lines for both of these proteins in the interest of further elucidating their functions. Our findings highlight Rab27b and its effector proteins as potential targets for therapeutic intervention in synucleinopathies.

Disclosures: K.J. Scholz: None. **T.A. Yacoubian:** None.

Poster

110. Dopamine Neuron Regulation

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 110.18

Topic: C.03. Parkinson's Disease

Support: NIH Grant NINDS R01NS112203

Title: 14-3-3θ Phosphorylation prevents 14-3-3θ's ability to regulate lrrk2 kinase activity

Authors: *R. PATTANAYAK, T. YACOUBIAN;
Neurol., Univ. of Alabama at Birmingham, Birmingham, AL

Abstract: LRRK2 mutations are the most common autosomal dominant cause of PD, and toxicity is associated with increased kinase activity. 14-3-3 proteins are major interactors of LRRK2 that regulate LRRK2 kinase activity. We previously demonstrated that the 14-3-3θ isoform reduces LRRK2-mediated toxicity by inhibition of kinase activity. More recently, we observed that 14-3-3θ phosphorylation at S232 is dramatically increased in human PD brains. Based on these findings, we hypothesized that 14-3-3θ phosphorylation may disrupt the ability of 14-3-3θ to regulate LRRK2 kinase activity. To test this, we cotransfected the nonphosphorylable S232A 14-3-3θ mutant or the phospho-mimetic S232D mutant with wildtype or mutant LRRK2 in HEK293T cells and kinase activity through autophosphorylation at S1292 and T1503 and through Rab10 phosphorylation. We found that both wildtype and S232A 14-3-3θ reduce the kinase activity of either wildtype or G2019S LRRK2, while S232D failed to reduce the kinase activity of wildtype or G2019S LRRK2. Surprisingly, wildtype, S232A, and S232D 14-3-3θ were all able to reduce the kinase activity of the R1441G LRRK2 mutant. To assess whether this differential effect of S232D on LRRK2 activity was related to differential LRRK2 binding, we did co-immunoprecipitation and proximal ligation assays. We found that wildtype 14-3-3θ and both S232 mutants showed similar binding to wildtype and G2019S LRRK2, suggesting that 14-3-3θ phosphorylation did not disrupt global binding of 14-3-3θ to LRRK2. We next examined if 14-3-3θ phosphorylation impacts LRRK2 kinase activity via more subtle conformation alterations in LRRK2. Recent studies have shown that 14-3-3s also interact with LRRK2 at the C-terminal end at T2524, and this C-terminal helix can fold back to interact with the kinase domain near the G2019 site. We tested the impact of 14-3-3θ phosphorylation on its interaction with LRRK2 at T2524 using molecular modeling. The binding at T2524 of LRRK2 was significantly higher for S232A than S232D when T2524 is phosphorylated. We conclude that 14-

3-3θ phosphorylation destabilizes the interaction at T2524 which then alters the impact of the C-terminal domain on kinase activity. We predict that 14-3-3θ phosphorylation has no impact of the ability of 14-3-3θ to regulate kinase activity of R1441G mutant as this mutant's effect on kinase activity may not be regulated by the C-terminal domain.

Disclosures: R. Pattanayak: None. **T. Yacoubian:** Other; Dr. Yacoubian has a U.S. Patent No. 7,919,262 on the use of 14-3-3s in neurodegeneration.

Poster

110. Dopamine Neuron Regulation

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 110.19

Topic: C.03. Parkinson's Disease

Support: MOST 110-2813-C-037-153-B
MOST 105-2628-B-037-003-MY3
U3002 (KMU)
KMU-M110002
KMU-109006
TYAFGH-D-111021
TYAFGH-D-111041

Title: Sleep associated intermittent hypoxia depletes the tyrosine hydroxylase containing neuron in mouse brain

Authors: *S.-L. CHEN[1], Y.-C. CHANG[2], C.-H. CHU[1], K.-T. LIU[2], Y.-C. LIU[3], M.-C. CHOU[4], C.-K. LIU[4], C.-H. CHEN[5], J.-L. CHANG[2];
[1]Grad. Inst. of Med., Kaohsiung Med. Univ., Kaohsiung, Taiwan; [2]Taoyuan Armed Forces Gen. Hosp., Taoyuan, Taiwan; [3]Anesthesiol., Kaohsiung Med. Univ. Hosp., Kaohsiung, Taiwan; [4]Kaohsiung Med. Univ. Hosp., Neurology, Taiwan; [5]Texas Heart Inst., Houston, TX

Abstract: Sleep apnea is a sleep disorder caused by an obstructive airway or central nervous system problems during sleep. In subjects with sleep apnea, the repeated sleep apnea leads to the intermittent hypoxia (IH) of brain. Studies have revealed that sleep apnea induced the significant neuronal dysfunctions in human subjects. However, the impact of IH of sleep apnea in brain need to be extensively investigated. In this study, an animal model of sleep associated IH was used to investigate the expression of tyrosine hydroxylase (TH)-containing neurons in rodents' brain. TH is a marker for catecholamine neuron *located* in the substantia nigra (SN) and locus coeruleus (LC). In SN, TH-containing neurons are mainly dopamine (DA) neurons, which are associated with the coordination of body movement. Apoptosis of DA neurons in SN induces motor deficiency and is believed to be a step in the progression of Parkinson's disease. In LC, TH-containing neurons are mainly norepinephrine (NE) neuron which are associated with the status of arousal and a variety of sensory-motor functions. Therefore, investigate the

pathophysiological changes of TH-containing neurons in sleep apnea is an important issue. Our data showed that mice expose to IH (5-21% oxygen) during sleep for 10-20 days (10 cycles/hr, 8 hours/day), the numbers of hippocampal pyramidal neuron in dentate gyrus and CA3 were not affected compared to the room air (RA, 21% oxygen) control mice. In the analysis of TH staining, significantly reduced numbers of DA and NE neurons in SN and LC were found in IH mice compared to RA mice. These findings indicate that under chronic IH, the degeneration of TH neurons are earlier than glutamatergic neuron in brain. In the novel arm recognition test used to analyze cognitive function, the ability to recognize novel and familiar arm was similar between the groups. In the open field test, compared with RA mice, IH mice showed significantly decreased of spontaneous locomotor activity. Our data provide the pathophysiological evidence for the degeneration of SN DA neurons and LC NE neurons in a mouse model of chronic IH. These findings reveal the progressive damage of TH neurons in the early stage of sleep apnea, which can provide important references for clinical observation of sleep apnea.

Disclosures: S. Chen: None. **Y. Chang:** None. **C. Chu:** None. **K. Liu:** None. **Y. Liu:** None. **M. Chou:** None. **C. Liu:** None. **C. Chen:** None. **J. Chang:** None.

Poster

110. Dopamine Neuron Regulation

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 110.20

Topic: C.03. Parkinson's Disease

Support: DGAPA PAPIIT IT201120

Title: Evaluation of the effect produced by the GGxN polymer in behavioral alterations in a murine model with induced Hemiparkinsonism

Authors: *E. GARCÍA VALDÉS[1], V. E. GALLEGOS HERNADEZ[2], S. GALAVIZ HERNANDEZ[2], B. HERNANDEZ TELLEZ[3], R. J. REYES RUIZ[3], A. J. ESPADAS, Jr.[4], M. R. JAIME FONSECA[2], P. VERGARA ARAGON[3];
[1]CICATA LEGARIA, Inst. Politécnico Nacional (IPN), CIUDAD DE MEXICO, Mexico; [2]CICATA LEGARIA, Inst. Politécnico Nacional (IPN), Ciudad de Mexico, Mexico; [3]Facultad de Medicina, Univ. Nacional Autónoma de México (UNAM), Ciudad de Mexico, Mexico; [4]Biociencias e Ingeniería, Univ. Nacional Autónoma De México (UNAM), Mexico, Mexico

Abstract: Parkinson's disease (PD) is a progressive and irreversible neurodegenerative disorder caused by the loss of dopaminergic neurons in the substantia nigra pars compacta.The purpose of this work is to formulate a functional food with chemical properties that contributes to reduce behavioral disorders (anxiety and hopelessness) in rats with induced hemiparkinsonism.Materials and Methods: Two foods were elaborated in an artisanal way with concentrations of the GGxN polymer of 8% (AA8) and 15% (AA15) p/p and a bromatological analysis was carried

out.Results: It was found that the processed foods AA 8 and AA 15 contain 10.65% and 19.57% of dietary fiber, respectively, which makes them a good source of prebiotic fiber. The rats were divided into 4 experimental groups: Control group, group with hemiparkinsonism (HEMI), hemiparkinsonism AA8 (Hemi AA8) and hemiparkinsonism AA15 (Hemi AA15).The HEMI AA8% and HEMI AA15% groups showed a higher number of frames traveled compared to the HEMI group.Conclusion: The experimental results showed that the administration of AA8 and AA15 foods improved anxiety and hopelessness disorders in rats with induced Hemiparkinsonism.

Disclosures: E. García Valdés: None. **V.E. Gallegos Hernadez:** None. **S. Galaviz Hernandez:** None. **B. Hernandez Tellez:** None. **R.J. Reyes Ruiz:** None. **A.J. Espadas:** None. **M.R. Jaime Fonseca:** None. **P. Vergara Aragon:** None.

Poster

110. Dopamine Neuron Regulation

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 110.21

Topic: C.03. Parkinson's Disease

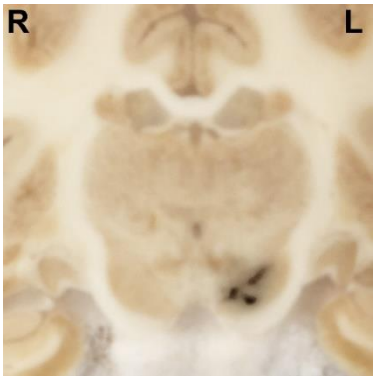
Support: ASAP Grant 020505
MCIN / AEI / 10.13039/501100011033 Grant No. PID2020-120308RB-I00

Title: Blaming neuromelanin for Parkinson's disease: time-dependent tyrosinase overexpression drives endogenous synucleinopathy in nonhuman primates

Authors: J. CHOCARRO[1], A. FAJARDO-SERRANO[1], A. J. RICO[1], G. ARIZNABARRETA[1], E. RODA[1], A. HONRUBIA[1], A. VAZQUEZ[2], A. I. RODRIGUEZ-PEREZ[3], J. L. LABANDEIRA-GARCIA[3], M. VILA[4], ***J. L. LANCIEGO**[1];
[1]Neurosciences, CIMA - Univ. of Navarra, Pamplona, Spain; [2]Neurosurg., Complejo Hospitalario de Navarra, Pamplona, Spain; [3]Neurosciences, Res. Ctr. for Mol. Med. and Chronic Dis. (CIMUS), Univ. de Santiago de Compostela, Santiago de Compostela, Spain; [4]Vall d'Hebron Res. Inst., Vall d'Hebron Res. Inst., Barcelona, Spain

Abstract: Although neuromelanin (NMel) is a dark pigment characteristic of dopaminergic neurons in the human substantia nigra pars compacta (SNpc), its potential role in the pathogenesis of Parkinson's disease (PD) has been neglected since most commonly used laboratory animals lack NMel. Here we took advantage of AAVs encoding tyrosinase for driving a time-dependent NMel accumulation within the SNpc in macaques up to similar levels as observed in elderly humans. Furthermore, NMel accumulation induced (i) an endogenous synucleinopathy mimicking intracellular inclusions typically observed in PD, (ii) a progressive degeneration of NMel-expressing dopaminergic neurons, and (iii) a pro-inflammatory phenotype mediated by activated microglial cells and perivascular macrophages. Moreover, Lewy body-like intracellular inclusions were observed in brain areas receiving dopaminergic innervation,

supporting a prionoid spread of endogenous synucleinopathy by permissive trans-synaptic templating. In summary, the conducted strategy resulted in the characterization and validation of a new macaque model of PD matching the known neuropathology of this disorder with unprecedented accuracy. Finally, evidence was provided showing that intracellular aggregation of endogenous alpha-synuclein is triggered by NMel accumulation, therefore any therapeutic approach intended to decrease NMel levels may provide appealing choices for the successful implementation of novel PD therapeutics.



Disclosures: **J. Chocarro:** None. **A. Fajardo-Serrano:** None. **A.J. Rico:** None. **G. Ariznabarreta:** None. **E. Roda:** None. **A. Honrubia:** None. **A. Vazquez:** None. **A.I. Rodriguez-Perez:** None. **J.L. Labandeira-Garcia:** None. **M. Vila:** None. **J.L. Lanciego:** None.

Poster

110. Dopamine Neuron Regulation

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 110.22

Topic: C.03. Parkinson's Disease

Support: The Nilsson-Ehle Endowments
Olle Engkvists Stiftelse
MultiPark

Title: Genetic and transcriptomic profiles associated to dopaminergic neurodegeneration in Engrailed-1 hemizygous mouse models of Parkinson's disease

Authors: *L. BELFIORI-CARRASCO[1], A. DUEÑAS-REY[3], D. RALBOVSZKI[4], S. S. BALIKAI[1], F. BÄCKSTRÖM[1], K. BROLIN[1], D. AHRÉN[2], M. SWANBERG[1];
[1]Dept. of Exptl. Med. Sci., [2]Dept. of Biol., Lund Univ., Lund, Sweden; [3]Ctr. for Med. Genet. Ghent, Ghent Univ. Hosp., Ghent, Belgium; [4]Dept. of Vet. and Animal Sci., Copenahgen Univ., Copenhagen, Denmark

Abstract: Engrailed 1 (En1) is a highly conserved transcription factor that plays an essential role in programming, survival, and maintenance of midbrain dopaminergic neurons. En1-hemizygosis ($En1^{+/-}$) leads to a spontaneous Parkinson's disease-like (PD-like) progressive nigrostriatal degeneration as well as motor impairment and depressive-like behavior in SwissOF1 mice. However, this phenotype is not present in C57Bl/6J mice. In this study we aimed to characterize the spontaneous PD-like phenotype and associated transcriptome profiles in SwissOF1- $En1^{+/-}$ mice and compare to that of resistant C57Bl/6J- $En1^{+/-}$ mice. Four groups of male mice were studied: wild-type (WT) SwissOF1, WT C57Bl/6J, SwissOF1-$En1^{+/-}$ and C57Bl/6J-$En1^{+/-}$. We used histology and stereology to assess neurodegeneration and axonal swellings in the substantia nigra pars compacta (SNpc) and striatum (n=7) at 4 and 16 wks. To detect early changes prior to neurodegeneration onset, we performed RNA-seq of 1wks SNpc (n=3). Finally, we assessed protein expression levels of genes of interest (GOI) at 1, 4 and 16wks through western blot (n=4) to assess their expression and cellular localization. SwissOF1-$En1^{+/-}$ mice showed a spontaneous and progressive neurodegenerative phenotype with an increase in axonal swellings from 4 to 16 wks and a 23% (±8%) loss of dopaminergic neurons at 16 wks. Axonal swellings were present in C57Bl/6J-$En1^{+/-}$ mice but did not increase over time. In addition, no cell loss was detected in C57Bl/6J-$En1^{+/-}$ mice at 16 wks. The transcriptomic data showed 134 differentially expressed genes (DEG) between $En1^{+/-}$ and WT SwissOF1 mice. In contrast, only 19 DEG were detected between $En1^{+/-}$ and WT C57Bl/6J mice. Genes associated with Ca^{+2} homeostasis, hormone secretion, and synaptic maintenance were enriched in SwissOF1-$En1^{+/-}$ DEG, while no enrichment was seen among C57Bl/6J-$En1^{+/-}$ DEG. Western blot analyses showed that initial expression differences were generally not maintained over time when comparing 1, 4 and 16wks WT and $En1^{+/-}$ SwissOF1 mice. Here we provide genetic, transcriptomic, and cellular profiles to strain-dependent susceptibility to PD-like nigrostriatal degeneration by comparing $En1^{+/-}$ vs WT SwissOF1 and C57Bl/6J mice. These candidate genes, proteins and pathways can provide valuable insight into processes associated with PD susceptibility and progression.

Disclosures: L. Belfiori-Carrasco: None. **A. Dueñas-Rey:** None. **D. Ralbovszki:** None. **S.S. Balikai:** None. **F. Bäckström:** None. **K. Brolin:** None. **D. Ahrén:** None. **M. Swanberg:** None.

Poster

110. Dopamine Neuron Regulation

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 110.23

Topic: C.03. Parkinson's Disease

Support: NRF Grant 2021R1I1A1A01044890

Title: Rumex japonicus Houtt. protects dopaminergic neurons by regulating mitochondrial function and gut-brain axis in SH-SY5Y cells and mice models of Parkinson's disease

Authors: *H.-Y. KIM[1], C.-H. BAE[2], J. SEO[2], H. LEE[2], S. KIM[2];
[1]Korean Med. Res. Ctr. for Healthy Aging, [2]Dept. of Korean Med. Sci., Pusan Natl. Univ., Yangsan-si, Korea, Republic of

Abstract: Parkinson's disease (PD) is the second most common neurodegenerative disease worldwide. *Rumex japonicus* Houtt. (RJ) has been used to treat gastrointestinal and inflammatory diseases in East Asia. However, it is unknown whether RJ can prevent PD. We investigated the neuroprotective effects of RJ in cellular and animal PD models, focused on mitochondrial function and the gut-brain axis. SH-SY5Y cells were treated with RJ (0.01 mg/mL) for 24 h, after which they were treated with the 1-methyl-4-phenylpyridinium ion (MPP+). MPP+-induced apoptosis increased mitochondrial reactive oxygen species and decreased ATP, PINK1, and DJ-1, which were inhibited by RJ. Ten-week-old C57BL/6N male mice were treated with 30 mg/kg of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) for 5 days and orally administered 50 or 100 mg/kg of RJ for 14 days. RJ alleviated MPTP-induced behavioral impairment, dopaminergic neuronal death, and mitochondrial dysfunction in the substantia nigra (SN) and suppressed the MPTP-induced increase in lipopolysaccharide, interleukin-1β, tumor necrosis factor-α, α-synuclein, and apoptotic factors in the SN and colon. Moreover, RJ inhibited the MPTP-mediated disruption of the tight junction barrier in the colon and blood-brain barrier of mice. Therefore, RJ alleviates MPTP-induced inflammation and dopaminergic neuronal death by maintaining mitochondrial function and tight junctions in the brain and colon.

Disclosures: H. Kim: None. **C. Bae:** None. **J. Seo:** None. **H. Lee:** None. **S. Kim:** None.

Poster

111. Transporters and Receptors: New Mechanisms and Insights

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 111.01

Topic: I.07. Data Analysis and Statistics

Title: Neurovascular unit associated aquaporin 4 (AQP4) reactivity depends on blood vessels width in the hippocampus

Authors: *N. RAHMANI, J. ADAMS, R. BRITTON, J. SIN, C. YANG, A. NGUYEN, N. VU, D. KIRSHER, D. LEONE, E. CZIRR, M. CAMPBELL;
ALKAHEST A Grifols Co., San Carlos, CA

Abstract: Aquaporin-4 (AQP4), a glial water channel expressed on the astrocytic endfeet, is an essential component of the blood-brain barrier (BBB) and important for maintaining BBB integrity. Bidirectional water transport between the astrocyte and the perivascular space is facilitated through these channels. Recent studies have shown that AQP4 expression, as well as localization, fluctuates in dysfunctional astrocytes in both aging and neurodegenerative diseases. However, the direction of the vessel associated with AQP4 expression remains unclear. Several studies identify a greater expression of AQP4 in aged or diseased mice, whereas others report the

opposite findings, implying that the precise balance of AQP4 expression may be essential for its function. For this study, we applied a variety of methods, including single-cell RNA sequencing, fluorescence imaging, and line scan analysis using ZEN microscope software to investigate AQP4 expression in the hippocampus. We utilized the line scan method to analyze the vessel associated AQP4 expression from 8 to 20 um widths within 2 um intervals. According to our findings, AQP4 expression varies dramatically with vessel width, which is more robust along specific vessel widths than others. In addition, RNA sequencing data confirmed that different vessel width have distinct gene expressions, which demonstrates the importance of vessel width when analyzing gene or protein expression. As a result, our data suggests that it's probable that some of the disparities in the literature are related to different types of vessels being analyzed. Finally, to avoid discrepancies in AQP4 analysis, we present an optimized protocol for analyzing vessels associated AQP4 in the hippocampus of mice, which is applicable in both transgenic, young, and aged mouse models.

Disclosures: N. Rahmani: None. **J. Adams:** None. **R. Britton:** None. **J. Sin:** None. **C. Yang:** None. **A. Nguyen:** None. **N. Vu:** None. **D. Kirsher:** None. **D. Leone:** None. **E. Czirr:** None. **M. Campbell:** None.

Poster

111. Transporters and Receptors: New Mechanisms and Insights

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 111.02

Topic: B.01. Transmitters, Transporters, and Other Signaling Molecules

Support: R01 NS107383
R01 GM112715
R01 NS11925

Title: Brain tissue oxygen dynamics and functional deficiency of interneurons in cerebral cortex

Authors: *D. P. AKSENOV, E. D. DOUBOVIKOV, N. A. SERDYUKOVA, D. A. GASCOIGNE, A. DROBYSHEVSKY;
NorthShore Univ. HealthSystem, NorthShore Univ. HealthSystem, Evanston, IL

Abstract: Excitatory-inhibitory balance (EIB) is the relative contribution of excitatory and inhibitory signaling, either on a single neuron or within a network. A shift in EIB towards excitation is a clinical characteristic of multiple neurological and psychiatric disorders. A possible etiology for an apparent shift towards excitation is the functional deficiency of gamma amino butyric acid (GABA)-ergic interneurons. The consequences of such an effect manifest as neuronal synchronization in the resting state. It is not clear whether such neuronal synchronization can affect brain tissue oxygen dynamics. To address this question we were able to record both neuronal activity and brain tissue oxygen signals (PO_2) simultaneously and from the same location in awake subjects. To experimentally modulate EIB in the resting state, we

were able to perform microinjections of the GABA antagonist, picrotoxin, in a concentration that was able to elicit a shift in EIB towards excitation, without producing volume effects or seizures. Our study led to the detection of two important phenomena. Firstly, a shift in EIB towards excitation resulted in the significant change in the power spectra of PO_2 oscillations. Secondly, for the first time, we were able to consistently show that that are brief periods of decreased oxygen levels (dips) during synchronized activity, which were followed by an overshoot of oxygen delivery. These findings indicate that the combination of the change in the power spectra of PO_2 oscillations and dips creates brief hypoxic conditions, and that the oxygen recovery is supported by a rapid vascular response. Furthermore, our results suggest that a shift in EIB towards excitation is potentially harmful to brain tissue, particularly considering that it is a chronic condition in multiple clinical scenarios.

Disclosures: D.P. Aksenov: None. **E.D. Doubovikov:** None. **N.A. Serdyukova:** None. **D.A. Gascoigne:** None. **A. Drobyshevsky:** None.

Poster

111. Transporters and Receptors: New Mechanisms and Insights

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 111.03

Topic: B.01. Transmitters, Transporters, and Other Signaling Molecules

Support: Grants-in-Aid for Scientific Research on Innovative Areas (Non-linear oscillology) #15H05872
Grants-in-Aid for Scientific Research (B) #21H02661
Grant-in-Aid for Transformative Research Areas（A）#21H05687

Title: Wnk3 kinase maintains neuronal excitability by regulating trafficking of kcc2 and inward rectifying k^+channels in layer v pyramidal neurons of mouse medial prefrontal cortex

Authors: *A. SINHA[1], T. WANG[1], M. WATANABE[2], E. SOHARA[3], T. AKITA[4], S. UCHIDA[3], A. FUKUDA[5];
[1]Dept. of Neurophysiol., Hamamatsu Univ. Sch. of Med., Hamamatsu, Japan; [2]Dept Neurophysiol, Hamamatsu Univ. Sch. Med., Hamamatsu, Japan; [3]Dept. of Nephrology, Tokyo Med. and Dent. Univ., Tokyo, Japan; [4]Dept. of Neurophysiology, Hamamatsu Univ. Sch. of Med., Hamamatsu, Shizuoka, Japan; [5]Dept Neurophysiol, Hamamatsu Univ. Sch. Med., Hamamatsu, Japan

Abstract: The with-no-lysine (WNK) family of serine-threonine kinases and its downstream kinases of STE20/SPS1-related proline/alanine-rich kinase (SPAK) and oxidative stress responsive kinase-1 (OSR1) regulate intracellular Cl^- homeostasis through phosphorylation of cation-Cl^- co-transporters, Na^+-K^+-$2Cl^-$ cotransporter NKCC1 and K^+-Cl^- cotransporter KCC2. WNK3 is expressed initially in fetal brain followed by a reduction after birth. Subsequently, their mRNA levels increase peaking at postnatal day 21 (P 21). Even though changes in WNK3 levels

parallel the excitatory to inhibitory switch of γ-aminobutyric acid (GABA) action, its role remains to be elucidated. Here, using a constitutive WNK3 knockout (KO) mice, we investigated the role of WNK3 in regulation of the intracellular Cl^- concentration $[Cl^-]_i$ and excitability of layer V pyramidal neurons in the medial prefrontal cortex (mPFC). Gramicidin-perforated patch-clamp recordings in neurons from acute slice preparation at P 21 showed depolarized reversal potential for $GABA_A$ receptor-mediated currents in KO neurons than wildtype (WT) neurons. However, phosphorylation levels of SPAK/OSR1 and those of NKCC1 and WNK1 did not significantly differ between KO and WT mice. In addition, total KCC2 expression levels were unchanged. Meanwhile, the resting membrane potential (RMP) of neurons was more hyperpolarized by 7 mV, resulting in rheobase current being significantly higher in KO mice. These effects were confirmed to be due to an increased inwardly rectifying K^+ conductance in KO neurons in comparison to WT neurons, mediated by classical inwardly rectifying (Kir) channels. Introduction of kinase active WNK3 fragment into the recorded neurons reversed these changes indicating phosphorylation dependent regulation of IRK currents. To confirm if KCC2 functional changes could explain both the depolarized E_{GABA} and increased IRK conductance, WNK3 KO neurons were treated with KCC2 activator drug CLP 290. The increase of IRK currents in KO neurons were reversed by enhancement of KCC2 membrane stability following CLP 290 treatment and current amplitudes were observed to be similar to WT neurons. Evaluation of synaptic transmission in mPFC revealed the frequency of miniature excitatory postsynaptic currents (mEPSCs) was reduced, whereas that of inhibitory currents was slightly increased in KO neurons. Incidentally it is well known that normal KCC2 membrane levels are important for excitatory neurotransmission. Thus, our results suggest that WNK3 plays a critical role in maintenance of neuronal excitability by regulating Cl^- homeostasis, RMP and excitatory synaptic transmission.

Disclosures: **A. Sinha:** None. **T. Wang:** None. **M. Watanabe:** None. **E. Sohara:** None. **T. Akita:** None. **S. Uchida:** None. **A. Fukuda:** None.

Poster

111. Transporters and Receptors: New Mechanisms and Insights

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 111.04

Topic: B.02. Transmitter Receptors and Ligand-Gated Ion Channels

Support: NINDS Grant NS108378

Title: Neuronal kinase LMTK3 modifies KCC2 chloride extrusion function via PP1-mediated dephosphorylation mechanism

Authors: *N. CHO[1], G. KONTOU[2], J. L. SMALLEY[2], G. GIAMAS[3], P. A. DAVIES[2], S. J. MOSS[2];
[1]Neurosci. Program, Tufts Univ. Grad. Sch. of Biomed. Sci., Boston, MA; [2]Dept. of Neurosci., Tufts Univ. Sch. of Med., Boston, MA; [3]Univ. of Sussex, Falmer, Brighton, United Kingdom

Abstract: In the adult mammalian CNS, fast hyperpolarizing postsynaptic inhibition is mediated by $GABA_A$ receptors. Deficits in GABAergic inhibitory transmission is implicated in the pathophysiology of epilepsy, anxiety, mood disorders, schizophrenia, and autism spectrum disorders. The establishment and maintenance of proper hyperpolarizing GABA signaling is dependent on the expression and activity of KCC2, a neuron-specific K^+/Cl^- cotransporter. KCC2 is dynamically regulated by phosphorylation of individual serine and threonine residues within the intracellular C-terminus. Using affinity purification coupled to LC-MS/MS, our lab has previously identified numerous proteins that comprise the KCC2 proteome on the mouse plasma membrane. Lemur tyrosine kinase 3 (LMTK3), a brain specific transmembrane serine/threonine-protein kinase, is highly enriched within KCC2-containing complexes (Smalley et al., 2020). Given the consequences of KCC2 dysfunction, it is of great interest to identify targets that can modulate KCC2 levels and transporter activity. Our current study focuses on evaluating the role of LMTK3 in regulating KCC2-mediated GABA signaling. Using biochemical experiments, immunocytochemistry, and immunohistochemistry, we have characterized the interaction between KCC2 and LMTK3 in the brain. To investigate the functional impact of LMTK3 and KCC2 in dentate granule neurons, we have utilized a whole-cell patch-clamp Cl^- loading electrophysiological assay to measure the reversal potential of $GABA_AR$-mediated currents (E_{GABA}) that reports KCC2 activity and Cl^- extrusion capacity under specific chloride loads. Our observations show a significant hyperpolarizing shift of E_{GABA} in dentate granule cells of 8-week-old $LMTK3^{-/-}$ mice. Furthermore, our immunoblotting experiments demonstrate a PP1-dependent dephosphorylation of S940-KCC2, complementing the functional downregulation of KCC2 directed by LMTK3. Our findings suggest that LMTK3 is a novel kinase regulator of inhibitory neurotransmission and we hope further investigation of the phosphorylation balance among key players that mediate GABAergic inhibition will provide a better understanding of how these are able to be modulated and used for novel therapies.

Disclosures: **N. Cho:** None. **G. Kontou:** None. **J.L. Smalley:** None. **G. Giamas:** None. **P.A. Davies:** None. **S.J. Moss:** None.

Poster

111. Transporters and Receptors: New Mechanisms and Insights

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 111.05

Topic: B.01. Transmitters, Transporters, and Other Signaling Molecules

Support: NIH R01AA025718
FONDECYT 1221080
ANID 21201459

Title: Structural evidence of the origin of glycinergic innervation in nucleus accumbens

Authors: *M. S. KONAR[1], S. S. GALLEGOS[1], H. U. ZEILHOFER[2], L. G. AGUAYO[1]; [1]Physiol., Univ. of Concepcion, Concepcion, Chile; [2]Inst. of Pharmacology, Univ. of Zurich, Zurich, Switzerland

Abstract: Few studies have been done on inhibitory glycinergic innervation in supraspinal regions. Our group recently reported the presence of glycine-mediated inhibitory synaptic currents in the nucleus accumbens (nAc). However, the origin of this glycinergic innervation remains unknown.
We used 6-month-old adult C57BL/6J male mice, which were stereotaxically injected into the nAc (coordinates: ML: +1.2 mm, AP: +1.1 mm, DV: -4.0 mm) with cholera toxin subunit B (CT-B conjugated to Alexa Fluor 546) for retrograde tracing. One week later, coronal brain sections were prepared and immunohistochemistry followed by confocal microscopy analysis were performed. We detected CT-B in an area near the 4th ventricle in midbrain neurons at bregma -4.83 mm. To test whether retrogradely labeled structures belonged to glycinergic neurons, we injected Cre recombinase-dependent pAAV-hSyn-DIO-EGFP retrograde virus into the nucleus accumbens of GlyT2::Cre mice (n=9). Four weeks later, sagittal slices containing the midbrain (lateral 0.36 mm) were examined. We found a group of EGFP^{+} neurons at 4.075 ± 0.32 mm distance from the injection site in the nAc. These midbrain neurons also exhibited immunoreactivity for Cre-recombinase and glycine. EGFP+ neurons did not express the classical GABAergic neuronal marker *Gad1*/GAD67, suggesting that this innervation is glycinergic but not GABAergic. Labeling of coronal and sagittal sections with other neuronal population antibodies led us to the conclusion that the glycinergic neurons innervating the nAc were located in the lateral periaqueductal gray (lPAG). These results demonstrate the existence of long-range glycinergic projections connecting the lPAG with the nAc. Since, the lPAG receives a variety of sensory inputs from the periphery and is a key component in many defensive and aversive behaviors, the glycinergic innervation described here may contribute to the control of nAc activation by sensory input. Our findings thus suggest a hitherto unexplored role of glycinergic inhibition in supraspinal CNS regions.

Disclosures: M.S. Konar: None. **S.S. Gallegos:** None. **H.U. Zeilhofer:** None. **L.G. Aguayo:** None.

Poster

111. Transporters and Receptors: New Mechanisms and Insights

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 111.06

Topic: B.01. Transmitters, Transporters, and Other Signaling Molecules

Title: Loss of PTEN C-terminus impairs brain glycine levels and NMDAR function through β-catenin dependent changes in transcriptome

Authors: *M. BAE[1], J. ROH[1], Y. KIM[3], S. KIM[4], H. HAN[5], E. YANG[6], H. KANG[7], S. LEE[2], J. KIM[6], R. KANG[3], H. JUNG[1], T. YOO[3], H. KIM[3], D. KIM[1], H. OH[3], S. HAN[3], D. KIM[3], J.

HAN[3], Y. BAE[5], H. KIM[6], S. AHN[4], A. CHAN[8], D. LEE[3], J. KIM[3], E. KIM[1];
[1]IBS, [2]IBS, Daejeon, Korea, Republic of; [3]KAIST, Daejeon, Korea, Republic of; [4]KRICT, Daejeon, Korea, Republic of; [5]Kyungpook Natl. Univ., Daegu, Korea, Republic of; [6]Korea Natl. Univ., seoul, Korea, Republic of; [7]KISTI, KISTI, Korea, Republic of; [8]Chinese Univ. of Hong Kong, Hong Kong, Hong Kong

Abstract: In addition to the canonical implication in the cancer field, PTEN -the lipid and protein phosphatase that antagonizes the phosphoinositide 3-kinase (PI3K) pathway- has been increasingly linked to brain development and synaptic/neuronal functions. While the lion's share of previous research has focused upon phosphatase activity of PTEN, comparatively less attention has been paid to the C-terminal tail and its function. We used a mouse line lacking the PTEN C-terminus ($Pten^{\Delta C/\Delta C}$) and studied behavioral, electrophysiological and molecular phenotypes. We find that these mice displayed noticeable increase in climbing behavior despite normal levels of locomotion and other behaviors. Electrophysiological measurements revealed reduction of excitatory synapse density in the hippocampus with corresponding decrease in excitatory transmission frequency. Moreover, both NMDAR-mediated synaptic transmission and synaptic plasticity (LTP and LTD) were impaired, which was accompanied by decrease in the extracellular brain glycine levels. Such abnormalities in synaptic plasticity as well as climbing were rescued by NMDAR activation by D-cycloserine and increasing brain glycine levels using a GlyT1 inhibitor sarcosine. Finally, in the $Pten^{\Delta C/\Delta C}$ mice, β-catenin nuclear localization was increased, which in turn led to altered transcriptomic profiles, including a candidate gene *Slc6a20a*. These results suggest that loss of PTEN C terminus in mice promotes nuclear localization of β-catenin and subsequent changes in gene transcription, which altered brain glycine level that was linked to deficit in NMDAR function and abnormal climbing behavior. Among the differentially expressed gene under control of β-catenin, a hitherto understudied transporter Slc6a20a was revealed, implying its tentative role in brain glycine regulation.

Disclosures: **M. Bae:** None. **J. Roh:** None. **Y. Kim:** None. **S. Kim:** None. **H. Han:** None. **E. Yang:** None. **H. Kang:** None. **S. Lee:** None. **J. Kim:** None. **R. Kang:** None. **H. Jung:** None. **T. Yoo:** None. **H. Kim:** None. **D. Kim:** None. **H. Oh:** None. **S. Han:** None. **D. Kim:** None. **J. Han:** None. **Y. Bae:** None. **H. Kim:** None. **S. Ahn:** None. **A. Chan:** None. **D. Lee:** None. **J. Kim:** None. **E. Kim:** None.

Poster

111. Transporters and Receptors: New Mechanisms and Insights

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 111.07

Topic: B.01. Transmitters, Transporters, and Other Signaling Molecules

Support: NIH Grant 226141323A

Title: Neuronal Expression of Glycine Transporter 1 in the CNS

Authors: *R. A. PEREZ[1], M. MIRANDA-ARANGO[2];
[1]Univ. of Texas At El Paso, EL PASO, TX; [2]Univ. of Texas at El Paso, EL PASO, TX

Abstract: Glycine is the main inhibitory neurotransmitter in caudal areas of the CNS. It participates in the regulation of sensory and motor functions. In the synaptic cleft, glycine is regulated by two membrane transporters, glycine transporter 1 and 2 (GlyT1 and GlyT2). While GlyT2 is recognized as the neuronal marker in charge of recycling glycine into presynaptic neurons, GlyT1 is in control of fast transport of glycine and termination of neurotransmission. These transporters differ in location within the CNS. Very few studies have focused on location of GlyT1 since it has been historically recognized as a glial marker. Therefore, the objective of this study is to identify the type of cells expressing GlyT1 in the mouse forebrain and midbrain. To do so, traditional immunohistochemical assays and transgenic technology were used. Results from wild type-stained tissue sections suggested the presence of cell bodies co-labeled with Neuronal Nuclei (NeuN) antibody (Ab) and GlyT1 (Ab) at the plasma membrane of midbrain and forebrain structures. Additionally, staining with glial fibrillary acidic protein (GFAP) Ab and GlyT1 Ab has shown poor colocalization in some brain structures. Furthermore, recently a knock-in mouse was created to label GlyT1 positive cells with the reporter td-Tomato. Preliminary results have shown td-Tomato expression in neurons as they were positively co-labeled with NeuN and GlyT1 antibodies in midbrain and forebrain structures. Overall, these experiments suggest that GlyT1 can be a neuronal marker in midbrain and forebrain areas. Yet, further experimentation will be done to characterize these neurons by intracranial deliver of adeno associated viral particles (AAV's) and study the expression of glial or neuronal reporters. Altogether, the data suggest neuronal expression of GlyT1 in the midbrain and forebrain exist, however location and function of these cells remain unknown.

Disclosures: R.A. Perez: None. **M. Miranda-Arango:** None.

Poster

111. Transporters and Receptors: New Mechanisms and Insights

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 111.08

Topic: B.01. Transmitters, Transporters, and Other Signaling Molecules

Support: NRF-2017R1A5A2015391
NRF-2017R1A2B3002862
NRF-2019R1C1C1010482
NRF-2017M3C7A1079692
K-18-L12-C08-S01
IBS-R002-A1
IBS-R002-D1

Title: Slc6a20a: a novel regulator of brain glycine homeostasis and NMDAR function

Authors: M. BAE[1], ***J. D. ROH**[2], Y. KIM[3], S. KIM[4], H. HAN[5], E. YANG[6], H. KANG[8], J. KIM[7], R. KANG[1], H. JUNG[1], T. YOO[1], H. KIM[1], D. KIM[1], H. OH[3], S. HAN[3], D. KIM[3], J. HAN[3], Y. BAE[9], H. KIM[10], S. AHN[4], A. M. CHAN[11], D. LEE[3], J. KIM[3], E. KIM[1];
[1]Inst. for Basic Sci. (IBS), IBS Inst. for Basic Sci., Daejon, Korea, Republic of; [2]Inst. for Basic Sci., IBS, Daejon, Korea, Republic of; [3]KAIST, Daejon, Korea, Republic of; [4]KRICT, Daejon, Korea, Republic of; [5]Kyungpook Natl. Univ., Daegu, Korea, Republic of; [7]Korea Univ., [6]Korea Univ., Seoul, Korea, Republic of; [8]KISTI, Daejon, Korea, Republic of; [9]Sch. of Dentistry, Kyungpook Natl. Univ., Sch. of Dentistry, Kyungpook Natl. Univ., Daegu, Korea, Republic of; [10]Korea Univ. Col. Med., Korea Univ. Col. Med., Seoul, Korea, Republic of; [11]Chinese Univ. of Hong Kong, Hong Kong, Hong Kong

Abstract: Glycine transporters that regulate the levels of brain glycine, a co-agonist for NMDARs, represent some of the most attractive therapeutic targets for disorders with altered NMDAR function. Canonically, GlyT1 and GlyT2 have been identified, yet whether there are other amino acid transporters with similar function remains unknown. We report that SLC6A20A, a hitherto understudied amino acid transporter thought to transport proline, regulates both proline and glycine levels, and thereby NMDAR function within the mouse brain. In a previous study, we have identified that in mice lacking PTEN C-terminus, Slc6a20A expression was increased in B-catenin dependent manner and was accompanied by decreased brain glycine levels and NMDAR function. Here, we additionally used the converse model of Slc6a20A HT for analysis. Fluorescence in situ hybridization revealed that Slc6a20 mRNA was enriched in the meninges and choroid plexus, likely placing it near the BBB. Within the Slc6a20A HT mice brain, microdialysis analyses revealed that the extracellular brain glycine levels were increased and was accompanied by significantly increased NMDA/AMPA ratio. Direct transport assay using both human Slc6a20 variants (V1 and V2) and mouse forms (slc6a20a and Slc6a20b) expressed in heterologous cells (HEK293T) revealed that both glycine and proline evoked transport currents in concentration dependent manner. Such current was sodium chloride dependent and did not show reversals at positive holding potentials. Finally, antisense oligonucleotide ASO against Slc6a20A in PTEN dC model mice successfully lowered Slc6a20A concentration and normalized brain glycine level, NMDAR function and also rescued abnormal climbing.
Our results indicate that Slc6a20A has substrate specificity for glycine in addition to proline. The meningeal and choroid plexus expression of SLC6A20A near BBB suggests that it could play a "gatekeeping" role to regulate brain glycine level and thereby NMDAR function. As such, SLC6A20 is a novel brain glycine transporter whose inhibition has therapeutic potential for brain disorders involving NMDAR hypofunction.

Disclosures: M. Bae: None. **J.D. Roh:** None. **Y. Kim:** None. **S. Kim:** None. **H. Han:** None. **E. Yang:** None. **H. Kang:** None. **J. Kim:** None. **R. Kang:** None. **H. Jung:** None. **T. Yoo:** None. **H. Kim:** None. **D. Kim:** None. **H. Oh:** None. **S. Han:** None. **D. Kim:** None. **J. Han:** None. **Y. Bae:** None. **H. Kim:** None. **S. Ahn:** None. **A.M. Chan:** None. **D. Lee:** None. **J. Kim:** None. **E. Kim:** None.

Poster

111. Transporters and Receptors: New Mechanisms and Insights

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 111.09

Topic: B.02. Transmitter Receptors and Ligand-Gated Ion Channels

Support: DFG SO328/9-1
DFG VI586/8-1
DFG GE2519/8-1
Research unit SYNABS FOR3004
GSLS Würzburg

Title: Autoantibodies against the glycine receptor bind to the extracellular receptor domain in a glycosylation-independent manner

Authors: V. RAUSCHENBERGER[1], I. PIRO[2], N. SCHAEFER[1], V. HÖRLIN[1], V. KASARAGOD[3], J. WICKEL[4], C. GEIS[4], E. TÜZÜN[5], K. DOPPLER[2], C. SOMMER[2], ***C. VILLMANN**[1];
[1]Inst. of Clin. Neurobio., [2]Dept. of Neurol., Univ. Hosp. Würzburg, Würzburg, Germany; [3]Neurobio. Div., MRC Lab. of Mol. Biol., Cambridge, United Kingdom; [4]Jena Univ. Hosp., Jena Univ. Hosp., Jena, Germany; [5]Inst. of Exptl. Med., Istanbul Univ., Istanbul, Turkey

Abstract: Glycine receptor (GlyR) autoantibodies are associated with stiff-person syndrome (SPS) or progressive encephalomyelitis with rigidity and myoclonus (PERM). SPS is characterized by stiffness and painful spasms in muscles of the lower trunk and legs, while PERM is a more complex form with additional sensory disturbance, brainstem dysfunctions, epilepsy, ataxia and/or dysautonomia. The pathology of GlyR autoantibodies includes receptor internalization and alteration of the GlyR function by receptor blocking and thus reducing inhibitory neurotransmission. GlyR autoantibodies target the extracellular receptor domain (ECD). A glycosylation site within the GlyR is closely located to the recently identified common binding epitope of GlyR autoantibodies. Protein glycosylation has been demonstrated for other autoantibodies to influence autoantibody binding. The present study investigates the importance of receptor glycosylation for binding of anti-glycine receptor autoantibodies. Although reduced, de-glycosylation of the GlyR did not prevent the receptor from surface expression. At the functional level, the de-glycosylated GlyR demonstrated reduced glycine potency, but patient GlyR autoantibodies were still able to bind to surface expressed de-glycosylated receptor protein. The previously identified common epitope in the GlyRalpha1 subunit at the N-terminus of the receptor encouraged us to use the purified the ECD to test the capacity to bind patient GlyR autoantibodies and thus to remove GlyR autoantibodies from patient sera. Preincubation of patient sera positive for GlyR autoantibodies with the purified GlyR ECD prevented binding to the native receptor expressed in HEK293 cells and primary spinal cord neurons. Similar results have been obtained for patient GlyR autoantibodies followingbinding to ECD-coated ELISA plates.Our results indicate that the glycine receptor autoantibody binding is independent of the receptor’s glycosylation state. The neutralization experiments clearly proved that purified receptor domains represent a suitable tool for fast and reliable detection auf GlyR autoantibodies which allows to screen larger cohorts for the presence of patient autoantibodies.

Disclosures: **V. Rauschenberger:** None. **I. Piro:** None. **N. Schaefer:** None. **V. Hörlin:** None. **V. Kasaragod:** None. **J. Wickel:** None. **C. Geis:** None. **E. Tüzün:** None. **K. Doppler:** None. **C. Sommer:** None. **C. Villmann:** None.

Poster

111. Transporters and Receptors: New Mechanisms and Insights

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 111.10

Topic: B.02. Transmitter Receptors and Ligand-Gated Ion Channels

Support: Swedish Research Council
Wellcome Trust
Medical Research Council

Title: A new serotonin receptor involved in learning with regulated plasma membrane trafficking

Authors: *J. MORUD[1], I. HARDEGE[2], W. R. SCHAFER[2];
[1]Univ. of Gothenburg, Gothenburg, Sweden; [2]MRC Lab. of Mol. Biol., Cambridge, United Kingdom

Abstract: Across animal phyla, monoamines signal through both metabotropic and ionotropic receptors. In worms as well as in humans, metabotropic monoamine receptors, which modulate neuronal activity through G-protein-mediated second messenger pathways, have received most attention. However, expression studies have indicated that the vast majority of *C. elegans* neurons postsynaptic to aminergic neurons do not express metabotropic amine receptors. This implies that synaptic monoamine transmission may be mediated by as yet uncharacterized ionotropic receptors. We have in our recent work identified endogenous ligands for five new amine-gated ion channels (LGC), all of which are found localised postsynaptically to aminergic neurons. In particular we have shown the serotonin-gated receptor LGC-50 to be a cation channel that is localised in the interneuron RIA, which is strongly innervated by the serotonergic neuron ADF. Previous work has indicated a role for ADF and RIA in aversive pathogen learning, through which animals learn to avoid odours released by pathogenic bacteria following infection. We have also shown that *lgc-50* mutants show a strong defect in pathogen learning, which can be rescued by expression of LGC-50 in RIA. These results suggest that serotonin may act through LGC-50 to modify the strength of specific synapses in the olfactory navigation circuit.Our recent work also indicated that the plasma membrane localisation of LGC-50 is tightly regulated, and that potential disruption of this trafficking influences memory formation. We have now identified a 17-amino acid long motif in the intracellular M3/4 domain of LGC-50 that conveys this regulated membrane localisation. Further, we have evidence that this motif might act as a binding site for the protein NRA-1 and that this protein-protein interaction might be involved in moving LGC-50 to the plasma membrane during memory formation. LGC-50 thus provides an

entry point to define the molecular and neural changes underlying learning and memory in the worm.

Disclosures: J. Morud: None. **I. Hardege:** None. **W.R. Schafer:** None.

Poster

111. Transporters and Receptors: New Mechanisms and Insights

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 111.11

Topic: B.02. Transmitter Receptors and Ligand-Gated Ion Channels

Support: NIH R21 NS125242

Title: Assessing the impact of varying zinc levels in the transcription profiles of human neurons.

Authors: *R. DEMPSKI;
Chem. and Biochem., Worcester Polytechnic Inst., Worcester, MA

Abstract: Zinc is an essential micro-nutrient that participates in catalytic and structural functions touching nearly every metabolic process in the cell. While alterations in neuronal Zn^{2+} distribution have been associated with multiple disease states including Alzheimer's Disease (AD), ALS, schizophrenia, and depression, the molecular mechanism of Zn^{2+} homeostasis in neurons is largely unexplored. The *Zinc and Iron-regulated transport Proteins* (ZIP) mediate the entrance of first row transition metals into the cytoplasm. At the same time, metallothioneins are critical chaperones which transport transition metals, including zinc, within neurons. Here, we will show how varying levels of zinc impacts the transcription profiles of proteins involved in transition metal transport and trafficking. Results from these studies initiate the definition of molecular and subcellular mechanisms of Zn^{2+} homeostasis in the brain.

Disclosures: R. Dempski: None.

Poster

111. Transporters and Receptors: New Mechanisms and Insights

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 111.12

Topic: B.02. Transmitter Receptors and Ligand-Gated Ion Channels

Support: Medical Research Council (MC-A023-5PB91)
Wellcome Trust (WT103784MA)

National Institute of Health (W.R.S.)
Swedish Research council (VR2017-00236)

Title: A novel polymodal ligand gated ion channel in C. elegans

Authors: *I. HARDEGE[1], J. E. MORUD[2], W. R. SCHAFER[1];
[1]MRC LMB, CAMBRIDGE, United Kingdom; [2]Dept. of Chem. and Mol. Biol., Univ. of Gothenburg, Gothenburg, Sweden

Abstract: Ligand-gated ion channels (LGICs) play important roles in synaptic communication and the regulation of behaviours. The cys-loop superfamily of LGICs, which contains mammalian nAChRs and GABA receptors, has undergone vast gene expansion in nematodes and includes channels gated by classical and non-classical neurotransmitters. Yet the majority of *C. elegans* LGICs remain uncharacterised. Using two-electrode voltage clamp recordings from *Xenopus* oocytes we have undertaken a deorpahnisation study of uncharacterised *C. elegans*. In this way, we identified ligands for 15 novel channels, ranging from cholinergic to monoamine-gated channels which are either excitatory or inhibitory.
Interestingly, we found a single channel, LGC-39 to be gated not only by acetylcholine but also by aminergic ligands, octopamine and tyramine. Thus LGC-39 has the capacity to form a polymodal receptor activated by chemically disparate neurotransmitters. The expression pattern of *lgc-39* reveals that it is present in neurons receiving both aminergic and cholinergic input, including AVA, the major synaptic target of the octopamine producing neurons. Fluorescent tagging of LGC-39 using CRISPR reveals that it is synaptically localised. Behavioural tracking experiments indicate that *lgc-39* mutant worms display altered reversal behaviours. By making specific point mutations within the ligand binding domain of LGC-39 we were able to alter ligand preference, we aim to use these mutant forms of the channel to identify which ligand mediates these *lgc-39* specific reversal phenotypes. In addition, we are in the process of undertaking structural studies of LGC-39 to investigate the molecular mechanism of ligand binding for this unique channel.

Disclosures: I. Hardege: None. **J.E. Morud:** None. **W.R. Schafer:** None.

Poster

111. Transporters and Receptors: New Mechanisms and Insights

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 111.13

Topic: B.02. Transmitter Receptors and Ligand-Gated Ion Channels

Support: AHA 19AIREA34470007

Title: Subunit-dependent potentiation of acid-sensing ion channel currents by cyanide

Authors: *X.-P. CHU, Q. JIANG, V. CEGIELSKI, M. WILLIAM, A. SIVILS, X.-M. ZHA;
Univ. of Missouri Kansas City, Kansas City, MO

Abstract: Cyanide (CN) is a rapid-acting toxicant and profoundly targets endogenous biomolecules in the nervous system including acid-sensing ion channels (ASICs), which play critical roles in neurological and psychological diseases. Here, we found that CN rapidly and dose-dependently potentiated the ASIC currents in cultured mouse cortical neurons and left-ward shifted the pH dose-response curve. Neither half-hour treatment of CN nor with or without of ATP in the recording pipette changed the rapid potentiation of ASIC currents in cortical neurons. Next, TPEN, a high-affinity zinc chelator, did not enhance the ASIC currents under CN pretreatment. CN also did not change the ASIC potentiation by TPEN pretreatment. The potentiation of the ASIC currents by CN was further inhibited or unchanged by treatment with low-affinity zinc. Pretreatment with low-affinity zinc blocked the potentiation of the ASIC currents by CN. Further, CN increased the ASIC currents on cultured cortical neurons from ASIC2, but not from ASIC1 knockout mouse. Moreover, CN potentiated the ASIC currents recorded from CHO cells expressing homomeric ASIC1a and heteromeric ASIC1a/2, but not homomeric ASIC1b, 2a and 3 channels. Lastly, we mutated lysine 133 (K133) to arginine (R) in the extracellular domain of ASIC1a subunit, which is responsible for high-affinity zinc effect on ASIC1a, CN had no effect on currents recorded from ASIC1a-K133R mutation. Collectively, our data suggest that potentiation of ASIC1a currents by CN is largely due to its high-affinity zinc binding effect and K133 in the extracellular domain of the ASIC1a subunit is responsible for this effect.

Disclosures: X. Chu: None. **Q. Jiang:** None. **V. Cegielski:** None. **M. William:** None. **A. Sivils:** None. **X. Zha:** None.

Poster

112. Presynaptic Organization and Synaptic Vesicle Dynamics

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 112.01

Topic: B.04. Synaptic Transmission

Support: ERC Advanced Grant 694539

Title: Induction of phasic neurotransmitter release via presynaptic $GABA_B$ receptors on medial habenula terminals

Authors: *P. KOPPENSTEINER[1], P. BHANDARI[1], C. ÖNAL[1], C. BORGES-MERJANE[1], E. LE MONNIER[1], Y. NAKAMURA[2], T. SADAKATA[3], N. BROSE[4], P. JONAS[1], R. SHIGEMOTO[1];
[1]Inst. of Sci. and Technol. Austria (ISTA), Klosterneuburg, Austria; [2]Dept. of Pharmacol., Jikei Univ. Sch. of Med., Tokyo, Japan; [3]Educ. and Res. Support Ctr., Gunma Univ. Grad. Sch. of Med., Gunma, Japan; [4]Dept. of Mol. Neurobio., Max Planck Inst. of Exptl. Med., Göttingen, Germany

Abstract: Activation of presynaptic $GABA_B$ receptors (GBR) reduces neurotransmitter release at most synapses. The only known exception is the synaptic connection from the medial habenula (MHb) to the interpeduncular nucleus (IPN), showing a several-fold increase in neurotransmitter release (Bhandari et al., 2021, eLife 10:e68274). To identify the underlying mechanism of GBR-mediated potentiation, we measured postsynaptic currents in response to 10-Hz electrical stimulations of mouse MHb axons in IPN neurons in 1 mm-thick slices at room temperature. Our electrophysiological results indicate that application of the GBR agonist baclofen (1 µM) induces a transition in the mode of neurotransmitter release from tonic to phasic release. This transition was mediated by a 3.5 ± 0.6-fold increase in the readily releasable vesicle pool size and a 2.3 ± 0.3-fold increase in release probability (n=17 recordings from 7 mice). To study the structural correlate of GBR-mediated potentiation, we performed timed high-pressure freezing after optogenetic stimulation of MHb terminals ("Flash and Freeze") in ChAT-ChR2-EYFP mice. We discovered that phasic release was associated with a 3.5 ± 0.4-fold increase in the density of docked synaptic vesicles. Furthermore, we identified two vesicle-associated proteins selectively involved in either tonic or phasic release. The augmentation of tonic release was attenuated in synaptoporin-deficient mice, and activity-dependent storage of phasic release sites was impaired in Ca^{2+}-dependent activator protein for secretion 2 (CAPS2)-deficient mice. Finally, we developed a new method, called "Flash and Freeze-Fracture", visualizing the insertion of synaptoporin and CAPS2 into the presynaptic active zone during tonic and phasic neurotransmission, respectively. In conclusion, we identified an unexpected two-pool mechanism underlying the potentiation of neurotransmitter release following GBR activation in MHb terminals.

Disclosures: P. Koppensteiner: None. **P. Bhandari:** None. **C. Önal:** None. **C. Borges-Merjane:** None. **E. Le Monnier:** None. **Y. Nakamura:** None. **T. Sadakata:** None. **N. Brose:** None. **P. Jonas:** None. **R. Shigemoto:** None.

Poster

112. Presynaptic Organization and Synaptic Vesicle Dynamics

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 112.02

Topic: B.04. Synaptic Transmission

Support: NIH Grant GM130459
NIH Grant NS117686
NSF Grant 1943514

Title: Dissecting multifaceted roles of dynamin-related protein 1 with subcellular targeting

Authors: S. CHOWDHRY[1], P. XU[1], K. ITOH[2], Y. ADACHI[2], I. ROK[1], S. SWAIN[1], H. SESAKI[2], ***R. RENDEN**[1];
[1]Univ. of Nevada, Reno Sch. of Med., Reno, NV; [2]Johns Hopkins Univ. Sch. of Med., Baltimore, MD

Abstract: Dynamin-related Protein 1 (DRP1) is the primary mediator of mitochondrial fission and is recruited to the mitochondrial outer membrane by multiple fission adapters. DRP1 has also been localized to plasma membrane, where it may act to facilitate synaptic membrane retrieval: both postsynaptic receptor endocytosis and compensatory SV retrieval and biogenesis are affected when DRP1 is eliminated. We previously examined the role of DRP1 at the calyx of Held, an extremely well-characterized synapse amenable to careful inspection of SV recycling and synaptic transmission. Selective loss of DRP1 in the calyx terminal profoundly impairs synaptic transmission, with reduced releasable pool of vesicles, and slowed pool replenishment. We also see an increase in cytosolic Ca2+ during activity, and loss of mitochondrial Ca2+ retention following presynaptic depolarization. Capacitance measurements of the calyx membrane, used to monitor SV exo/endocytosis, show a deficit in SV retrieval when DRP1 is absent, suggesting a direct role in SV recycling. Notably, SV endocytosis and transmission were also impaired at the calyx of Held in mouse KOs for $DRP1_{ABCD}$, a membrane-associated splice isoform found in brain. Mitochondrial morphology and respiration is intact in $DRP1_{ABCD}$ knockouts, suggesting DRP1 facilitates SV retrieval and recycling directly. We also examine colocalization of DRP1 with mediators of SV endocytosis at calyx of Held active zones using super-resolved STED imaging. We attempt to dissect the role of DRP1 in mitochondrial and synaptic membrane fission, by targeting DRP1 expression to mitochondria outer membrane or the plasma membrane, respectively. Mouse embryonic fibroblasts (MEFs) were used to screen constructs containing GFP-tagged DRP1 with in-frame localization signals inserted in the variable domain. MEFs lacking mitochondrial fission factor (MFF) were used to confirm that localization was not occurring via adapter protein interaction. Rescuing DRP1 mitochondrial fission in DRP1-KO MEFs were used to validate that function was retained. Organelle-targeted DRP1 constructs will clarify the importance of multifaceted roles of DRP1 at neuronal synapses.

Disclosures: S. Chowdhry: None. **P. Xu:** None. **K. Itoh:** None. **Y. Adachi:** None. **I. Rok:** None. **S. Swain:** None. **H. Sesaki:** None. **R. Renden:** None.

Poster

112. Presynaptic Organization and Synaptic Vesicle Dynamics

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 112.03

Topic: B.04. Synaptic Transmission

Support: R01NS110533

Title: Sphk1/s1p axis regulates synaptic vesicle endocytosis via trpc5 channels

Authors: *Z. JIANG, L.-W. GONG;
Univ. of Illinois at Chicago, Chicago, IL

Abstract: Synaptic vesicle endocytosis is indispensable for normal brain functions and deficiency in endocytic machinery has been highlighted in many neurological disorders,

including Huntington's disease and Alzheimer's disease. Defects of synaptic vesicle endocytosis and altered SphK1/S1P (sphingosine-1-phosphate) metabolisms have been concurrently identified as pathological features for these neurodegenerative disorders, however, it remains largely unknown whether SphK1/S1P axis may regulate synaptic vesicle endocytosis in neurons. In the present study, we evaluate any potential functions of SphK1/S1P axis in synaptic vesicle endocytosis by determining effects of a dominant negative catalytically inactive SphK1 ($SphK1^{DN}$) in neurons and neuroendocrine chromaffin cells. Our data from sypHy based live-cell imaging in neurons and cell-attached capacitance recording in neuroendocrine chromaffin cells, identifies a critical role of SphK1/S1P axis in endocytosis in neurons and neuroendocrine chromaffin cells for the first time. Furthermore, our Ca^{2+} imaging study indicates that SphK1/S1P axis may be important for presynaptic Ca^{2+} influx during prolonged stimulations by regulating the Ca^{2+} permeable TRPC5 channels, which *per se* regulates the kinetics of synaptic vesicle endocytosis. Collectively, our findings point out that SphK1/S1P axis may be important for synaptic vesicle endocytosis via its regulation of TRPC5 channels in neurons.

Disclosures: Z. Jiang: None. **L. Gong:** None.

Poster

112. Presynaptic Organization and Synaptic Vesicle Dynamics

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 112.04

Topic: B.04. Synaptic Transmission

Support: The Wellcome Trust Strategic Award 104033/z/14/z
Epilepsy Research UK Project Grant P1806
The Wellcome Trust PhD Studentship 203795/Z/16/Z
Medical Research Council UK Project Grant MR/T002786/1

Title: Asynchronous glutamate release is enhanced in low release efficacy synapses and dispersed across the active zone

Authors: P. MENDONCA[1], E. TAGLIATTI[1], H. LANGLEY[1], D. KOTZADIMITRIOU[1], C. ZAMORA-CHIMAL[2], Y. TIMOFEEVA[2], *K. VOLYNSKI[1];
[1]UCL Queen Square Inst. of Neurol., London, United Kingdom; [2]Dept. of Computer Sci., Univ. of Warwick, Coventry, United Kingdom

Abstract: The balance between fast synchronous and delayed asynchronous release of neurotransmitters has a major role in defining computational properties of neuronal synapses and regulation of neuronal network activity. However, how it is tuned at the single synapse level remains poorly understood. Here, using the fluorescent glutamate sensor SF-iGluSnFR, we image quantal vesicular release in tens to hundreds of individual synaptic outputs from single pyramidal cells with 4 millisecond temporal and 75 nm spatial resolution. We find that the ratio between synchronous and asynchronous synaptic vesicle exocytosis varies extensively among

synapses supplied by the same axon, and that the synchronicity of release is reduced at low release probability synapses. We further demonstrate that asynchronous exocytosis sites are more widely distributed within the release area than synchronous sites. These findings are consistent with a model in which functional presynaptic properties are regulated via a synapse-specific adjustment of the coupling distance between presynaptic calcium channels and release-ready synaptic vesicles. Together, our results reveal a universal relationship between the two major functional properties of synapses - the timing and the overall efficacy of neurotransmitter release.

Disclosures: P. Mendonca: None. **E. Tagliatti:** None. **H. Langley:** None. **D. Kotzadimitriou:** None. **C. Zamora-Chimal:** None. **Y. Timofeeva:** None. **K. Volynski:** None.

Poster

112. Presynaptic Organization and Synaptic Vesicle Dynamics

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 112.05

Topic: B.04. Synaptic Transmission

Support: ISF 1310/19

Title: Differences in the synaptic function of human and murine alpha-synuclein

Authors: H. RIBA, A. STAVSKY, *D. GITLER;
Dept. of Physiol. and Cell Biol., Ben-Gurion Univ. of the Negev, Beer-Sheva, Israel

Abstract: Alpha-synuclein (α-syn) is an abundant presynaptic protein that associates with the surface of synaptic vesicles (SVs). It is the main component of Lewy bodies, abnormal protein aggregates that serve as a hallmark of both sporadic and familial forms of Parkinson's disease (PD). While its physiological role in the synapse is still elusive, recent studies propose it is an attenuator of synaptic transmission and that it regulates SV clustering next to the active zone. Specifically, when human α-syn (h-α-syn) is over-expressed in mouse neurons, either by viral transduction or in transgenic mice, it inhibits SV recycling and disperses the SV clusters. Murine α-syn (m-α-syn) and h-α-syn are 95% identical, differing in 7 out of their 140 amino acids (human->murine: A53T, S87N, L100M, N103G, A107Y, D121G, and N122S). We found that, unlike h-α-syn, m-α-syn does not attenuate SV recycling, as measured using synaptophysin-pHluorin, a sensor of exocytosis/endocytosis. Furthermore, by analyzing the presynaptic distribution and density of vGlut1, an SV marker in glutamatergic neurons, we found that over-expression of h-α-syn disperses the SV clusters, but the quantitatively-comparable expression of m-α-syn did not have this effect. Our results thus illustrate significant functional differences between these two homologous proteins. Intriguingly, A53T is a major PD-related mutation in h-α-syn; we confirmed that the A53T mutation conserves the capability of h-α-syn to inhibit SV recycling. Thus, the functional divergence between the two proteins is linked to one or more of the other differences between them.

Disclosures: H. Riba: None. **A. Stavsky:** None. **D. Gitler:** None.

Poster

112. Presynaptic Organization and Synaptic Vesicle Dynamics

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 112.06

Topic: B.04. Synaptic Transmission

Title: Effects of the human cognition-enhancing CORD7 mutation on Drosophila melanogaster abdominal wall muscle 4 NMJ, containing exclusively tonic 1b boutons

Authors: *Z. POSGAY[1], S. DANNHÄUSER[1], M. PAUL[1,2], A. MRESTANI[1,3], M. HECKMANN[1];
[1]Neurophysiol., Univ. Wuerzburg - Inst. of Physiol., Wuerzburg, Germany; [2]Orthopaedic Trauma, Hand, Plastic and Reconstructive Surgery, Univ. Hosp. of Wuerzburg, Wuerzburg, Germany; [3]Neurol., Leipzig Univ. Med. Ctr., Leipzig, Germany

Abstract: The autosomal dominant cone-rod dystrophy 7 (CORD7) mutation is caused by a point mutation in the Rab3A interacting molecule 1 (RIM1) gene (Michaelides et al., 2005). This Arg844His mutation leads to progressive loss of the retinal photoreceptors, causing continuously decreased central and peripheral vision but in a fascinating way, it is also concomitant with increased cognitive abilities in verbal and executive domains (Sisodiya et al., 2007). The mutation affects synaptic function and increases active zone number and synaptic release, as shown at the Drosophila melanogaster neuromuscular junction (NMJ) on abdominal wall muscle 6/7 containing both, 1b and 1s boutons (Paul et al., 2022). The two types of boutons differ in structure and function (Atwood & Karunanithi, 2002; Aponte-Santiago & Littleton, 2020). Therefore, we turned to third instar, male Drosophila larval NMJs in segments A2 and A3 of abdominal wall muscle 4, which is innervated only by tonic 1b boutons. We used a combination of the immunohistochemical markers α-BrpNc82, Alexa Fluor488 and α-horseradish peroxidase conjugated Cy3 in RIM^{rescue} (32 NMJs of 16 animals) and $RIM^{R>H}$ (28 NMJs of 16 animals) larvae. The analysis of 1b endings revealed an increase in length, longest branch length, number of 1b boutons and number of active zones per NMJ in $RIM^{R>H}$ larvae compared to controls (RIM^{rescue}), as shown by parametric, unpaired t-test. As a next step, functional characterization will be performed using two-electrode voltage clamp (TEVC) recordings and focal electrophysiological recordings. Furthermore, imaging using direct stochastic optical reconstruction microscopy (*d*STORM) is in preparation.

Disclosures: Z. Posgay: None. **S. Dannhäuser:** None. **M. Paul:** None. **A. Mrestani:** None. **M. Heckmann:** None.

Poster

112. Presynaptic Organization and Synaptic Vesicle Dynamics

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 112.07

Topic: B.04. Synaptic Transmission

Support: SFB1089
SPP1757
INST1172 15
DI853/3-5&7
INST 217/785-1

Title: Quantification of the number and mobility of presynaptic RIM1 molecules using single synapse spectroscopy

Authors: *G. VAN DYK[1], J. SANTOS-TEJEDOR[2], S. SCHOCH[2], D. DIETRICH[1];
[1]Dept. of Neurosurg., [2]Dept. of Neuropathology, Univ. clinic Bonn, Bonn, Germany

Abstract: RIM1 proteins are integral regulators of synaptic function and strength. However, so far little is known about their abundance and mobility within the active zone (AZ) of a presynapse. We addressed this question by applying 2-photon fluorescence correlation spectroscopy (2ph-FCS) in the context of single cortical synapses expressing RIM1 or single RIM1 domains fused to the fluorescent reporter GFP. We directed our Ti:Sa IR laser on top of single synapses, thereby enclosing the putative AZ in a tiny observation volume of approximately 0.2 fl. As the GFP fused RIM1 proteins traverse this observational volume, they give rise to fluorescent fluctuations, that are collected over time. Through autocorrelation analysis and subsequent fitting of a “free 3D-diffusion model”, we could estimate the average number of RIM1 molecules per synapse and more specifically, in the AZ. Moreover, we often times found two RIM1 fractions with diverging mobilities. One generally smaller fraction, with a much lower diffusion coefficient, that we think is due to a very tight integration of some RIM1 molecules into the AZ and a larger and more mobile fraction that we assume represents the cytoplasmic pool of RIM1 proteins. As a first step, we wanted to probe if one of RIM1’s structural domains mediates the tight integration of the protein into the cytomatrix at the AZ. To this end, we examined the properties of four RIM1 truncation mutants, each containing one of the domains, namely ZN, PDZ, C2A and C2B and flanking sequences. We found that, especially the RIM1 C2B domain appears to be a likely candidate for AZ anchoring, because it also had a relatively high fraction of very low-mobility entities. Now, combining these findings with unpublished STORM data from our lab, we could estimate the number of RIM1 molecules per release site. We found that a small fraction of RIM1 molecules in a synapse can be virtually immobile compared to a larger more mobile fraction within the same synapse. We think of this “low diffusion coefficient fraction” as tightly integrated RIM1 molecules in the cytomatrix of the AZ. We also estimate that less than 10 RIM1 proteins are associated with one release site.

Disclosures: G. van Dyk: None. **J. Santos-Tejedor:** None. **S. Schoch:** None. **D. Dietrich:** None.

Poster

112. Presynaptic Organization and Synaptic Vesicle Dynamics

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 112.08

Topic: B.04. Synaptic Transmission

Support: R37-MH080046
R01-MH119826

Title: An optical analysis framework for measuring the presynaptic function of individual synapses using GluSnFR3

Authors: *S. T. BARLOW, T. A. BLANPIED;
Dept. of Physiol., Univ. of Maryland Sch. of Med., Baltimore, MD

Abstract: Over the last decade, rapid progress in the development of fluorescent protein sensors for neurotransmitter release has made optical measurements of presynaptic function possible at the level of individual synapses. Specifically, the newest version of the intensity-based glutamate sensing fluorescent reporter (GluSnFR3) possesses excellent on/off kinetics, improved ΔF/F upon glutamate binding, and traffics readily to the synapse, where it can sense glutamate release from putative single vesicles. GluSnFR3 thus exhibits extraordinary promise for unpacking fundamental properties of presynaptic function, from profiling the intrinsic heterogeneity of presynaptic release properties *in vitro* and in specific circuits, to identifying where and when specific glutamate release modes (e.g. synchronous, asynchronous, or spontaneous) occur within the synapse relative to different Ca^{2+} channel sub-types. Understanding these fundamental qualities of presynaptic function are likely a precondition to appreciating how they are disrupted in disease-associated states.
While GluSnFR3 enables the measurement of presynaptic function at tens to hundreds of synapses in parallel, extracting information from these optical recordings in an efficient and unbiased manner requires the development of new analysis frameworks. Here we present an analysis pipeline to extract presynaptic functional properties (e.g. release probability, frequency, and quantal content) of individual synapses using GluSnFR3 during electrical stimulation or action potential-independent paradigms. The pipeline extracts intensity-time traces from automatically segmented, putative synapses according to their GluSnFR3 activity. As regions-of-interest display broad variation in noise levels and baseline stability, we implement an iterative outlier detection approach which enables flexible identification of the baseline across a variety of trace conditions and improves the accuracy and precision with which we can determine GluSnFR3 ΔF/F. After peak identification, we implement an exponential decay fitting routine for peak quantification and post-hoc quality control. By deploying these routines in parallel with spatial analysis, we can characterize glutamate release at identified synapses in cultured neurons, including identification of putative glutamate release mode, subsynaptic release site position, and correlation with concurrent optical readout of postsynaptic activity.

Disclosures: S.T. Barlow: None. **T.A. Blanpied:** None.

Poster

112. Presynaptic Organization and Synaptic Vesicle Dynamics

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 112.09

Topic: B.04. Synaptic Transmission

Support: NIH Grant NS096092

Title: Presynaptic diversity of PV GABAergic inputs on subicular pyramidal cells

Authors: *N. CASTRO BORJAS, G. MACCAFERRI;
Neurosci., Northwestern Univ., Chicago, IL

Abstract: The subiculum is an important brain region involved in complex physiological functions, and has been suggested to initiate pathological activity in epileptic patients. Although many studies have already unequivocally established the presence of a strong dichotomy of subicular pyramidal neurons (based on their membrane properties and excitability (Fiske et al., 2020), the diversity of the inhibitory presynaptic inputs that they receive has remained virtually unexplored. Yet, this is critical for understanding how these two diverse classes of pyramidal neurons are physiologically controlled by specific populations of GABAergic cells. Furthermore, as subicular parvalbumin-expressing interneurons (PVs) may drive epileptiform activity (Anstötz et al., 2021), functional differences in their terminals targeting specific subtypes of postsynaptic pyramidal cells may reveal novel points of circuit regulation and/or vulnerability. We directly compared the role of specific subtypes of voltage-gated calcium channels in governing the release of GABA from PVs onto regular firing (RF) and intrinsically bursting (IB) pyramidal neurons. In order to classify cells, their excitability and firing patterns were initially evaluated using potassium-based intracellular solutions. Then, the same neurons were re-patched with pipettes containing cesium and QX314 and held in voltage-clamp at +10 mV to record outward inhibitory postsynaptic currents (IPSCs), which were triggered by brief blue light pulses (0.5 ms) in slices prepared from PV-channelrhodopsin mice. IPSCs were recorded at 0.1 Hz and, after a baseline of 3 minutes, selective blockers of either N- or P/Q-type voltage-gated calcium channels were applied (ω-Conotoxin GVIA, 1μM and ω-Agatoxin IVA, 630 nM, respectively). ω-Conotoxin had little effect on the responses as it reduced the IPSC amplitude by 25.7 ± 3.1% in RF (n= 14) and by 21.1 ± 2.5% in IB (n=14) pyramidal cells. In contrast, the application of ω-Agatoxin IVA completely abolished the IPSCs in both cell subtypes (n=14 RF and n=14 IB cells). No sex-related differences were observed. We conclude that specific subtypes of subicular pyramidal neurons receive GABAergic input from PVs that in both cases is mostly controlled by presynaptic P/Q voltage-gated calcium channels.

Disclosures: N. Castro Borjas: None. **G. Maccaferri:** None.

Poster

112. Presynaptic Organization and Synaptic Vesicle Dynamics

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 112.10

Topic: B.04. Synaptic Transmission

Support: Korea NRF Grant 2017R1C1B3005476
Korea NRF Grant 2020R1A2C1005492
Korea NRF Grant 2021R1A4A1031644
Korea NRF Grant 2022M325E8017907

Title: Gabaergic-like dopamine synapses in health and parkinson's disease

Authors: *H.-J. KIM[1], B. HWANG[2], M. REVA[3], J. LEE[1], B. LEE[1], Y. LEE[1], E. CHO[1], S. LEE[4], K. MYUNG[5], J.-H. BAIK[6], J.-H. PARK[2], J.-I. KIM[1];
[1]Dept. of Biol. Sci., [2]Dept. of Biomed. Engin., UNIST, Ulsan, Korea, Republic of; [3]BBP, EPFL, Geneva, Switzerland; [4]Dept. of Res. Animal Resource Ctr., Korea Inst. of Sci. and Technol., Seoul, Korea, Republic of; [5]Dept. of Ctr. for Genomic Integrity, Inst. for Basic Sci., Ulsan, Korea, Republic of; [6]Dept. of Life Sci., Korea Univ., Seoul, Korea, Republic of

Abstract: Dopaminergic neurons exist in the midbrain and their axons establish synapses throughout the whole brain. Synaptic transmission at these synapses is crucial for volitional movement and reward-related behaviors, while dysfunction of these synapses causes various psychiatric and neurological disorders. Despite this significance, true biological nature of dopamine synapses remains poorly understood due to difficulties defining functional dopamine synapses at the molecular and physiological levels. Here we show that GABA co-transmission co-exists with dopamine transmission across the brain and a significant portion of dopamine synapses are structured and function like GABAergic synapses with marked regional heterogeneity, which we call GABAergic-like dopamine synapses identified by triple co-localization of tyrosine hydroxylase (TH), bassoon, and neuroligin-2 (NL2). GABAergic-like dopamine synapses show higher density, but lower clustered patterns compared to conventional GABAergic synapses on the dendrites of spiny projection neurons in the dorsal striatum. Moreover, GABA transmission at dopamine synapses has physiological properties distinct from conventional GABA transmission in terms of its calcium channel dependency and quantal properties. Interestingly, 6 weeks knockdown of NL2, a key postsynaptic protein at GABAergic synapses, unexpectedly does not weaken GABA co-transmission but instead temporarily facilitates it at dopamine synapses in striatal neurons. As expected, longer periods of NL2 knockdown (12 weeks) significantly diminishes GABA co-transmission. On the other hand, dopamine transmission and GABAergic-like dopamine synapses are considerably downregulated in both 6 weeks and 12 weeks of NL2 knockdown. More importantly, the attenuation of GABA co-transmission precedes deficits in dopaminergic transmission in animal models of Parkinson’s disease. Our findings reveal unknown spatial and functional nature of GABAergic-like dopamine synapses in health and disease. Furthermore, the broader implication of our results is that GABAergic-like features of dopamine synapses can be utilized to better understand the real complexity of synaptic actions at dopamine synapses in regulating neural circuits.

Disclosures: **H. Kim:** None. **B. Hwang:** None. **M. Reva:** None. **J. Lee:** None. **B. Lee:** None. **Y. Lee:** None. **E. Cho:** None. **S. Lee:** None. **K. Myung:** None. **J. Baik:** None. **J. Park:** None. **J. Kim:** None.

Poster

112. Presynaptic Organization and Synaptic Vesicle Dynamics

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 112.11

Topic: B.04. Synaptic Transmission

Support: 1K99GM141449-01
4R00GM141449-03
The Frazier Institute at McLean Hospital

Title: Determining the neural circuits underlying female aggression in Drosophila

Authors: K. M. MARTINEZ, I. J. SANTIAGO, S. SENGUPTA, *C. B. PALAVICINO-MAGGIO;
Basic Neurosci., McLean Hosp., Belmont, MA

Abstract: Aggression is an intrinsic behavior that aids in defense, resources, and survival. While both males and females elicit aggression, female aggression research has received less attention. Previously, our work in *Drosophila* identified a female-specific subgroup of cells in the pC1 brain region, known as pC1α neurons (Palavicino-Maggio et al., 2019; Schretter et al., 2020; Deutsch et al., 2020). Activation of pC1α neurons triggered female flies to fight at high intensity levels. With this observance, our aim was to identify the neuronal clusters that relay sensory information to the pC1α neurons and ultimately lead to the activation of the female high aggression circuitry. To build on the circuitry of the pC1α neurons, our lab used available electron microscopy database of the adult female fruit fly brain (FAFB). Our tracings revealed that pC1α neurons are morphologically distinct and present in both hemispheres of the female brain and are comprised of five neurons (pC1a-e). It also revealed interconnectivity between five subtypes. In general, pC1α neurons exhibited interconnectivity within the hemisphere (ipsilateral) and between hemispheres (contralateral). Interestingly, we uncovered several asymmetries in connectivity between and within the right and left hemisphere. We determined that pC1α neurons in the right hemisphere exhibit interconnectivity, while those in the left hemisphere do not. Additionally, we found more contralateral connections from left to right (207) than right to left (50). We also searched for non- pC1α neurons that send presynaptic inputs into the pC1α population. One major input contributor and presynaptic partner, the SMP093 L/R neurons, is in the superior medial protocerebrum (SMP) area, which is involved in circadian rhythm, feeding, and courting behavior. SMP093 showed a great deal of projections onto the left and right pC1α neurons indicating inputs not only bilaterally (L>R:263; R>L:157) but having interconnectivity (L>L: 163; R>R:387). Although it was examined that the left had a limited interconnectivity, SMP093 L/R showed strong projections to those left pC1α neurons

(320). We thus hypothesize that neurons found in the SMP region play a vital role in the circuitry of female aggression. Since pC1α neurons are only found in females, understanding how the circuitry behind fruit fly aggression works can be used to find new principles of how a sexually dimorphic brain works. In addition, this model might serve as a foundation for the development of sex-specific of therapeutic targets that can ameliorate aggression behavioral abnormalities observed in disease.

Disclosures: K.M. Martinez: None. **I.J. Santiago:** None. **S. Sengupta:** None. **C.B. Palavicino-Maggio:** None.

Poster

112. Presynaptic Organization and Synaptic Vesicle Dynamics

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 112.12

Topic: B.04. Synaptic Transmission

Support: NIH F31NS122424
NIH R01 NS078179

Title: Calcium channels and their auxiliary subunits in establishing diverse synaptic properties

Authors: A. T. MEDEIROS, S. J. GRATZ, A. DELGADO, K. M. O'CONNOR-GILES; Neurosci., Brown Univ., Providence, RI

Abstract: Communication in the nervous system is mediated by neurotransmission at synapses, where Ca2+ influx triggers neurotransmitter release at specialized synaptic sites called active zones. Clustered Ca2+ channels at active zones result in higher concentrations of localized intracellular Ca2+, which increases synaptic probability of release. Channel levels have been shown to correlate with release probability in some cases, but not others, so we investigated Ca2+ channel organization at synapses of distinct functions to understand their role in determining synaptic release properties. Here, I take advantage of two motor neuron subtypes at the Drosophila neuromuscular junction, type Ib and type Is. Type Is synapses have higher probability of release and action potential-induced Ca2+ influx than Ib. Using functional Ca2+ imaging at single synapses we found that Ca2+ channel levels correlate with probability of release at type Ib and type Is active zones, indicating that Ca2+ channel levels predict synaptic release properties at these two subtypes. However, we found that average per synapse Ca2+ channel levels are similar at the two subtypes despite their distinct release probabilities, supporting a model that channel levels predict probability of release within a synaptic subtype, but not between them. We hypothesize that this is due to differences in molecular organization between synapse subtypes, so I assessed the levels of key Ca2+ channel-interacting active zone proteins, Bruchpilot (Brp) and Rim-Binding Protein (RBP), and observed lower levels of both proteins at type Is synapses. Beyond the pore-forming subunit, physiological Ca2+ currents through Ca2+ channels require auxiliary subunits, which influence channel organization and

function, specifically β and α2δ subunits. To determine auxiliary subunit molecular composition at type Ib and Is synapses, I used CRISPR to endogenously tag the sole Drosophila β subunit Ca-beta, and the three α2δ subunits, Straightjacket, Stolid and Ma2d. I found that Ca-beta and Straightjacket are expressed at Ib and Is synapses, whereas Stolid is not present at either. Ma2d is still under investigation. Ca-beta levels are similar between the two synaptic subtypes, whereas Straightjacket levels, like Brp and Rbp, are lower at type Is synapses. My findings support the model that differences in the molecular organization of type Ib and Is synapses may influence the role of Ca2+ channel levels in establishing release properties. I am currently using superresolution imaging to probe sub-synaptic organization to gain insight into how distinct release probabilities are established to support effective neural communication.

Disclosures: A.T. Medeiros: None. **S.J. Gratz:** None. **A. Delgado:** None. **K.M. O'Connor-Giles:** None.

Poster

112. Presynaptic Organization and Synaptic Vesicle Dynamics

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 112.13

Topic: B.04. Synaptic Transmission

Support: R01 MH084989 to K.B

Title: Fragile X mental retardation protein regulates corkscrew/SHP2 phosphatase translation to control MAPK-dependent presynaptic transmission

Authors: *S. N. LEAHY, C. SONG, D. J. VITA, K. BROADIE;
Biol. Sci., Vanderbilt Univ., Nashville, TN

Abstract: Noonan syndrome (NS) and NS with Multiple Lentigines (NSML) patients exhibit cognitive dysfunction resulting from SH2 domain-containing protein tyrosine phosphatase-2 (SHP2) gain-of function (GOF) and loss-of-function (LOF), respectively. SHP2 is a protein tyrosine phosphatase that acts downstream of receptor tyrosine kinase (RTK) function, operating as a core regulator of MAPK/ERK signaling. It is well established that both SHP2 LOF/GOF mutations similarly upregulate this key signaling cascade. We hypothesized that elevated MAPK/ERK signaling driving altered synaptic transmission could be a mechanistic foundation for the cognitive deficits in NS/NSML patients. To address this hypothesis, we used *Drosophila* NS/NSML disease models to assay both human patient-derived SHP2 mutants and *Drosophila* homolog *corkscrew* (*csw*) mutants. As a glutamatergic model synapse, we used the very well-characterized *Drosophila* neuromuscular junction (NMJ). We find that patient-derived SHP2 LOF/GOF mutations and *csw* homolog LOF/GOF mutations all elevate glutamatergic transmission. Cell-targeted *csw* RNAi and neurotransmitter release analyses both reveal a consistent presynaptic requirement. Moreover, mutants exhibit reduced synaptic depression and neurotransmission fatigue during high frequency stimulation. Both LOF and GOF mutants also

display impaired synaptic plasticity, including reduced facilitation, augmentation and post-tetanic potentiation. NS/NSML disease states are characterized by elevated MAPK/ERK signaling, and drugs suppressing this signaling restore normal presynaptic neurotransmission in all the mutants. As an intersecting disease condition, Fragile X syndrome (FXS) is likewise characterized by elevated MAPK/ERK signaling. Indicating a common pathway, Fragile X Mental Retardation Protein (FMRP) binds to *csw* mRNA and neuronal Csw protein level is elevated in *Drosophila fragile X mental retardation 1* (*dfmr1*) null mutants in the FXS disease model. Moreover, phosphorylated ERK (pERK) is increased within presynaptic boutons of *dfmr1* and *csw* null mutants, as well as patient-derived SHP2 LOF/GOF mutants. We find presynaptic pERK activation in response to acute stimulation is reduced in both *dfmr1* and *csw* nulls. Importantly, the trans-heterozygous *csw*/+; *dfmr1*/+ double mutant recapitulates both the presynaptic pERK hyper-activation and elevated presynaptic transmission phenotypes, showing that FMRP and Csw/SHP2 act in the same pathway. Thus, an FMRP—SHP2—MAPK/ERK pathway controls both basal neurotransmission strength and activity-dependent modulation of synaptic function.

Disclosures: **S.N. Leahy:** None. **C. Song:** None. **D.J. Vita:** None. **K. Broadie:** None.

Poster

112. Presynaptic Organization and Synaptic Vesicle Dynamics

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 112.14

Topic: B.04. Synaptic Transmission

Support: IA/I/12/1/500529/WTDBT_/DBT-Wellcome Trust India Alliance/India

Title: Form-function relation: Implications of synaptic design on pattern separation in hippocampal neurons

Authors: *N. SINGH[1], S. NADKARNI[2];
[1]Biol., Indian Inst. of Sci. Educ. and Research, Pune, Pune, India; [2]Indian Inst. of Sci. Educ. and Res. Pune, Pune, India

Abstract: The ability to dramatically modulate neurotransmitter release rate in an activity-dependent manner is a characterizing feature of the mossy fiber (MF) synapses of the hippocampus. This form of short-term plasticity (STP), rather than long-term plasticity, underlies several vital functions, including working memory attributed to these synapses. We hypothesize the complex presynaptic design observed in these synapses that includes multiple active zones and clusters of voltage-dependent calcium channels complements its function. To this end, we developed a biophysical scale model of the MF bouton to investigate the influence of synaptic design on the pronounced STP profile associated with this synapse. Thus far, studies consider MF as an extension of the CA3 terminal (characterized by a single active zone) with multiple autonomous signal transmission lines. In direct contrast, our 3-D in-silico model shows crosstalk

across multiple release sites and that this communication is crucial for the observed plasticity. Additionally, we report the detailed contribution of synaptotagmin-7 (Syt7), a family of calcium sensors for vesicle release, and calcium buffers to the observed facilitation. MFs indirectly inhibit CA3 synapse via barely-plastic inhibitory interneurons apart from sending direct excitatory inputs to the CA3 pyramidal neurons. This peculiar network motif is ascribed to the role of discerning between two similar activity patterns (pattern separation), an important property of the part of the brain involved in the distinct storage of experiences. We show that abolition of STP in the MFs, severely compromises temporal pattern separation. Our physiological computational model showcases how details of synaptic organization and biophysical properties of molecular machinery transcend organization levels and profoundly influence network function.

Disclosures: **N. Singh:** None. **S. Nadkarni:** None.

Poster

112. Presynaptic Organization and Synaptic Vesicle Dynamics

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 112.15

Topic: B.04. Synaptic Transmission

Title: Compaction of the active zone scaffold during presynaptic homeostatic potentiation is independent from Bruchpilot acetylation

Authors: *M. ZETTNER[1], A. MRESTANI[2,1], M. HECKMANN[1];
[1]Dept. of Neurophysiol., Julius Maximilian Univ. of Würzburg, Würzburg, Germany; [2]Dept. of Neurol., Univ. of Leipzig Med. Ctr., Leipzig, Germany

Abstract: We employed direct stochastic optical reconstruction microscopy (*d*STORM) at *Drosophila melanogaster* neuro-muscular junctions (NMJs) to study the arrangement of the major active zone (AZ) scaffold protein Bruchpilot (Brp; Kittel et al., 2006; Mrestani et al., 2021). Brp acetylation was shown to decrease the size of AZs and cause impaired vesicle tethering (Miśkiewicz et al., 2011; Miśkiewicz et al., 2014). Focusing on Brp subclusters (SCs) in AZs we found that increased Brp acetylation in HDAC6 knock-out mutants as well as decreased acetylation in overexpression constructs increase SC area. Furthermore, during presynaptic homeostatic potentiation (PHP) both AZ density and SC density increased in HDAC6 knock-out mutants. Thus, Brp compaction during PHP (Mrestani et al., 2021) is independent from Brp acetylation.Kittel RJ, Wichmann C, Rasse TM, Fouquet W, Schmidt M, Schmid A, Wagh DA, Pawlu C, Kellner RR,Willig KI, Hell SW, Buchner E, Heckmann M*, Sigrist SJ*. (2006) Bruchpilot promotes active zoneassembly, Ca2+ channel clustering, and vesicle release. Science 312:1051-4.Mrestani A, Pauli M, Kollmannsberger P, Repp F, Kittel RJ, Eilers J, Doose S, Sauer M, Sirén AL,Heckmann M, Paul MM. (2021) Active zone compaction correlates with presynaptic homeostaticpotentiation. Cell Rep. 37:109770.Miśkiewicz K, Jose LE, Yeshaw WM, Valadas JS, Swerts J, Munck S, Feiguin F, Dermaut B, Verstreken P.(2014)

HDAC6 is a Bruchpilot deacetylase that facilitates neurotransmitter release. Cell Rep. 8:94-102.Miśkiewicz K, Jose LE, Bento-Abreu A, Fislage M, Taes I, Kasprowicz J, Swerts J, Sigrist S, Versées W,Robberecht W, Verstreken P. (2011) ELP3 controls active zone morphology by acetylating the ELKS family member Bruchpilot. Neuron. 72:776-88.

Disclosures: **M. Zettner:** None. **A. Mrestani:** None. **M. Heckmann:** None.

Poster

112. Presynaptic Organization and Synaptic Vesicle Dynamics

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 112.16

Title: WITHDRAWN

Poster

112. Presynaptic Organization and Synaptic Vesicle Dynamics

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 112.17

Topic: B.04. Synaptic Transmission

Support: CIHR Grant PJT-159548

Title: Ultrastructural comparison of synaptic inputs in the substantia nigra pars compacta

Authors: *C. COPAS[1], K. L. LE GRATIET[1,2], N. PUENTE[4,5], P. GRANDES[4,5], K. R. DELANEY[2], R. NASHMI[1,2,3], P. C. NAHIRNEY[1,3];
[1]Div. of Med. Sci., [2]Dept. of Biol., [3]Ctr. for Biomed. Res., Univ. of Victoria, Victoria, BC, Canada; [4]Dept. of Neurosciences, Univ. of the Basque Country UPV/EHU, Leioa, Spain; [5]Achurro Basque Ctr. for Neurosci., Sci. Park of the UPV/EHU, Leioa, Spain

Abstract: Dopaminergic (DA) neurons in the substantia nigra pars compacta (SNc) form the foundation of the nigrostriatal pathway and are most notably discussed in the context of Parkinson's Disease (PD) pathology. Despite an ever-growing body of literature on the broad effects of their outputs, one question that remains unanswered is how DA neurons are modulated by their afferent inputs. Previous research has shown that γ-aminobutyric acid (GABA), glutamate and acetylcholine (ACh) are the major neurotransmitters that can modulate the activity of midbrain DA neurons. Interestingly, these findings also suggest that there is a population of terminals that co-localize both ACh and GABA vesicles, implying that DA neurons are under extremely fine-tuned afferent control. The aims of this study were to examine the morphology of ACh and GABA vesicles, gauge whether they are indeed packaged in the same terminals,

determine the frequency of this co-transmission, and finally investigate whether there is heterogeneity in the prevalence of these inputs between the medial and lateral adult mouse SNc. Immunohistochemical staining for tyrosine hydroxylase (TH), Vesicular GABA Transporter (VGAT) and Vesicular Acetylcholine Transporter (VAChT) was employed to visualize synaptic terminals at the confocal level. We show that there is in fact overlap between VGAT and VAChT in terminals on DA dendrites, however this occurs less frequently than ACh or GABA only inputs. Using electron microscopy (EM), several distinct types of synapses were seen in this region. Putative cholinergic-type terminals were filled with large uniformly-sized round vesicles ~50-60 nm in diameter, GABAergic-type terminals were filled with small oblong vesicles ~20 x 80 nm in size, and glutamate terminals contained medium-sized round vesicles (~30-50 nm diameter) and an associated dendrite with a distinct post-synaptic density. Some terminals showed a mixture of oblong vesicles and large round vesicles. To determine if ACh and GABA vesicles co-exist in the same terminal, multiple gold tags were used in immuno-EM experiments to visualize VGAT and VAChT localization along TH positive dendrites. Immuno-EM labeling revealed that VGAT and VAChT labels were co-localized in the same terminal along these dendrites, suggesting that some terminals have a mixed composition. The results of this study offer a glimpse into the afferent input of these essential modulatory neurons, filling a void left by the lack of research concerning basic ultrastructure and normal functioning of the SNc.

Disclosures: C. Copas: None. **K.L. Le Gratiet:** None. **N. Puente:** None. **P. Grandes:** None. **K.R. Delaney:** None. **R. Nashmi:** None. **P.C. Nahirney:** None.

Poster

112. Presynaptic Organization and Synaptic Vesicle Dynamics

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 112.18

Topic: B.04. Synaptic Transmission

Support: NIH grant 1R21HD097565-01

Title: Regulation of oxytocin neurons by oxytocin receptor expressing neurons in the perinuclear zone of the hypothalamus.

Authors: *B. GHIMIRE, A. A. GOVER, R. TERUYAMA;
Dept of Biol. Sci., Louisiana State Univ., Baton Rouge, LA

Abstract: The neuropeptide hormone oxytocin induces contraction of the mammary gland during milk ejection. Oxytocin is synthesized by oxytocin neurons in the supraoptic nucleus (SON) and paraventricular nucleus (PVN) of the hypothalamus and is released from the axon terminals of oxytocin neurons in the posterior pituitary into the general circulation. Oxytocin neurons display synchronized high frequency bursts of action potentials preceding each milk ejection. This synchronized burst results in a bolus release of oxytocin necessary for contraction of the mammary gland during milk ejection. Oxytocin is also released from the soma and

dendrites of oxytocin neurons. The somato-dendritic release of oxytocin increases during milk ejection and facilitates synchronous bursting activity of oxytocin neurons. It is believed that the effect of oxytocin on oxytocin neurons is mediated by the oxytocin receptor (OXTR) expressed on oxytocin neurons themselves. However, our study on OXTR reporter (OXTR-Venus) mice did not find OXTR-Venus on oxytocin neurons. Instead, OXTR-Venus was found in non-oxytocin neurons in the perinuclear zone (PNZ) area immediately dorsal to the SON. The OXTR-Venus neurons had processes projecting to oxytocin neurons in the SON. These findings suggest that OXTR neurons in the PNZ mediate the action of oxytocin on oxytocin neurons. The objective of our research is to elucidate the regulatory mechanism of OXTR neurons in the PNZ on the activity of oxytocin neurons in the SON during lactation. To examine the type of neurotransmitter from the OXTR neurons, we created double reporter mice that express glutamic acid decarboxylase2 (GAD_2)-mCherry and OXTR-Venus. Most of the OXTR-Venus neurons in the PNZ also expressed GAD2-mCherry. Moreover, the total number of OXTR-Venus x GAD2-mCherry neurons was significantly higher in lactating females than in virgin females. These findings suggest that OXTR neurons in the PNZ are GABAergic and increase in number during lactation. Brain slice whole-cell patch clamp recordings on oxytocin neurons were conducted to examine if oxytocin induces GABA inputs to oxytocin neurons. Significantly higher frequency of GABA post synaptic currents burst was observed in lactating females than in virgin females. Bath application of selective OXTR agonist (TGOT) caused an increase in frequency of intra-burst post synaptic currents in oxytocin neurons in lactating females, but not in virgin females. These findings suggest that the somato-dendritic release of oxytocin stimulates GABAergic inputs from OXTR neurons in the PNZ to oxytocin neurons in the SON during lactation.

Disclosures: B. Ghimire: None. **A.A. Gover:** None. **R. Teruyama:** None.

Poster

112. Presynaptic Organization and Synaptic Vesicle Dynamics

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 112.19

Topic: B.04. Synaptic Transmission

Support: NIH Grant NS091546
NIH Grant NS111414

Title: Electrophysiological properties and nanoscale distinctions that define tonic vs phasic glutamatergic synapses

Authors: *K. HE[1], Y. HAN[2], X. LI[1], R. X. HERNANDEZ[4], D. V. RIBOUL[6], T. FEGHHI[5], K. A. JUSTS[6], O. MAHNEVA[7], G. T. MACLEOD[7], D. K. DICKMAN[3];
[2]Neurosci. Grad. Program, [3]Neurobio., [1]USC, Los Angeles, CA; [4]Neurosci., Max Planck Florida Inst. for Neurosci., Jupiter, FL; [5]Physics, Max Planck Florida Inst. for Neurosci., Boca Raton, FL; [6]Dept. of Biol. Sci., Florida Atlantic Univ., Boca Raton, FL; [7]Wilkes Honors Col., Florida Atlantic Univ., Jupiter, FL

Abstract: Neurons exhibit a striking degree of functional diversity, tuning activity according to the needs of the circuitry in which they are embedded. A fundamental functional dichotomy occurs in firing patterns, with some neurons firing with a lower frequency, constant “tonic” pattern, while others fire in a “phasic” pattern, characterized by bursts of activity separated by periods of relative inactivity. Synapses generated by tonic vs phasic neurons are also endowed with functional differences, yet the reasons for their distinctive properties remain enigmatic. One major challenge towards illuminating the synaptic differences between tonic and phasic neurons is accurately isolating their physiological properties. At the *Drosophila* neuromuscular junction (NMJ), most muscle targets are co-innervated by two motor neurons, the tonic “type Ib” and phasic “type Is”. However, electrophysiological approaches have rarely been able to electrophysiologically separate them. Here, we employed a botulinum neurotoxin (BoNT-C) that enables selective silencing of tonic or phasic motor neurons to reveal substantial differences in quantal size and presynaptic release probability at tonic vs phasic synapses. Furthermore, calcium imaging demonstrated approximately two-fold greater calcium influx at phasic release sites relative to tonic, which also exhibit tighter synaptic vesicle coupling. We then characterized the extent to which action-potential waveforms differ between tonic vs phasic neurons, properties that may contribute to the differences in presynaptic calcium influx. Finally, confocal and super resolution (STED) imaging revealed that phasic active zones are organized in a more compact arrangement, with enhanced stoichiometry of voltage-gated calcium channels relative to other active zone scaffold proteins. These data suggest that nanoscale distinctions in core active zone machinery may collaborate with activity-dependent voltage differences to differentially tune glutamate release at tonic vs phasic synapses.

Disclosures: K. He: None. **Y. Han:** None. **X. Li:** None. **R.X. Hernandez:** None. **D.V. Riboul:** None. **T. Feghhi:** None. **K.A. Justs:** None. **O. Mahneva:** None. **G.T. Macleod:** None. **D.K. Dickman:** None.

Poster

112. Presynaptic Organization and Synaptic Vesicle Dynamics

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 112.20

Topic: B.04. Synaptic Transmission

Support: Korean Ministry of Science and ICT 2020R1A2B5B02002070

Title: L-type Ca^{2+} channels mediate regulation of glutamate release by subthreshold potential changes

Authors: *B. LEE, S. LEE, S.-H. LEE, W.-K. HO;
Seoul Natl. Univ., Jongno-gu, Korea, Republic of

Abstract: Subthreshold depolarization enhances neurotransmitter release evoked by action potentials and plays a key role in modulating synaptic transmission by combining analog and

digital signals. This process is known to be Ca^{2+}-dependent. However, the underlying mechanism of how small changes in basal Ca^{2+} caused by subthreshold depolarization can regulate transmitter release triggered by a large increase in local Ca^{2+} is not well understood. This study aimed to investigate the source and signaling mechanisms of Ca^{2+} that couple subthreshold depolarization with the enhancement of glutamate release in hippocampal cultures and CA3 pyramidal neurons. Subthreshold depolarization increased presynaptic Ca^{2+} levels, the frequency of spontaneous release, and the amplitude of evoked release, all of which were abolished by blocking L-type Ca^{2+} channels. A high concentration of intracellular Ca^{2+} buffer or blockade of calmodulin and phospholipase C abolished depolarization induced increases in transmitter release. Estimation of the readily releasable pool size using hypertonic sucrose showed depolarization induced increases in readily releasable pool size, and this increase was abolished by blockade of calmodulin or phospholipase C. Our results provide mechanistic insights into the modulation of transmitter release by subthreshold potential change and highlight the role of L-type Ca^{2+} channels in coupling subthreshold depolarization to the activation of Ca^{2+}-dependent signaling molecules that regulate transmitter release.

Disclosures: **B. Lee:** None. **S. Lee:** None. **S. Lee:** None. **W. Ho:** None.

Poster

112. Presynaptic Organization and Synaptic Vesicle Dynamics

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 112.21

Topic: B.04. Synaptic Transmission

Support: DFG (SCHO 820/8-1, SFB 1089), BONFOR

Title: Mapping the orientation of synaptic proteins in mammalian synapses and Drosophila NMJs by two photon polarization microscopy

Authors: ***M. GALKOV**[1], K. PATIL[3], G. TAVOSANIS[3], M. FUHRMANN[4], D. DIETRICH[2], S. SCHOCH[1];
[1]Dept. of Neuropathology, [2]Dept. of Neurosurg., Univ. Hosp. Bonn, Bonn, Germany; [3]Dynamics of Neuronal Circuits, [4]Neuroimmunology and Imaging Group, German Ctr. for Neurodegenerative Dis. (DZNE), Bonn, Germany

Abstract: The synaptic conversion of an electrical to a chemical signal is mediated by the multi-component pre- and postsynaptic cytomatrix. In recent years, the composition of these cytomatrixes has been resolved and progress has been made in resolving the ultrastructural organization on both sides of the synapse. However, we still lack a detailed understanding of the 3-D organization of individual cytomatrix components. In this study we aimed to investigate synapse geometry using the effect of linear dichroism (LD) and two-photon polarization microscopy (2PPM). To this end, two parameters were analyzed: the angle of laser beam polarization providing maximal fluorophore emission (β angle) and the proportion of uniformly

oriented molecules (LD-fraction). We validated our approach by demonstrating high LD in methoxy-X04 stained amyloid plaques and in a membrane-bound eGFP variant expressed in HEK293T cells and primary neurons. Moreover, we fused the actin filament reporter LifeAct to eGFP via several non-structured linkers and found regular and robust β angle values for all of these constructs in filopodia of HeLa cells. We next measured the LD-fraction in synapses of cultured mouse primary neurons and Drosophila larval NMJs expressing key active zone proteins tagged with eGFP. We did not observe LD of the active zone proteins excluding certain linear regularities of their spatial arrangements while complexes with radial symmetry would remain undetected. Our data form the basis for further analyses aiming at resolving the spatial orientation of components of the presynaptic cytomatrix at the active zone.

Disclosures: M. Galkov: None. **K. Patil:** None. **G. Tavosanis:** None. **M. Fuhrmann:** None. **D. Dietrich:** None. **S. Schoch:** None.

Poster

112. Presynaptic Organization and Synaptic Vesicle Dynamics

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 112.22

Topic: B.04. Synaptic Transmission

Support: R01 AG062655
OCAST
PHF
OCNS

Title: Behavioral and neuronal functional characterization of Synaptobrevin-1 deficient mice

Authors: A. RAFIQ[1], E. VU[1], J. B. MILLER[1], A. SETH[1], A. OROCK[2], H. BAO[2], ***F. DEAK**[1]; [1]Neurosci. & Regenerative Med., Augusta Univ., Augusta, GA; [2]Oklahoma Ctr. for Neurosci., Univ. of Oklahoma Hlth. Sci. Ctr., Oklahoma City, OK

Abstract: Introduction: Cognitive function requires precise regulation of synaptic neurotransmission. This is achieved by a spatially and temporally well-coordinated molecular mechanism of exocytosis of synaptic vesicles. The SNAP receptor (SNARE) proteins are essential for the fusion of vesicle membrane with the plasma membrane consists three proteins: the target SNARE syntaxin1 and SNAP-25and the vesicular SNARE synaptobrevin (syb)-1 or syb2. While overwhelming data support the role of syb2 in neurotransmission, the function of syb1 in the mammalian CNS is not well characterized. The goal of this study was to clarify the exact molecular interactions, distribution of syb1 in the mouse brain and its role in learning and memory during aging.
Methods: We used lethal wasting (lew) syb1$^{+/-}$ mice at various age groups up to 24 months of age. We analyzed syb1 expression profile in WT brains and confirmed selectivity of a specific syb1 antibody in young homozygous (-/-) brain tissue. We performed behavioral tests for spatial

learning and memory using a radial arm water maze (RAWM) and the novel object assays. We performed long-term potentiation (LTP) tests to assess hippocampal memory acquisition and storage capacity of syb1$^{+/-}$ mice. We used a fluorescent FM dye assay to measure the rate of synaptic vesicle release in neuronal cultures from syb1$^{+/-}$ and wild-type controls.
Results: We found that syb1$^{-/-}$ mice are lethal at P15 due to paralysis and used $^{+/-}$ mice for the detailed behavioral studies. These behavioral assays showed that syb1$^{+/-}$ mice performed similarly in spatial learning tasks (RAWM) and reversal learning task when compared to WT controls. Syb1$^{+/-}$ mice also have maintained hippocampal CA1 LTP and synaptic vesicle release rates equal to that in controls, while syb1$^{-/-}$ cortical neurons have impaired vesicular release. We found that overall expression pattern of syb1 is markedly different from syb2 in brain histological profiles, syb1 is dominating in brain stem and cerebellum, while syb2 is more prevalent in hippocampus.
Conclusions: To our best knowledge this is the first comprehensive study of syb1 deficiency in the CNS. Our results provide better understanding of the role of syb1 in the synapses of CNS and its role in learning and memory.

Disclosures: **A. Rafiq:** None. **E. Vu:** None. **J.B. Miller:** None. **A. Seth:** None. **A. Orock:** None. **H. Bao:** None. **F. Deak:** None.

Poster

112. Presynaptic Organization and Synaptic Vesicle Dynamics

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 112.23

Topic: B.04. Synaptic Transmission

Support: NIH R01 #NS117588

Title: Molecular Logic of Structural and Functional Synaptic Diversity in Drosophila Tonic and Phasic Motoneurons

Authors: *S. K. JETTI[1], A. B. CRANE[1], Y. AKBERGENOVA[1], C. A. WHITTAKER[2], J. T. LITTLETON[1];
[1]The Picower Inst. for Learning and Memory, Dept. of Biol. and Dept. of Brain and Co, [2]David H. Koch Inst. for Integrative Cancer Res., MIT, Cambridge, MA

Abstract: Synapses exhibit striking diversity in morphology, synaptic strength, response kinetics, and short-term plasticity. Although extensive progress has been made in characterizing mechanisms of synaptic transmission, the molecular logic that specifies functional synapse diversity remains unclear even when transcriptional differences have been defined for major neuronal types. To address this broad question, we generated and characterized gene expression profiles for *Drosophila* tonic and phasic glutamatergic motoneuron (MN) subclasses, evolutionarily conserved populations that play an important role in neural coding. *Drosophila* tonic and phasic motoneurons show multiple distinctions in dendritic patterning, synaptic

connectivity, intrinsic excitability, and synaptic properties, providing an attractive model system to examine molecular and structural differences that contribute to these core properties. We used GAL4 drivers specific for tonic Ib and phasic Is MN subtypes in *Drosophila* larvae to genetically label and examine synaptic properties. We confirmed physiological differences in synaptic release at these two distinct synapses using synaptic GCaMP imaging, optogenetics, and electrophysiological analyses. In addition, STED nanoscopy revealed differential active zone organization of key proteins between Ib and Is motoneurons that likely contribute to their unique differences in synaptic transmission. A collection of several hundred differentially expressed genes (DEGs) and splice isoforms were identified using single-neuron isoform Patch-Seq. To investigate molecular mechanisms that specify structural and functional synapse diversity, we carried out genetic screening of highly enriched DEGs using available mutants and RNAi lines. We identified multiple DEGs that contribute to differences in tonic and phasic synaptic properties, including the transmembrane receptor Toll-6, the calcium-binding protein Cbp53E, cytoskeletal protein CG3085, the trans-Golgi protein Mayday, and the signaling ligand Wnt4. In addition, our genetic screen revealed that differences in posttranslational modifications contribute to differences in synapse growth and function between the two neuron classes. These findings demonstrate that the unique nanoscale organization of AZs, together with differences in gene expression profiles and posttranslational modifications, contributes to functional diversity in synaptic transmission.

Disclosures: S.K. Jetti: None. **A.B. Crane:** None. **Y. Akbergenova:** None. **C.A. Whittaker:** None. **J.T. Littleton:** None.

Poster

112. Presynaptic Organization and Synaptic Vesicle Dynamics

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 112.24

Topic: B.04. Synaptic Transmission

Support: National Institute on Ageing grant AG055577-01 to E.T.K
National Institute of Mental Health grant MH66198-19 to E.T.K.

Title: Non-cell autonomous regulation of neurotransmitter release synchrony in human synapses

Authors: *B. UZAY[1], A. HOUCEK[2], Z. MA[2], C. L. KONRADI[2], L. M. MONTEGGIA[3], E. T. KAVALALI[1];
[1]Vanderbilt Univ., [2]Vanderbilt Univ., Nashville, TN; [3]Vanderbilt Brain Inst., Vanderbilt Brain Inst., Nashville, TN

Abstract: Rapid release of neurotransmitters in synchrony with action potentials is considered a key hard-wired property of synapses. Here, in glutamatergic synapses formed between induced human neurons, we show that evoked neurotransmitter release becomes progressively desynchronized as synapses mature and age. In this solely excitatory network, the emergence of

NMDAR-mediated transmission elicits endoplasmic reticulum (ER) stress leading to downregulation of key presynaptic molecules, synaptotagmin-1, and cysteine string protein α (CSPα), that synchronize neurotransmitter release. The emergence of asynchronous release is maintained by the high-affinity Ca^{2+} sensor synaptotagmin-7 and suppressed by the introduction of GABAergic transmission into the network, inhibition of NMDARs, or ER stress. These results suggest in human synapses long-term disruption of excitation-inhibition balance affects the synchrony of excitatory neurotransmission in a non-cell autonomous manner.

Disclosures: B. Uzay: None. **A. Houcek:** None. **Z. Ma:** None. **C.L. Konradi:** None. **L.M. Monteggia:** None. **E.T. Kavalali:** None.

Poster

113. Pathological Synaptic Transmission and Modulation

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 113.01

Topic: B.04. Synaptic Transmission

Support: NAM 2000012740

Title: Longitudinal Study of Aging at the Mouse Neuromuscular Junction and the Therapeutic Effect of a Novel Calcium Channel Modifier

Authors: *Y. LI[1], M. PATEL[1], J. BAROUDI[1], M. WU[1], S. GATTI[2], P. WIPF[3], M. LIANG[3], G. VALDOMIR[3], Y. BADAWI[1], S. MERINEY[1];
[1]Univ. of Pittsburgh, Univ. of Pittsburgh Ctr. For Neurosci., Pittsburgh, PA; [2]Tufts Univ., Medford, MA; [3]Chem., Univ. of Pittsburgh, Pittsburgh, PA

Abstract: There is still a gap in the literature regarding longitudinal changes of the neuromuscular junction (NMJ) during aging, and such knowledge is vital to discoveries of novel therapeutic treatments and to the timing of prophylactic strategies. In this study, we used electrophysiology and immunohistochemistry to investigate functional and structural changes in the mouse NMJ between 3 and 30 months of age. We observed significant and dynamic changes in neurotransmitter release in the epitrochleoanconeous (ETA) nerve-muscle preparation from both male and female C57/BL6 mice. The changes are time-dependent, leading us to further separate the aging time course into epochs named “Young Adult” (3-5 months), “Adult” (7-18 months), “Early Aging” (19-24 months), and “Later Aging” (25-30 months). We have applied these epochs to our morphological data on the motor axons (with antibody against neurofilament-M) and acetylcholine receptors (AChR, with α-Bungarotoxin) at the NMJ and characterized their changes during the aging process. Next, we assessed muscle strength using the forelimb grip strength test. This longitudinal study revealed a continuous increase in action potential-triggered transmitter release starting at the Young Adult epoch until the Later Aging epoch, which shows decreased transmitter release - a biphasic change. After the Young Adult epoch, the miniature amplitude decreases and stay consistent through the rest of the epochs,

while the end plate potential increases in Early Aging and quickly decreases in Later Aging. This suggests a compensatory homeostatic mechanism during Early Aging that is not maintained in Later Aging. We have applied the same epochs when analyzing morphological changes over time. Behaviorally, grip strength (normalized to body weight) exhibits a continuous decreasing trend. Finally, we treated the aged ex vivo nerve muscle preparation with our small molecule calcium channel gating modifier, GV-58, and found a 1.64-fold increase in quantal content. To summarize, we have studied aging at the NMJ in a longitudinal fashion, identifying important time epochs for structural and functional changes, and our small molecule acutely and successfully rescued loss of transmitter release in aged NMJs.

Disclosures: **Y. Li:** None. **M. Patel:** None. **J. Baroudi:** None. **M. Wu:** None. **S. Gatti:** None. **P. Wipf:** None. **M. Liang:** None. **G. Valdomir:** None. **Y. Badawi:** None. **S. Meriney:** None.

Poster

113. Pathological Synaptic Transmission and Modulation

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 113.02

Topic: B.04. Synaptic Transmission

Support: NRF Korea 2021R1A6A3A13041249
NRF Korea 2021R1A2C3004572

Title: Primary cilia of Schwann cells are essential to control neuromuscular junction abnormalities caused by chronic inflammation

Authors: *H. JEONG, S. KIM, J. LEE;
Hlth. Sci. and Technology, SAIHST, SungKyunKwan Univ., Seoul, Korea, Republic of

Abstract: Aging causes various diseases including obesity, skin diseases, and neurological diseases. Neuropathy occurs when the peripheral nervous system (PNS) loses its ability to repair nerves as it ages. While neurons are regenerating, Schwann cells work with immune cells to aid neurons. Inflammatory factors accumulate with age, causing chronic inflammation and interfering with nerve regeneration. Although Schwann cells have been suggested as a key player in PNS regeneration, how Schwann cells regulate the PNS in chronic inflammatory conditions is poorly understood. In the present study, we hypothesize that primary cilia, organelles of Schwann cells are required to regulate inflammation, which affects nerve regeneration. Neuromuscular junction (NMJ) is the synapse between motor neuron and muscle fiber in the PNS. Recently, interest has shifted from the research of neuronal regeneration to the study of the NMJ recovery mechanism in order to overcome peripheral neuropathy. Thus, we investigated the role of Schwann cells in the formation of NMJ and the effect of chronic inflammation on Schwann cells-dependent NMJ function. First, we observed the presence of primary cilia in Schwann cells in the NMJ of the transverse abdominal and lumbrical muscles of mice. We then

treated mice with dextran sulfate sodium (DSS) and examined the levels of inflammatory cytokines to determine whether chronic inflammation was induced. Intriguingly, we found that in chronic inflammatory conditions, Schwann cells near the NMJ have more or longer primary cilia. Further experiments with aged mice revealed that aging-related NMJ defects and abnormal primary cilia in Schwann cells were similar to those caused by chronic inflammation. We also observed primary cilia in the S16 cell line and in mouse primary cultured Schwann cells. Consistent with data from mice tissues, both types of Schwann cells showed abnormal primary cilia in a chronic inflammatory condition induced by trinitrobenzene-sulfonic acid (TNBS) treatment. Taken together, our data suggest that the primary cilia in Schwann cells are involved in chronic inflammatory regulation, which affect NMJ formation and function. Thus, we propose that the primary cilia of Schwann cells may be a therapeutic target for chronic inflammation-related NMJ disease.

Disclosures: H. Jeong: None. **S. Kim:** None. **J. Lee:** None.

Poster

113. Pathological Synaptic Transmission and Modulation

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 113.03

Topic: B.04. Synaptic Transmission

Support: R01 EY028212

Title: Intranasally administered ketamine regulates mechanisms of visual cortical plasticity in adult mice

Authors: *X. QIAO, S. GRIECO, X. XU;
Univ. of California Irvine, Irvine, CA

Abstract: Ketamine is a non-competitive antagonist of N-methyl-D-aspartate receptors and has traditionally been used for anesthesia. A subanesthetic dose of ketamine is shown to have sustained antidepressant effects, likely by modulating mechanisms of brain plasticity. Our previous studies address this mechanism and find that a subcutaneously administered dose of subanesthetic ketamine downregulates NRG1 expression in PV inhibitory cells, resulting in sustained cortical disinhibition to enhance cortical plasticity in adult visual cortex (Grieco SF 2020, 2021). We hypothesize that intranasally-administered ketamine may similarly activate cortical plasticity; this is important because SPRAVATO (esketamine) is FDA approved as a nasal spray. To test our hypothesis, we delivered a subanesthetic dose of ketamine (10 mg/kg) intranasally to young adult mice (~8 weeks). We then recorded synaptic inputs onto pyramidal neurons and PV interneurons in layer 2/3 of the visual cortex 24 and 48 hours after nasal delivery of the drug. Electrically-evoked inhibitory postsynaptic currents (IPSCs) in pyramidal neurons in C57BL/6J mice without ketamine treatment (1073 ± 30.04 pA, n=11 cells) were significantly stronger than those recorded in mice treated with ketamine (24 hours, 603.8 ± 19.63 pA, n=10

cells and 48 hours, 586.4 ± 19.33 pA, n=10 cells). NRG1 bath application increases IPSCs in pyramidal neurons from mice treated with ketamine intranasally (NRG1/baseline ratio: 24 hours, 1.73 ± 0.1, n=10 cells and 48 hours, 2.03 ± 0.15, n=10 cells), but not in control mice (NRG1/baseline ratio: 1 ± 0.04, n=11 cells). We then measured electrically-evoked excitatory postsynaptic currents (EPSCs) in PV interneurons in PV-Cre; Ai9 mice. The baseline EPSCs from mice without ketamine treatment (397.4 ± 17.73 pA, n = 10 cells) are not significantly influenced by NRG1 bath application (NRG1/baseline ratio: 1.04 ± 0.04, n=10 cells). However, the baseline EPSCs from mice treated with ketamine are significantly weaker than control mice (24 hours, 205.8 ± 8.37 pA, n = 10 cells and 48 hours, 207.6 ± 7.76 pA, n = 10 cells). NRG1 bath application restores excitatory postsynaptic responses in PV interneurons (NRG1/baseline ratio: 24 hours, 1.92 ± 0.09, n = 10 cells and 48 hours, 2.05 ± 0.08, n = 10 cells). Together, our results indicate that intranasally-administered ketamine modulates NRG1 signaling and reduces excitatory inputs onto PV interneurons, which in turn decreases PV inhibitory inputs onto pyramidal neurons. These findings support the use of intranasally-administered ketamine to regulate mechanisms of adult visual cortical plasticity with implications for the treatment of adult amblyopia.

Disclosures: **X. Qiao:** None. **S. Grieco:** None. **X. Xu:** None.

Poster

113. Pathological Synaptic Transmission and Modulation

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 113.04

Title: WITHDRAWN

Poster

113. Pathological Synaptic Transmission and Modulation

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 113.05

Topic: B.04. Synaptic Transmission

Support: NIH Grant R01AA026531

Title: The sex-dependent acute ethanol modulation of GABA release from parvalbumin neurons in the basolateral amygdala is mediated by a rapid cellular inflammatory response

Authors: S. MUNSHI[1], ***R. C. DOS-SANTOS**[1], C. E. STEELY[1], J. G. TASKER[1,2];
[1]Tulane Univ., [2]Tulane Brain Inst., Tulane Univ., New Orleans, LA

Abstract: Chronic alcohol exposure causes neuroinflammation involving the cellular inflammatory response mediated by activation of the nucleotide-binding oligomerization domain-like receptor protein 3 (NLRP3) inflammasome and proinflammatory cytokine production. Acute alcohol administration in the basolateral amygdala (BLA) has been shown to rapidly stimulate GABA release from parvalbumin-expressing GABA interneurons and to decrease anxiety-like behavior. In this study, we tested whether the acute ethanol (EtOH) facilitation of inhibitory transmission in the BLA is mediated by a rapid cellular inflammatory response. In whole-cell patch clamp recordings of BLA principal neurons in acute brain slices, EtOH increased the frequency of spontaneous inhibitory postsynaptic currents (sIPSCs) ($p < 0.05$) in a concentration-dependent manner in principal neurons from male, but not female, rats. The effect of EtOH was inhibited by blocking the NLRP3 inflammasome with MCC950 (10 μM) and by blocking downstream IL-1β actions with the IL-1 receptor antagonist (IL1RA, 11.63 nM). The EtOH facilitation of inhibitory synaptic transmission was also blocked by inhibiting Toll-like receptor 4 (TLR4) receptors with TAK-242 (50 nM). Therefore, our data demonstrate that acute EtOH in the BLA causes a sex and concentration-dependent facilitation of GABA release from parvalbumin interneurons that is stimulated by a rapid local cellular neuroinflammatory response involving TLR4 activation of the NLRP3 inflammasome and IL-1β release. This neuroinflammatory response may be responsible for the BLA anxiolytic behavioral effect of EtOH seen in male, but not female, rats. This work was supported by NIH R01AA026531.

Disclosures: **S. Munshi:** None. **R.C. dos-Santos:** None. **C.E. Steely:** None. **J.G. Tasker:** None.

Poster

113. Pathological Synaptic Transmission and Modulation

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 113.06

Topic: B.04. Synaptic Transmission

Support: NIH Grant DA044121
NIH Grant NS112292

Title: Differential regulation of glutamate and GABAergic currents at ventral tegmental area - dentate gyrus of hippocampal synapses via the mu opioid receptor activation is altered in neuropathic pain mouse model

Authors: *H. R. KIM, M. MARTINA;
Northwestern Univ. Med. Sch., Chicago, IL

Abstract: The ventral tegmental area (VTA) is a center of the mesolimbic reward pathway and mainly consists of dopaminergic neurons. In parallel, a substantial population of VTA is non-dopaminergic. Glutamatergic (vGlut2-positive) VTA neurons (~35%) project to the nucleus accumbens and lateral habenula, and are involved in aversive behavior and associative learning.

Innervations of these glutamatergic terminals are also found in dentate gyrus of hippocampus (DG). Interestingly, VTA-DG synapses co-release glutamate and GABA (Ntamati and Luscher, 2016). Although this VTA-DG projection was shown to contribute to the formation of fear-inducing context memories (Han et al., 2020), not much is known concerning the modulation and plasticity of these synapses. In the present study, we investigate how VTA-DG synapses are modulated by opioids in neuropathic pain. By taking advantage of vGlut2-cre mice, we selectively expressed channel rhodopsin in VTA glutamatergic neurons. We confirmed that optogenetic activation of VTA-DG synapses in hippocampal brain slices evoked both glutamatergic and GABAergic current in dentate gyrus granule cells as previously reported. When a mu opioid receptor (MOR) agonist was bath-applied, the glutamatergic current was reduced by ~83% in both sham control and neuropathic pain (SNI; the spared nerve injury) mouse groups. For GABAergic current the MOR-induced current decrease was smaller than that of the glutamatergic current in normal conditions, while it was almost the same as glutamatergic current in SNI mice (68.0±4.1% for sham and 85.9±1.5% for SNI, n=28 and 22 respectively; $p<0.0001$ by Mann-Whitney test). These results suggest that the release of glutamate and GABA may be independently regulated at the VTA-DG synapse, and that the excitatory/inhibitory signal balance might be differently affected by MOR activation.

Disclosures: H.R. Kim: None. **M. Martina:** None.

Poster

113. Pathological Synaptic Transmission and Modulation

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 113.07

Topic: B.04. Synaptic Transmission

Title: Circuit architecture of serotonergic signaling in the Drosophila mushroom body, and transcriptomic responses following antidepressant-like perturbations

Authors: S. BONANNO[1], Y. KURMANGALIYEV[2], P. SANFILIPPO[2], D. KRANTZ[1]; [1]Psychiatry, [2]Biol. Chem., UCLA, Los Angeles, CA

Abstract: Though serotonergic neurons represent only ~1/200,000 neurons in humans, they project to and influence nearly every region of the brain, with some areas receiving denser input than others. Serotonergic circuits are the most commonly targeted system in pharmacological treatment of psychiatric disorders, with selective serotonin reuptake inhibitors (SSRIs) consistently listed among the top prescribed drugs across all of medicine. Despite such important roles in brain function, deeper understanding of serotonergic systems and therapeutic interventions remain elusive due to the heterogeneity and complexity of serotonin neurons themselves and the cells that they innervate. Similar to the mammalian CNS, the *Drosophila* brain is innervated broadly by processes elaborating from relatively few serotonergic cells. The bilateral mushroom bodies (MBs), centers of learning and memory in the fly, are each predominantly innervated by a single serotonergic neuron. Previous functional and phenotypic

studies have shown that serotonin release from this neuron onto 5-HT1A receptors on postsynaptic MB cells is important in the regulation of many behaviors, yet little has been reported on the subcellular distribution of pre- and post-synaptic components involved in this signaling. Here, we create novel tools to visualize several key components of this system in restricted cell populations, and reveal unexpected patterns of expression that suggest complexity in serotonergic signaling. Using these insights, we conduct RNA-seq experiments to analyze transcriptomic changes in different postsynaptic MB cells that express different serotonin receptors, following antidepressant-like increases in serotonergic signaling.

Disclosures: S. Bonanno: None. **Y. Kurmangaliyev:** None. **P. Sanfilippo:** None. **D. Krantz:** None.

Poster

113. Pathological Synaptic Transmission and Modulation

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 113.08

Topic: B.04. Synaptic Transmission

Support: AA026601
AA 026421

Title: Maternal Ethanol Exposure Causes Anxiety Phenotype and Alters Synaptic Nitric Oxide and Endocannabinoid Signaling in Dorsal Raphe Nucleus of Adult Male Offspring Rats

Authors: *S. OUBRAIM[1], R. WANG[2], K. A. HAUSKNECHT[3], M. KACZOCHA[4], R.-Y. SHEN[5], S. HAJ-DAHMANE[6];
[2]Dept. of Pharmacol. and Toxicology, [1]Univ. At Buffalo, Buffalo, NY; [3]Univ. Buffalo, SUNY, Buffalo, NY; [4]Dept. of Anesthesiol., Stony Brook Univ., Stony Brook, NY; [5]Res. Inst. on Addictions, Univ. at Buffalo, Buffalo, NY; [6]Dept. of Pharmacol. and Toxicology, Univ. of Buffalo, Buffalo, NY

Abstract: Mood disorders, including anxiety-like phenotype and depression caused by prenatal ethanol exposure (PE) are prevalent conditions in fetal alcohol spectrum disorders (FASDs). Prenatal ethanol exposure is associated with persistent dysfunctions of several neurotransmitter systems, including the serotonin (5-HT) system, which plays a major role in mood regulation and stress homeostasis. While PE is known to disrupt the development of the 5-HT system, the cellular mechanisms by which PE alters the function of dorsal raphe nucleus (DRn) 5-HT neurons and their synaptic inputs remain unknown. Here, we used a second trimester binge-drinking pattern PE (two daily gavages of 15% w/v ethanol at 3 g/kg, 5-6 hours apart) during gestational days 8-20 and measured anxiety-like behaviors of adult male rats using elevated plus (EPM) and zero (ZM) mazes. We also employed ex-vivo electrophysiological and pharmacological approaches to unravel the mechanisms by which PE alters the excitability and synaptic transmission onto DRn 5-HT neurons. We found that PE enhanced anxiety-like

behaviors in adult rats. This anxiety-like phenotype was correlated with a persistent activation of DRn 5-HT neurons, which was largely mediated by potentiation of DRn glutamate synapses. In addition, we showed that the PE-induced potentiation of DRn synapses was mediated by activation of the nitrergic system and impaired endocannabinoid signaling. As such, the present work reveals that PE exerts a "push-pull" effects on nitrergic and eCB signaling, respectively, which mediate the enhanced activity of DRn 5-HT neurons and could contribute to the anxiety-like phenotype in animal model of FASD.

Disclosures: S. Oubraim: None. **R. Wang:** None. **K.A. Hausknecht:** None. **M. Kaczocha:** None. **R. Shen:** None. **S. Haj-Dahmane:** None.

Poster

113. Pathological Synaptic Transmission and Modulation

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 113.09

Topic: B.04. Synaptic Transmission

Support: Presbyterian Health Foundation
Whitehall Foundation
National Institues of Health

Title: Deficiency of very long chain-saturated fatty acids impairs synaptic transmission and plasticity in the cerebellum of a rat model of human SCA34

Authors: *R. Y. NAGARAJA[1], M.-P. AGBAGA[1,2], D. M. SHERRY[1], M. AHMAD[1];
[1]Dept. of Cell Biol., [2]Dept. of Ophthalmology and Dean McGee Eye Inst., Univ. of Oklahoma Hlth. Sci. Ctr., Oklahoma City, OK

Abstract: Spinocerebellar ataxias (SCA) are neurodegenerative disorders characterized by progressive loss of motor coordination due to degeneration of the cerebellum, a part of the brain critical for motor function. A number of different mutations cause different types of SCA with characteristic ages of onset, progression and symptomology. SCA34 is caused by mutations in the Fatty Acid Elongase-4 (ELOVL4) enzyme that mediates biosynthesis of Very Long Chain-Saturated Fatty Acids (VLC-SFA; ≥28 carbons), which are essential for proper function of the central nervous system. We generated a novel rat model of human SCA34 by knocking-in W246G mutation in the *Elovl4* gene. Our initial analyses of homozygous SCA34 rats (MUT) revealed early-onset gait dysfunction and impaired synaptic transmission and plasticity at glutamatergic parallel and climbing fiber synapses onto cerebellar Purkinje cells prior to neurodegeneration. However, the underlying physiological and molecular mechanisms that caused these defects remained unknown. We have now performed detailed patch-clamp electrophysiology recordings from Purkinje cells to identify functional impairments at parallel fiber-to-Purkinje cell (PF-PC) and climbing fiber-to-Purkinje cell (CF-PC) synapses. Our results show that miniature Excitatory Postsynaptic Current (mEPSC) frequency is reduced in MUT rats

with no change in mEPSC amplitude compared to wild-type (WT), suggesting a presynaptic defect of excitatory synaptic transmission on Purkinje cells. We also find alterations in inhibitory synaptic transmission as miniature Inhibitory Postsynaptic Current (mIPSC) frequency and amplitude are increased in MUT Purkinje cells. Paired-pulse ratio is reduced at PF-PC synapses and increased at CF-PC synapse in MUT rats, which along with results from high frequency stimulation suggest opposite changes in the release probability at these two sets of synapses. These results indicate that VLC-SFA have a synapse-specific mechanism of action on the synaptic vesicle release probability in the cerebellum. In addition, we discovered that metabotropic glutamate receptor-dependent slow EPSCs are impaired at PF-PC synapses in MUT cerebellum. These results have uncovered novel mechanisms of action of VLC-SFA in maintaining cerebellar synaptic transmission and plasticity, and elucidated the synaptic dysfunction underlying SCA34 pathology.

Disclosures: R.Y. Nagaraja: None. **M. Agbaga:** None. **D.M. Sherry:** None. **M. Ahmad:** None.

Poster

113. Pathological Synaptic Transmission and Modulation

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 113.10

Topic: B.04. Synaptic Transmission

Support: Department of Biotechnology, Ministry of Science and Technology, Govt. of India [BT/MED/122/ SP24580/2018]
Office of the Principal Scientific Adviser to the Government of India wide sanction number: Prn.SA/Epilep/2017(G)

Title: Differential synaptic activity in tumor linked and non-tumor linked pathologies of drug-resistant epilepsy

Authors: *J. BANERJEE[1], S. DEY[2], A. B. DIXIT[3], M. TRIPATHI[2], R. DODDAMANI[2], M. C. SHARMA[2], P. S. CHANDRA[2];
[1]All India Inst. of Med. Sci. (AIIMS), N, All India Inst. of Med. Sci. (AIIMS), New Delhi, India, New Delhi Delhi, India; [2]All India Inst. of Med. Sci. (AIIMS), New Delhi, New Delhi, India; [3]Univ. of Delhi, ACBR, Univ. of Delhi, Delhi, India

Abstract: Low-grade supratentorial tumors, like dysembryoplastic neuroepithelial tumors (DNETs), gangliogliomas etc., is associated with neoplasms responsible for focal epilepsy. These glioneuronal tumors constitute the second largest group of brain lesions responsible for early-onset drug-resistant epilepsy (DRE). Non-neoplastic peritumoral cortex in glioneuronal tumors could develop epileptogenic networks due to complex tumors environment, which may be different from abnormal neuronal networks in the cortex of non-tumor linked DRE pathologies. Synaptic transmission is known to be modulated in the DRE pathologies,

significantly contributing to epileptogenicity in these patients. Here we compared the spontaneous glutamatergic and GABAergic activity from resected brain samples obtained from patients with DNET and non-tumor linked DRE pathology cortical dysplasia (CD). Brain specimens were obtained from patients undergoing electrocorticography-guided surgery for DNET (FCD type IIIb) and CD (FCD type I and II). Whole-cell patch clamp technique was used to record spontaneous glutamatergic and GABAergic currents from normal-looking pyramidal neurons in slice preparations of resected brain samples. We detect increased frequency and amplitude of glutamatergic events in the non-neoplastic samples of DNET patients compared to non-seizure controls. We did not observe any alteration in the $GABA_A$ receptor-mediated synaptic transmission in the pyramidal neurons of non-neoplastic samples obtained from patients with DNET. In cortical samples of FCD type I and II, we observed that frequency and amplitude of spontaneous GABAergic was higher compared to that in case of non-epileptic controls. Further, we observed that glutamatergic activity remains unaltered in FCD type I and II samples. Our findings indicate that in the non-neoplastic samples obtained from patients with DNET glutamatergic activity was enhanced, without affecting the GABAergic synaptic transmission. While in cortical samples of CD, increased GABAergic activity was recorded, without any significant change in glutamatergic synaptic transmission. These findings support the concept that epileptogenic mechanisms in patients with tumor-linked DNET could be different from non-tumor linked CD pathology of DRE.

Disclosures: **J. Banerjee:** None. **S. Dey:** None. **A.B. Dixit:** None. **M. Tripathi:** None. **R. Doddamani:** None. **M.C. Sharma:** None. **P.S. Chandra:** None.

Poster

113. Pathological Synaptic Transmission and Modulation

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 113.11

Topic: B.04. Synaptic Transmission

Support: NIH grant R01GM038765
FRIPRO-FRINATEK 230470
Duke University Anesthesiology Research Funds

Title: Neuroprotectin D1 analogue inhibits acute and chronic itch and modulates spinal cord synaptic transmission in mice

Authors: *K. FURUTANI[1], O. CHEN[1], A. K. MCGINNIS[1], C. N. SERHAN[3], T. V. HANSEN[4], R.-R. JI[2];
[1]Ctr. for Translational Pain Medicine, Dept. of Anesthesiol., [2]Ctr. for Translational Pain Medicine, Dept. of Anesthesiology, Cell biology, and Neurobio., Duke Univ. Med. Ctr., Durham, NC; [3]Ctr. for Exptl. Therapeut. and Reperfusion Injury, Dept. of Anesthesiology, Periopera, Brigham and Women's Hosp. and Harvard Med. Sch., Boston, MA; [4]Dept. of Pharmacy, Section for Pharmaceut. Chem., Univ. of Oslo, Oslo, Norway

Abstract: Specialized pro-resolving mediators (SPMs), such as resolvins, protectins, and maresins, have demonstrated potent anti-inflammation, pro-resolution, and antinociception actions in different animal models of inflammation (Xu et al., Nat Med, 2010). Recently, we reported that a stable analog of neuroprotection D1 (NPD1), 3-oxa-PD1$_{n\text{-}3\ DPA}$ (Oxa-PD1), produced potent inhibition in itching behaviors (scratching) in cutaneous T cell lymphomas (CTCL) mice following intrathecal injection (Nesman et al., 2021). However, the mechanism by which Oxa-PD1 suppresses chronic itch is unknown. Here, we show that Oxa-PD1 can inhibit both acute and chronic itch in different mouse models. Acute itch models were induced by intradermal injection of histamine and chloroquine, and chronic itch models were induced by lymphoma (CTCL) and atopic dermatitis by dinitrofluorobenzene (DNFB). To investigate synaptic mechanisms of itch, whole-cell patch-clamp recordings were also made from spinal cord dorsal horn (SDH) neurons of naïve and CTCL mice. Strikingly, intrathecal administration of Oxa-PD1 (100 ng) significantly and substantially suppressed scratching behavior in all the models of acute and chronic itch. The baseline frequency of spontaneous excitatory postsynaptic current (sEPSC) in SDH neurons was significantly increased in CTCL mice compared with that of naïve mice. Perfusion of spinal cord slices with Oxa-PD1 (10 ng/ml, 3 min) rapidly and significantly decreased both the frequency and amplitude of sEPSC in SDH neurons from CTCL mice but had no effects on SDH neurons from naïve mice. We also recorded spontaneous inhibitory postsynaptic current (sIPSC) from CTCL mice. There was not a significant difference in baseline frequency and amplitude of sIPSCs between CTCL mice and naïve mice. Notably, perfusion of Oxa-PD1 (10 ng/ml, 3 min) increased the frequency of sIPSC in the CTCL mice (1.8 vs. 3.8 Hz, P=0.014). These results indicate that 1) Oxa-PD1 can potently inhibit acute and chronic itch in mice and 2) Oxa-PD1 may inhibit itch via modulating both excitatory and inhibitory synaptic transmission. Our results suggest that certain SPMs and their analogs, such as Oxa-PD1 may be used to treat pruritus associated with different types of skin injuries.
References Xu et al., Nat Med. 2010;16(5):592-7. Nesman et al., Org Biomol Chem. 2021;19(12):2744-2752.

Disclosures: **K. Furutani:** None. **O. Chen:** None. **A.K. McGinnis:** None. **C.N. Serhan:** None. **T.V. Hansen:** None. **R. Ji:** None.

Poster

113. Pathological Synaptic Transmission and Modulation

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 113.12

Topic: B.04. Synaptic Transmission

Support: Grant #GCRLE-1920

Title: Investigation of the role of autonomic transmission in the regulation of ovarian aging

Authors: *O. A. MALAK, P. HAGHIGHI;
Buck Inst. for Res. on Aging, Novato, CA

Abstract: After the age of 30, women experience a drastic decline in fertility accompanied by a sharp decrease in egg quality, and by the age of 40 their chance of becoming pregnant is only 5%. However, we know little about the mechanisms responsible for this age-dependent decline. We have been investigating the role of neuronal innervation of the ovaries in the regulation of egg quality and ovarian longevity in aging mice. Ovaries and their vasculature are highly innervated by sympathetic neurons, and mounting evidence over the past decade in women and animal models suggests that aging is accompanied by an increase in sympathetic activity. In addition, accumulating evidence in women with polycystic ovarian syndrome (PCOS) and animal PCOS models indicates that they are prone to metabolic conditions such as diabetes and obesity, which in return can further compromise ovarian function and egg quality while increasing sympathetic drive. It is, therefore, plausible that intervention which could reduce sympathetic neural transmission in old mice could improve ovarian function and increase reproductive span. Despite these studies, the functional link between sympathetic activity and ovarian function is poorly understood, and we do not know how this functional link is affected by aging or chronic metabolic diseases. We have been developing a model for studying the role of sympathetic innervation in the regulation of ovarian function using a combination of genetics, electrophysiology, biochemistry and imaging in mice. We are investigating the outcomes of genetic and/or pharmacological manipulation of sympathetic input in ovarian health and egg quality. Our proposed experiments will provide important insights into ovarian biology and will establish a novel paradigm for testing pharmacological and genetic interventions aimed at countering ovarian function decline as a result of aging.

Disclosures: O.A. Malak: None. **P. Haghighi:** None.

Poster

113. Pathological Synaptic Transmission and Modulation

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 113.13

Topic: B.04. Synaptic Transmission

Support: NSF 1943514, NIH NS117686to R.R
NSF 1750295 to JJW
Heart and Stroke Foundation of Canada (G-18-0021605); Dalhousie University Brain Repair Centre (Knowledge Translation Grant) to GSR

Title: Mitochondrial calcium uniporter inhibitor Ru265 elicits asynchronous neuronal spiking activity at synapses

Authors: P. XU[1], ***S. SWAIN**[1], R. J. NOVOROLSKY[2], T. HUANG[4], J. J. WILSON[4], G. S. ROBERTSON[3], R. B. RENDEN[1];
[1]Dept. of Physiol. and Cell Biol., Univ. of Nevada, Reno, NV; [2]Dept. of Psychiatry, [3]Dept. of Pharmacol., Dalhousie Univ., Halifax, NS, Canada; [4]Dept. of Chem. and Chem. Biol., Cornell Univ., Ithaca, NY

Abstract: Mitochondrial calcium dysregulation by mitochondrial calcium overload can trigger cell death in neurons. Inhibiting the mitochondrial calcium uniporter (MCU), eliminating mitochondrial calcium overload, has been proposed as a therapeutic target to slow neurodegeneration. Ru265 is a cell-permeable inhibitor of the mitochondrial calcium uniporter (MCU) with nanomolar affinity. In vivo, Ru265 pretreatment reduces sensorimotor deficits and neuronal death following an ischemic episode. However, Ru265 also induced seizure-like behaviors, an undesirable side effect. Identifying the source of these side effects will allow development of better compounds to selectively inhibit MCU. We examined the effect of Ru265 on neuronal function in whole-cell patch-clamp recordings of neurons in brain slice, and Ca^{2+} imaging of primary hippocampal cells from mouse. Whole cell voltage clamp recordings from postsynaptic MNTB principal neurons, which receive excitatory inputs from the calyx of Held, show that treatment with Ru265 decreased evoked EPSC amplitude, but induced spontaneous, synchronized synaptic events which sensitive to TTX. Extracellular recordings form this synapse show that Ru265 causes spontaneous AP-mediated spikes, with presynaptic APs preceding the postsynaptic AP. These results suggest the presynaptic neuronal membrane is depolarized. Ca^{2+} imaging of hippocampal cells with fluo-4 showed spontaneous spiking activity after pretreatment with GABA and glycine inhibitors. Cells were classified by spiking patterns into high spiking, medium spiking, and low spiking populations. Ru265 treatment decreased spontaneous spiking activity but increased synchronized, high-amplitude events across all populations. MCU-fl mice treated with AAV-cre were used to determine whether the MCU contributes to these effects. Ru265 still accumulated in MCU-KO neurons, and the effects of Ru265 persisted in both experimental preparations described above when MCU was eliminated. These results suggest the effects of Ru265 are through a different molecular target. These interesting off-target effects of Ru265 on neuronal function provide mechanistic insight into the effect of ruthenium-based compounds, and assist in the design and validation of future compounds to engage MCU in electrically excitable cells.

Disclosures: **P. Xu:** None. **S. Swain:** None. **R.J. Novorolsky:** None. **T. Huang:** None. **J.J. Wilson:** None. **G.S. Robertson:** None. **R.B. Renden:** None.

Poster

113. Pathological Synaptic Transmission and Modulation

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 113.14

Topic: B.04. Synaptic Transmission

Support: 2016M3C7A1905481
2018R1A5A2024418
2020R1A2C3011464

Title: Thalidomide causes synaptic and cognitive dysfunctions by increasing BK channel activity

Authors: *H.-Y. LEE, T.-Y. CHOI, S.-Y. CHOI;
Seoul Natl. Univ. Sch. of Dent., Seoul Natl. Univ. Sch. of Dent., Seoul, Korea, Republic of

Abstract: Thalidomide is an immunomodulatory medicine usually prescribed for patients with multiple myeloma, but causes cognitive dysfunctions such as reversible memory loss. However, the mechanism of thalidomide causing cognitive dysfunction is still unknown. The effects of thalidomide on synaptic functions and cognitive behavior have been examined in a mouse model. The cognitive effects of thalidomide were evident in behavioral tests, including an avoidance test and a recognition test involving novel objects. In addition, thalidomide increased anxiety and depressive behaviors in an elevated plus maze test and in a tail suspension test. Interestingly, thalidomide elevated BK channel activity in the brain including hippocampus. Furthermore, thalidomide increased the paired pulse ratio of excitatory postsynaptic current (EPSC), which is consistent with a decreased rate of glutamate release. Paxilline, a BK channel blocker, blocked changes in the paired pulse ratio and in BK channel activity. Treatment with paxilline restored the cognitive dysfunctions caused by thalidomide. In conclusion, the findings suggest that thalidomide-induced BK channel hyperfunction is responsible for the pathological mechanism of cognitive dysfunctions caused by thalidomide.

Disclosures: H. Lee: None. **T. Choi:** None. **S. Choi:** None.

Poster

113. Pathological Synaptic Transmission and Modulation

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 113.15

Topic: B.04. Synaptic Transmission

Support: 1ZIANS003140-08

Title: Differential cleavage pathways of the synaptic adhesion molecule neuroligin-3

Authors: *K. MCDANIEL[1], K. W. ROCHE[2];
[1]Receptor Biol. Section, NIH/Brown Univ., Bethesda, MD; [2]Receptor Biol. Section, NIH, Bethesda, MD

Abstract: Communication between neurons is essential for basic brain function and is dependent on the formation and function of synapses. Pre- and post-synaptic neurons communicate via synapses and require proteins, such as cell adhesion molecules, for development and maintenance. Neuroligins are a family of post-synaptic transmembrane proteins that bind to pre-synaptic neurexins. Neuroligin-3 (NLGN3) is present in both excitatory and inhibitory synapses. Many nonsense, frameshift, and missense mutations in NLGN3 have been associated with autism spectrum disorder (ASD), greatly implicating NLGN3 in this disease. Additionally, the extracellular domain of NLGN3 has been shown to signal to glioma cells and a NLGN3 KO decreases glioma growth in animal models. It has previously been found that NLGN3 can be cleaved by proteases, creating at least two fragments: an extracellular domain (ECD) and a c-

terminal fragment (CTF). Cleavage of the ECD is thought to be mediated by the metalloproteases ADAM10, MMP3, and MMP9 and cleavage differs in basal and active states. Despite robust evidence of ECD cleavage in multiple models, little is known about the fragment's fate or neuronal signaling abilities post-cleavage. Even less is known about the CTF, despite its reliable stability in biochemical experiments. Here, we have found there are several CTF species revealing multiple cleavage events that differ in sensitivity to protease inhibitors. Our work is critical for understanding how NLGN3 functions physiologically and in disease conditions such as glioma and ASD. This work is supported by the NINDS Intramural Research Program.

Disclosures: K. McDaniel: None. **K.W. Roche:** None.

Poster

113. Pathological Synaptic Transmission and Modulation

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 113.16

Topic: B.04. Synaptic Transmission

Support: JSPS KAKENHI Grant Number JP18K05342

Title: Humanin, a bioactive peptide,enhances neurotransmitter release

Authors: N. IKEGAWA, A. KOZUKA, N. MORITA, M. MURAKAMI, N. SASAKAWA, ***T. NIIKURA**;
Sophia Univ., Sophia Univ., Tokyo, Japan

Abstract: Humanin (HN) is a 24-residue polypeptide and initially identified as a neuroprotective factor against Alzheimer's disease (AD) -related insults. HN suppresses neuronal death caused by amyloid beta, which plays the central role in AD pathogenesis, in vitro, and ameliorates memory deficit of AD mouse models. HN is a secretive peptide and the HN level in circulation decreases age-dependently. It is thus assumed that the change in HN level is implicated in aging-associated cognitive decline. S14G-HN, HN in which 14th serine is replaced by glycine, is a highly potent HN derivative, which has 1000-fold higher potency than HN. S14G-HN ameliorates memory impairment caused by muscarinic receptor antagonists in normal mice as well as AD model mice. To understand HN's function in cognitive activities, we first examined the acetylcholine (ACh) level in the hippocampus of mice by microdialysis. Intraperitoneal injection of S14G-HN increased ACh level in hippocampus in normal young mice. In a neuronal cell model, rat pheochromocytoma PC12 cells, S14G-HN increased ACh-induced dopamine release. Further, we performed amperometric analysis to examine the exocytotic time-course kinetics of single secretory events in adrenal chromaffin cells, widely utilized neuroendocrine cells. S14G-HN increased the frequency of secretory events and changed some other parameters in response to the ACh stimulation, indicating that HN directly enhances exocytosis in neuronal cells. These results suggest that HN functions as a modulator of neurotransmitter release under

the normal physiological condition, which can contribute to the maintenance of cognitive activities.

Disclosures: N. Ikegawa: None. **A. Kozuka:** None. **N. Morita:** None. **M. Murakami:** None. **N. Sasakawa:** None. **T. Niikura:** None.

Poster

113. Pathological Synaptic Transmission and Modulation

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 113.17

Topic: B.04. Synaptic Transmission

Support: Chellgren fellowship (RLC)
Neuroscience Summer fellowship (SM)

Title: Enigmatic actions of lipopolysaccharides (LPS) on membrane potential and glutamate receptors.

Authors: *R. L. COOPER[1], S. MCCUBBIN[1], D. A. HARRISON[2];
[1]Univ. of Kentucky Dept. of Biol., [2]Biol., Univ. of Kentucky, Lexington, KY

Abstract: The gram-negative endotoxin of lipopolysaccharides (LPS) triggers a pathological cytokine response in mammals due to bacterial sepsis. Upon treatment of sepsis with antibiotics, bacterial lysis results in a surge in LPS, causing cytokine storm, a rapid and potentially fatal inflammatory syndrome. However, in animal models LPS itself also has direct rapid cellular effects that include hyperpolarizing membrane potential, blocking glutamate receptors and even promoting release of glutamate. The mechanisms of action for these immediate responses are still unresolved. In addressing the action of membrane hyperpolarization, voltage gated K+ channel blockers 4-aminopyridine (4-AP at 3 mM), quinidine hydrochloride monohydrate (0.1 mM) and tetraethylammonium (TEA at 20 mM) were examined along with RNAi knockdowns of potential calcium activated K+ channels. The responses of LPS were not blocked. Even in the presence of glutamate, the membrane still hyperpolarizes with LPS. When the driving gradient for the ionotropic glutamate receptors is enhanced during hyperpolarization, spontaneous quantal responses are dampened in amplitude. Thus, glutamate receptors are blocked, and the mechanism of hyperpolarization remains unresolved. The larval Drosophila glutamatergic neuromuscular junction is used as a model synaptic preparation.

Disclosures: R.L. Cooper: None. **S. McCubbin:** None. **D.A. Harrison:** None.

Poster

114. Pre- and Postsynaptic Mechanisms in Long-Term Plasticity

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 114.01

Topic: B.05. Synaptic Plasticity

Support: NIH R01MH117130
NIH R21MH116315
NIH R01NS062736
NIH T32GM007377
`NIH T32MH082174

Title: D-serine inhibits non-ionotropic NMDAR-mediated LTD and dendritic spine shrinkage

Authors: E. V. BARRAGAN[1], M. ANISIMOVA[1], K. ZITO[1], ***J. A. GRAY**[2];
[1]Ctr. for Neurosci., Univ. of California Davis, Davis, CA; [2]Ctr. for Neurosci., Univ. of California, Davis, Davis, CA

Abstract: Long-term changes in synaptic strength are mediated throughthe activation of NMDA-type glutamate receptors, which are ionotropic glutamatereceptors and master regulators of synaptic plasticity. NMDARs are unique amongneurotransmitter receptors in that, in addition to glutamate binding, they alsorequire simultaneous binding of a co-agonist, which can be either glycine orD-serine, for the receptor channel to open. The identity of the co-agonist isdevelopmentally and spatially regulated in the brain, and most mature forebrainsynapses use D-serine as the primary co-agonist. Interestingly, there is agrowing literature demonstrating NMDAR-mediated LTD and spine shrinkage in thepresence of co-agonist-site competitive antagonists, and therefore the absenceof ion flux, a phenomenon that has been termed non-ionotropic NMDAR signaling.Thus, we hypothesized that the NMDAR co-agonism might regulate non-ionotropicNMDAR-mediated LTD. To test this hypothesis, we manipulated co-agonistavailability in mouse hippocampal slices during the induction of synapticplasticity using pharmacological and enzymatic scavenging approaches. We foundthat in the third postnatal week, scavenging endogenous co-agonists facilitatesnon-ionotropic NMDAR-mediated LTD and spine shrinkage independent ofinduction frequency. Surprisingly, we also find that a saturating concentrationof D-serine completely inhibits both non-ionotropic NMDAR-mediated LTD andspine shrinkage. These results suggest that the developmental increase inD-serine levels at forebrain synapses may act to limit non-ionotropic NMDARsignaling, thereby enhancing synapse stabilization and promoting mature forms ofsynaptic plasticity.

Disclosures: E.V. Barragan: None. **M. Anisimova:** None. **K. Zito:** None. **J.A. Gray:** None.

Poster

114. Pre- and Postsynaptic Mechanisms in Long-Term Plasticity

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 114.02

Topic: B.05. Synaptic Plasticity

Support: NCATS 1UH2 TR0022082
1P50 AA22534
Sanofi

Title: Moderate prenatal alcohol exposure deficits-induced in long-term potentiation (LTP), rhythmic activity, and glutamate release in the dentate gyrus. Enhancement in LTP following administration of the histamine H3 receptor inverse agonist SAR153954.

Authors: *M. GONCALVES-GARCIA[1], G. ACOSTA[1], S. DAVIES[2], D. D. SAVAGE[2], D. A. HAMILTON[1];
[1]Psychology, [2]Sch. of Med. - Neurosciences, Univ. of New Mexico, Albuquerque, NM

Abstract: The hippocampus is susceptible to the effects of prenatal alcohol exposure (PAE) which can result in persistent functional impairments. Although there have been many investigations, deficits in synaptic plasticity following PAE remain poorly understood. Previous studies have identified deficits in long-term potentiation (LTP) in the perforant pathway to dentate gyrus synapses as a robust consequence of PAE. Currently, there are no known, clinically effective pharmacotherapeutic interventions for these deficits. This study sought to investigate the effects of PAE on LTP in the dentate gyrus and the H3 receptor inverse agonist, SAR152954, as a possible agent to reverse deficits in LTP associated with PAE utilizing a rat model of moderate PAE (42 mg/dl peak blood alcohol content). A principal function of H3Rs is the modulation of glutamate release. In adulthood, rats were given a single injection of SAR152954 (0.1 or 1.0 mg/kg) or saline (vehicle) 30 min prior to the recording session. Saline-treated PAE rats displayed reduced LTP relative to controls ($p = 0.05$). Control rats receiving 0.1 mg/kg SAR152954 displayed decreased LTP relative to VEH. PAE rats receiving 0.1 mg/kg SAR152954 did not show reversal of PAE-induced deficits ($p > 0.8$). However, the 1.0 mg/kg dose reversed PAE-induced deficits to levels comparable to the control animals ($p > 0.7$) and greater than PAE animals that received either the vehicle or low dose SAR152954 conditions ($p = 0.02$). this observation suggests that glutamate release may be altered in PAE and may be a target for intervention. Additionally, we investigated how PAE influences continuous EEG signaling and time-frequency relationships in evoked responses after high-frequency stimulation (HFS). Time-frequency analyses performed on individual evoked responses revealed a greater increase in power associated with the fEPSP in SAC rats, consistent with PAE-related alterations that affect the earliest components of excitatory synaptic transmission. To determine if glutamate release is altered in PAE, a second experiment was conducted in which a glutamate biosensor was implanted into the dentate gyrus. The fractional amplitude measure revealed less change in the PAE group compared to controls ($p = 0.037$). These observations suggest that deficits in LTP following PAE may be related to alterations in the presynaptic mechanisms associated with LTP.

Disclosures: M. Goncalves-Garcia: None. **G. Acosta:** None. **S. Davies:** None. **D.D. Savage:** None. **D.A. Hamilton:** None.

Poster

114. Pre- and Postsynaptic Mechanisms in Long-Term Plasticity

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 114.03

Topic: B.05. Synaptic Plasticity

Support: NIH intramural funding

Title: Enhanced depotentiation in a Kv4.2 mouse model of improved cognitive flexibility

Authors: *C. MALLOY[1], J.-H. HU[2], A. PRATT[2], M. WELCH[2], M. AHERN[2], D. A. HOFFMAN[2];
[1]Natl. Inst. of Child Hlth. and Human Develop., [2]NIH, Bethesda, MD

Abstract: The A-type potassium current (I_A) is a vital regulator of neuronal excitability and synaptic plasticity. In rodent hippocampal CA1 pyramidal cells, this current is carried primarily by voltage-gated Kv4.2 K+ channels. Along with other voltage-gated ion channels localized in the somatodendritic compartment of pyramidal cells, Kv4.2 contributes to dendritic integration by filtering synaptic inputs. Kv4.2 functions in a macromolecular complex together with the auxiliary subunits K+ channel interacting proteins (KChIPs) and DPLP(s) in the mouse hippocampus. Proper assembly and dynamic regulation of this complex is integral in facilitating its role in neuronal signal processing and plasticity. To illuminate potential molecular modifiers of the complex, we used a proteomic screen. We identified a molecular cascade involving p38 kinase-mediated Pin1 isomerization of a C-terminal motif in Kv4.2 as a crucial regulator of Kv4.2-DPP6 binding dynamics. To probe the role of this p38-Pin1 cascade in regulating the Kv4.2 complex and neuronal function, Crispr-cas9 technology was utilized to generate a knock-in mouse model (Kv4.2TA) with abolished p38 and Pin1-Kv4.2 binding. We have used whole-cell patch clamp electrophysiology to investigate the consequences of this impaired binding and loss of dynamic regulation on neuronal physiology and behavior. Kv4.2TA mice display reduced neuronal excitability which can be traced to an increase in I_A density. In multiple behavioral tests of hippocampal-dependent learning and memory, Kv4.2TA mice demonstrated enhanced reversal learning, indicative of improved cognitive flexibility. To decipher the detailed mechanisms underlying this cognitive phenotype, single-cell measures of spike timing-dependent long-term potentiation (STD-LTP) and long-term depression (LTD) were performed in CA1 pyramidal neurons in acute hippocampal slices. Intriguingly, while synaptic plasticity from basal state is preserved in Kv4.2TA mice relative to WT, a notable enhancement in the removal of STD-LTP (depotentiation magnitude) was observed in Kv4.2TA mice, suggestive of a synapse state-dependent difference in synaptic plasticity in CA1 stratum-radiatum of the hippocampus. We have, therefore, revealed a novel metaplasticity mechanism in a Kv4.2 mouse model. Further insights into the correlation of this plasticity and the cognitive flexibility phenotype exhibited by this mouse model are on-going.

Disclosures: C. Malloy: None. **J. Hu:** None. **A. Pratt:** None. **M. Welch:** None. **M. Ahern:** None. **D.A. Hoffman:** None.

Poster

114. Pre- and Postsynaptic Mechanisms in Long-Term Plasticity

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 114.04

Topic: B.05. Synaptic Plasticity

Support: DoD Grant A2170142

Title: Hippocampal synaptic excitability in a repeat traumatic brain injury Alzheimer's disease mouse model

Authors: *E. WEBBER[1], N. BARRINGTON[1], D. STEINBRENNER[1], J. MCDAID[2], G. STUTZMANN[1];
[1]Neurosci., Rosalind Franklin Univ. of Med. and Sci., North Chicago, IL; [2]Div. of Neurosurg., NorthShore Univ. HealthSystem, Chicago, IL

Abstract: Alzheimer's disease (AD) shares several comorbidities with traumatic brain injury (TBI), such as deficits in memory function and behavioral regulation. These shared qualities impart a unique relationship; effects resulting from TBI, including altered Ca^{2+} homeostasis, increase the likelihood of developing neurodegenerative disorders such as AD. The long-term effects of repeat impact TBI (rTBI) and their contribution to synaptic deficits remain unknown. Our research objective is to identify connections between AD and rTBI at the synaptic signaling level. To study synaptic transmission and plasticity outcomes, we subjected male and female 3xTg-AD mice and age-matched non-transgenic controls to rTBI consisting of three closed-head controlled-cortical impacts or sham treatment protocols. 30-days post procedure, hippocampal slices were harvested for electrophysiological recordings of synaptic transmission and plasticity properties in the Schaffer collateral CA1-synapse of the hippocampus, 2-photon calcium imaging, or immunostaining of histopathological markers. Current data indicate that rTBI-induced synaptic deficits contribute further to alteration of long-term potentiation, the cellular correlate of learning and memory. To date, our findings support common upstream pathogenic signaling mechanisms in TBI and AD, such as Ca^{2+} dyshomeostasis, which may play a role in increased vulnerability to developing dementia after brain injury.

Disclosures: E. Webber: None. **N. Barrington:** None. **D. Steinbrenner:** None. **J. McDaid:** None. **G. Stutzmann:** None.

Poster

114. Pre- and Postsynaptic Mechanisms in Long-Term Plasticity

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 114.05

Topic: B.05. Synaptic Plasticity

Support: CIHR
NSERC
OGS
FRQNT
Brain and Mind Research Institute

Title: Features of a novel form of extended time scale synaptic plasticity supports the presence of eligibility traces in the prefrontal cortex

Authors: *L. CAYA-BISSONNETTE[1,2], R. NAUD[1,2], J.-C. BEIQUE[2];
[2]Cell. and Mol. Med., [1]Univ. of Ottawa, Ottawa, ON, Canada

Abstract: Learning and memory processes are fundamental to survival in dynamic environments. At the crux of current cellular models of learning is Long-Term Potentiation (LTP), a mechanism reinforcing synaptic weights over extended periods of time. LTP can be induced by Spike-Timing-Dependent Plasticity protocols that typically require dozens of near-simultaneous (0ms-50ms) firing of pre- and postsynaptic neurons. In striking opposition, supervised learning operating in behavioural contexts can occur with few repetitions, and on longer timescale. To reconcile these timescales, eligibility traces, an unknown biochemical process priming synapses to remain eligible for potentiation for extended periods of time, have long been hypothesized as a solution to this temporal credit assignment problem. Yet their existence and exact nature have not been conclusively established. Here, using whole-cell recordings and 2-photon microscopy, we examined the ability of pre- and postsynaptic events to induce LTP at behaviourally relevant timescale in layer 5 pyramidal neurons of mice prefrontal cortex (male and female; P21-P45). We observed that pairing a few pre- and postsynaptic events with significant temporal delays (0.5s–1.5s) reliably and robustly induced LTP. This novel plasticity followed unexpected rules that depended on bursting and that were modulated by noradrenaline, a neuromodulator involved in conveying saliency signals. The temporal and spatial rules of this form of plasticity were further investigated by 2-photon uncaging and Calcium (Ca^{2+}) imaging that highlighted a spatially-constrained, latent memory trace of Ca^{2+} dynamics generated from the binding of pre- and postsynaptic events. We developed a Ca^{2+} threshold-based model that captures these plasticity rules. The features of this novel plasticity support the existence of eligibility traces, and provide a potential avenue of solution to the temporal credit assignment problem in binding synaptic and behavioural forms of learning.

Disclosures: L. Caya-Bissonnette: None. **R. Naud:** None. **J. Beique:** None.

Poster

114. Pre- and Postsynaptic Mechanisms in Long-Term Plasticity

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 114.06

Topic: B.05. Synaptic Plasticity

Support: P&K Puehringer Foundation

Title: Dopamine modulation of motor skill acquisition and synaptic plasticity after stroke

Authors: *Y. TIAN[1], C. VITRAC[1], A. R. LUFT[1,2], M.-S. RIOULT-PEDOTTI[1,3];
[1]Vascular Neurol. and Neurorehabilitation, Univ. Hosp. Zurich, Zurich, Switzerland; [2]Cereneo, Vitznau, Switzerland; [3]Brown Univ., Providence, RI

Abstract: Dopamine (DA) has been shown to modulate motor skill acquisition and activity-dependent synaptic plasticity (long-term potentiation, LTP) in the forelimb area of the primary motor cortex. Blocking DA receptors in healthy rats impairs motor skill acquisition and LTP. We tested the hypothesis that dopaminergic modulation is involved in the motor recovery following ischemic strokes. After a stroke DAergic modulation was transiently altered in the penumbra of the affected hemisphere as well as in the unaffected contralateral hemisphere. One week post-stroke DA receptor antagonists had no effect on LTP. Two weeks post-stroke, LTP was impaired as in healthy rats. These results were paralleled by the expression of DA2 receptor expression: at one week. DA2 receptor expression was highly reduced. This transient independence of DA modulation similarly affected the learning abilities of rats post-stroke. Stroke rats treated with DA receptor antagonists or saline were re-trained in the skilled reaching task. There was no difference of the success rate between saline and DA receptor antagonist treated rats during the 1st week post-stroke. However, the learning curve of DA antagonist treated rats started to slow in the second week post-stroke and plateaued on a significantly lower success rate than the saline treated rats. Our results indicate that DA modulation of motor skill acquisition and LTP is transiently impaired after stroke, and only involved in a later phase of recovery. This suggests that mechanisms of post-stroke motor learning and post- stroke LTP are different from healthy condition.

Disclosures: Y. tian: None. **C. Vitrac:** None. **A.R. Luft:** None. **M. Rioult-Pedotti:** None.

Poster

114. Pre- and Postsynaptic Mechanisms in Long-Term Plasticity

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 114.07

Topic: B.05. Synaptic Plasticity

Support: Fondecyt Postdoctoral Grant #3190843
Fondecyt Postdoctoral Grant #3190793
Fondecyt Regular Grant #1190833
Fondecyt Regular Grant #1171840
Fondecyt Regular Grant #1201848
DIUV-CI Grant #01/2006
Millenium Science Initiative Program ACE210014

Title: Eaat3 overexpression leads to impaired excitatory plasticity in the medial prefrontal cortex

Authors: *A. P. ESCOBAR[1,2], R. C. MEZA[3,4], C. MORALES-MORAGA[3,4], C. ANCATÉN-GONZÁLEZ[3,4], P. R. MOYA[1,4], A. E. CHÁVEZ[3,4], C. Q. CHIU[3,4];
[1]Inst. de Fisiología, Univ. De Valparaíso, Valparaiso, Chile; [2]Ctr. de Neurobiología y Fisiopatología Integrativa, Valparaiso, Chile; [3]Insituto de Neurociencias, Univ. De Valparaiso, Valparaiso, Chile; [4]Ctr. Interdisciplinario de Neurociencias de Valparaiso, Valparaiso, Chile

Abstract: Glutamate is a major excitatory neurotransmitter, whose synaptic and extra-synaptic levels are tightly controlled by excitatory amino acid transporters (EAATs) that are thought to be located in glial cells. The contribution of EAAT3, which is expressed in neurons, is less clear. We previously reported that mice overexpressing EAAT3 in principal forebrain neurons (EAAT3glo/CMKII mice) show increased anxiety and compulsive behavior, and impaired extinction of fear conditioning, which is accompanied by an increased contribution of Glu-N2B-containing NMDA receptors and absent long-term depression (LTD) at cortico-striatal synapses. Since the medial prefrontal cortex (mPFC) is involved in the generation of these behaviors, we assessed whether EAAT3 overexpression may impact pyramidal neuronal function and plasticity in this region. In coronal mPFC slices of EAAT3glo/CMKII mice and control littermates, whole-cell patch-clamp recordings revealed unchanged basal excitatory synaptic transmission and mostly similar intrinsic electrophysiological properties such as resting potential, action potential kinetics and rheobase. However, we found a higher hyperpolarization in response to negative somatic current injections in EAAT3glo/CMKII pyramidal cells, suggesting subtle modifications in membrane ionic conductances and excitability. 2-photon microscopy experiments show that a back-propagated action potential triggers comparable Ca^{2+} increases in dendritic spines in both genotypes. Additionally, in field recordings in mPFC layer 1, low-frequency electrical stimulation (1 Hz, 15 min) induced long-term depression (LFS-LTD) in control animals which was blunted in EAAT3glo/CMKII mice, indicating impaired excitatory plasticity in mPFC due to EAAT3 overexpression. Given that this LFS-LTD is dependent on metabotropic glutamate receptor activation, the lack of LTD in EAAT3glo/CMKII mice suggests decreased glutamate spillover to activate extra-synaptic glutamate receptors when EAAT3 function is increased. In conclusion, EAAT3 may be recruited to control excitatory synaptic transmission and plasticity during repetitive activity and EAAT3 gain of function may underlie impaired learning and cognitive control.

Disclosures: **A.P. Escobar:** None. **R.C. Meza:** None. **C. Morales-Moraga:** None. **C. Ancatén-González:** None. **P.R. Moya:** None. **A.E. Chávez:** None. **C.Q. Chiu:** None.

Poster

114. Pre- and Postsynaptic Mechanisms in Long-Term Plasticity

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 114.08

Topic: B.05. Synaptic Plasticity

Support: FONDECYT Regular # 1201848
FONDECYT Regular # 1171840

FONDECYT Regular # 1190203
FONDECYT postdoctoral grant #3190793
Millennium Science Initiative Program ACE210014

Title: Presynaptic BK channels mediate mGluR-LTD in neonatal hippocampus

Authors: C. ANCATÉN-GONZÁLEZ, R. C. MEZA, N. GONZÁLEZ, I. SEGURA, R. LATORRE, C. Q. CHIU, ***A. E. CHÁVEZ**;
Ctr. Interdisciplinario de Neurociencias de Valparaíso (CINV), Univ. De Valparaiso, Valparaiso, Chile

Abstract: BK channels are expressed in synaptic terminals, which have been shown to control transmitter release. Still, their role in activity-dependent long-term changes of synaptic function remains unclear. Here, we report that presynaptic BK channels are essential in long-term depression induced by repetitive low-frequency stimulation of Schaffer collaterals onto CA1 pyramidal neurons (LFS-LTD) in hippocampal slices from P4-P10 mice. Consistent with the dependence of LFS-LTD on metabotropic glutamate receptors (mGluRs), we find that 12-(s)-HPETE, an arachidonic acid metabolite produced downstream of postsynaptic mGluRs, is required to trigger this depression. LTD induced by LFS or by direct activation of mGluRs with the agonist DHPG was mimicked and occluded by application of 12-HPETE or by the BK channel opener NS11021, suggesting that the metabolite and the channel converge on the same plasticity expression process. This form of mGluR-LTD is presynaptic as both the paired-pulse ratio and the coefficient of variation were increased after induction. Importantly, paxilline but not iberiotoxin blocked both LFS- or DHPG-induced mGluR-LTD, suggesting the specific involvement of BK channels formed by α and β4 subunits. Consistent with this idea, 12-(s)-HPETE strongly increases the channel open probability of (α + β4)BK but not αBK channels expressed in *Xenopus laevis* oocytes. In addition, we found that paxilline failed to reverse mGluR-LTD, indicating that presynaptic BK channels are only required during mGluR-LTD induction, but not during maintenance. Notably, intracellular loading of paxilline does not prevent mGluR-LTD but reduces afterhyperpolarization in CA1 pyramidal neurons, strongly suggesting that presynaptic rather than postsynaptic BK channels are involved. Altogether, our findings reveal a previously unknown interaction between 12-(s)-HPETE and BK channels to regulate synaptic strength at central synapses and elucidate novel key players in mGluR-LTD during development that may contribute to circuit maturation.

Disclosures: C. Ancatén-González: None. **R.C. Meza:** None. **N. González:** None. **I. Segura:** None. **R. Latorre:** None. **C.Q. Chiu:** None. **A.E. Chávez:** None.

Poster

114. Pre- and Postsynaptic Mechanisms in Long-Term Plasticity

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 114.09

Topic: B.05. Synaptic Plasticity

Support: NIH-R35 GM124824
NIH-R01 NS118014

Title: Regulation of hippocampal long-term depression (LTD) and learning and memory by a novel endosomal proton activated chloride (PAC) channel

Authors: *K. H. CHEN, J. YANG, C. JIANG, Z. QIU;
Physiol., Johns Hopkins Univ., Baltimore, MD

Abstract: Proper endosomal acidification is essential for the trafficking of AMPA receptors (AMPAR) during synaptic plasticity, a core neuronal process underlying complex behaviors such as learning and memory. Mutations in sodium proton exchangers (NHEs) and chloride transporters (CLCs), endosomal ion transporters that regulate pH, are both implicated in human and mouse neurological disorders. Through an unbiased RNAi screen, our lab has recently identified a new proton activated chloride (PAC) channel and established its role in regulating endosomal chloride concentration and lumen acidification. Because PAC is highly expressed in the central nervous system, we hypothesized that PAC regulates activity-dependent AMPAR trafficking and synaptic plasticity. To test this, we first examined the localization of PAC using immunofluorescence in primary hippocampal neurons and found that PAC traffics to dendritic endosomes, vesicles that supply AMPARs for synaptic plasticity. We then generated pyramidal neuron-specific PAC conditional knockout (cKO) mice using NEX-Cre. PAC cKO mice were grossly normal with normal neuronal morphology and basal synaptic transmission. Interestingly, while LTP was unaffected, we observed marked impairments in LTD in acute hippocampal slices from 5-week-old male and female mice (n=7). To explore cellular mechanisms of PAC in synaptic plasticity, we performed a well-established NMDA-induced chemical LTD assay in primary cortical neurons. NMDA treatment induced a decrease in surface AMPAR subunit GluA2 in control neurons treated with scramble shRNA. Notably, acute knockdown of PAC using PAC shRNA abolished the internalization of GluA2 during chemical LTD (n=3), suggesting an important role of endosomal PAC channel in activity-dependent AMPAR endocytosis. Finally, to assess the physiological consequences of impaired LTD in PAC cKO mice, we conducted several behavioral tests on male PAC cKO mice aged 2-5 months to assess learning and memory. Consistent with the electrophysiological and biochemical data, PAC cKO mice performed poorly in the Morris Water Maze behavioral assay (n=13-14). Altogether, we propose that by regulating postsynaptic endosomal acidification, the novel PAC channel is an important new player in modulating synaptic plasticity and learning and memory.

Disclosures: K.H. Chen: None. **J. Yang:** None. **C. Jiang:** None. **Z. Qiu:** None.

Poster

114. Pre- and Postsynaptic Mechanisms in Long-Term Plasticity

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 114.1

Topic: B.05. Synaptic Plasticity

Title: Changes in concentration of NMDA receptor subunits in the hippocampus upon chemically induced LTP and LTD during developmental growth spurts

Authors: *T. L. SKJERVOLD, S. DAVANGER;
Mol. Med., Univ. of Oslo, Oslo, Norway

Abstract: The glutamate receptor composition of different subunits determines a wide range of physiological characteristics in the postsynaptic spine. The AMPA receptors change rapidly between extrasynaptic sites and the synaptic zone upon NMDA receptor stimulation during long-term potentiation. The NMDA receptor subunits are important for both synaptic stability and change, and further the evolution of memory. The NMDA receptor subunit composition is known to vary during development. Synaptic NMDA receptors switch from containing mostly GluN2B subunits to a more GluN2A-rich heterotrimers during development. The pathways and vesicular machinery behind this type of synaptic change, however, is rather poorly understood. The SNARE-protein machinery, known to exist in the presynaptic active zone, also plays a role in regulation of receptor composition in the postsynaptic spine. SNARE proteins would likely be susceptible to changes during chemical stimulation of long-term potentiation (LTP) and long-term depression (LTD). In the present study, we report changes in the distribution of synaptic glutamate receptor subunits under basal and stimulated conditions during postnatal development in the rat hippocampus. We demonstrate the effective separation of synaptic compartments through biotinylation of treated hippocampal slices, and, for the first time, the effect of chemically induced LTP and LTD on NMDA receptor subunit composition. The change in subsynaptic distribution of NMDA receptor subunits in untreated synaptosomes during development supports a switch in receptor composition. The AMPA receptor subunit GluA1 was found to be continuously declining in the total synaptosomal fraction throughout the developmental stages investigated. Forskolin stimulation evokes a shift from the cytosolic or extrasynaptic membrane pools to the PSD at p30, for both NMDA receptor subunits GluN2A and GluN2B. This effect was protein kinase A dependent. While chemically induced LTD through (S)-3,5-DHPG had a similar effect as LTP induced by forskolin on NMDA receptor subunits at p30, but not at p60. Chemical LTP stimulation also seems to evoke a direct insertion of GluA1 into the PSD. Contrary to our hypothesis, (S)-3,5-Dihydroxyphenylglycine induced a similar increase. We also found that the PSD concentration of the vesicle associated protein VAMP2 decreased upon both chemically induced LTP and LTD, indicating a retraction of postsynaptic vesicles. These aspects of synaptic plasticity are probably related to learning and normal cognitive development in children, but may possibly also be a risk factor for epilepsy.

Disclosures: T.L. Skjervold: None. **S. Davanger:** None.

Poster

114. Pre- and Postsynaptic Mechanisms in Long-Term Plasticity

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 114.11

Topic: B.05. Synaptic Plasticity

Support: NIH Grant NS111986

Title: Endocannabinoid-mediated enhancement of hippocampal long-term potentiation

Authors: *F. LEMTIRI-CHLIEH, E. S. LEVINE;
Neurosci., Univ. of Connecticut Sch. of Med., Farmington, CT

Abstract: It is widely accepted that exogenous cannabinoids can impair short-term memory and cognition in humans and other animals. This is likely related to inhibition of long-term potentiation (LTP), a form of synaptic plasticity, by the global and sustained activation of CB1 cannabinoid receptors in the presence of exogenous agonists. Conversely, the temporally and spatially-restricted release of endogenous cannabinoid (eCB) ligands may enhance synaptic plasticity in a synapse-specific manner. We examined the role of eCB signaling in LTP by recording fEPSPs in the CA1 stratum radiatum in hippocampal slices from juvenile mice. LTP was induced either electrically, by theta burst stimulation (TBS), or pharmacologically, by treatment for 15 min with a cocktail of forskolin and rolipram designed to increase intracellular cAMP (chem-LTP). TBS-LTP lasted greater than 60 min and the magnitude of this potentiation was significantly reduced by blocking cannabinoid receptor activation with the selective CB1 receptor antagonist NESS-0327 or the inverse agonist SR-141716A. Chem-LTP caused a sustained 2-fold increase in fEPSP slope and was also blocked by CB1 receptor antagonists. Because endogenous cannabinoids can also activate the VR1 receptor, we examined the effects of the VR1 antagonist capsazepine, which had no effect on TBS-LTP or chem-LTP. We next attempted to identify the eCB ligand(s) that are involved in LTP modulation. The synthesis of the endogenous ligand 2-AG was inhibited using the DAG lipase inhibitor DO34 and anandamide synthesis was targeted using the NAPE-PLD inhibitor LEI-401. TBS-LTP was inhibited by ~50% by LEI and DO34 individually. Combined, they had an additive effect that caused a complete block of TBS-LTP. Similarly, chem-LTP was partially inhibited by DO34 and LEI-401 individually, and a greater effect when combined. We hypothesized that activation of CB1 receptors by endogenous 2-AG and anandamide enhanced LTP due to eCB-mediated suppresson of inhibition. We therefore examined the effect of blocking inhibitory synapses with the GABA-A receptor blocker picrotoxin (PTX). PTX completely prevented the effect of CB1 antagonists or inhibition of eCB synthesis on TBS-LTP and chem-LTP, indicating that intact GABAergic transmission is required for eCB modulation. The presence of PTX did not unmask any enhancing effect of CB1 receptor blockade, suggesting minimal eCB-mediated suppression of glutamate release under these conditions. These results indicate that activation of CB1 receptors by 2-AG and anandamide enhances TBS-induced and pharmacologically-induced LTP, and this effect is caused by the actions of eCBs at inhibitory synapses.

Disclosures: F. Lemtiri-Chlieh: None. **E.S. Levine:** None.

Poster

114. Pre- and Postsynaptic Mechanisms in Long-Term Plasticity

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 114.12

Topic: B.05. Synaptic Plasticity

Support: MOST 110-2320-B-A49A-503
MOST 110-2320-B-A49A-504

Title: Physiological regulation and underlying mechanisms of synaptic plasticity by direct current modulation

Authors: *C.-H. CHANG[1], C.-W. LEE[1], M.-C. CHU[1], T.-N. PENG[1], T.-J. YANG[1], H. CHI[1], Y.-C. LIN[1], H.-C. LIN[1,2];
[1]Inst. of Physiology, Natl. Yang Ming Chiao Tung Univ., Taipei, Taiwan; [2]Brain Res. Center, Natl. Yang Ming Chiao Tung Univ., Taipei, Taiwan

Abstract: Transcranial direct current stimulation (tDCS) is a non-invasive therapy widely progressed to improve several neuronal disorders by modification of neuronal plasticity in clinical and neuroscientific researches. In previous studies, tDCS modulates the resting membrane potentiation of local neurons by depolarization and hyperpolarization at the targeted area of the brain, which expect to exhibit excitatory and inhibitory effects in appropriate conditions. Plasticity change often occurs in such types of brain activities, which mediated by alternation of synaptic strength and connection, is the basis for neuronal function such as learning and memory. Activation of excitatory glutamate receptors, N-methyl-D-aspartate receptors (NMDARs), was implicated in molecular pathways of plasticity change. FK506-binding protein 51 (FKBP51), stress-related gene, is considered as an important molecular pathway which modulate the synaptic function in such disease models. To clarify whether tDCS treatment regulates synaptic plasticity in physiological condition, we applied *in vivo* tDCS model on C57BL/6 mice, and *ex vivo* DCS model on hippocampal brain slice. First, Increased synaptic responses were detected after anodal DCS treatment in electrophysiological recordings, while no change of tau and decay time were detected. Decreased synaptic responses were detected after cathodal DCS treatment in electrophysiological recordings, while no change of tau and decay time were detected. Next, NMDAR and FKBP51 expression were upregulated by anodal DCS and downregulated by cathodal DCS, which detected by western blot assay. Last, Increased neuronal activation was detected in the hippocampus of C57BL/6 mice after *in vivo* tDCS treatment by immunofluorescence. As mentioned above, *ex vivo* data showed that anodal and cathodal DCS treatment performed excitatory and inhibitory effects on neuronal plasticity with involvement of NMDAR and FKBP51 under physiological situations, *in vivo* data were indicating that neuronal activities modulated by tDCS treatment.

Disclosures: C. Chang: None. **C. Lee:** None. **M. Chu:** None. **T. Peng:** None. **T. Yang:** None. **H. Chi:** None. **Y. Lin:** None. **H. Lin:** None.

Poster

114. Pre- and Postsynaptic Mechanisms in Long-Term Plasticity

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 114.13

Topic: B.05. Synaptic Plasticity

Support: P&K Pühringer Foundation

Title: Transient modification of synaptic transmission and plasticity during stroke recovery

Authors: A. LUFT[1,2,3], ***M.-S. RIOULT-PEDOTTI**[4,1];
[1]Vascular Neurol. and Rehabil., Univ. of Zürich, Zürich, Switzerland; [2]Neurol., Univ. Hosp. Zürich, Zürich, Switzerland; [3]Ctr. for Neurol. and Rehabil., Cereneo, Weggis, Switzerland; [4]Brown Univ., Brown Univ., Providence, RI

Abstract: Advancement of the needed progress in the recovery from a stroke requires the comprehension of mechanisms underlying spontaneous repair in the subacute and chronic phase after stroke. A plethora of plasticity related modifications have been reported at different times after stroke in the past (molecular targets, motor maps, spines, dendrites etc) with a treatment focus on the acute phase. However, treatment in the acute phase is almost impossible mainly due to the narrow time windows of molecular targets and their biphasic roles after stroke: initially detrimental, later required for plasticity. However, understanding of functional change remains largely unanswered. Here, we studied the timeline of synaptic transmission using evoked field potentials as well as short- and long-term plasticity in the peri-infarct area in rat brain slices after photothrombotic stroke and compared the results to sham treated rats.We found that the variability of synaptic transmission as assessed by input-output curves started to increased 2-4 days post-stroke and returned to pre-injury at 3 weeks. At 2 weeks post-stroke, the synaptic modification range shifted upwards while average baseline amplitudes remained unchanged resulting in a larger amount of LTP and reduced LTD. At the same time, short-term plasticity assessed by paired pulse ratio indicated the involvement of a presynaptic mechanism absent in sham and healthy rats suggesting that plasticity mechanisms are not solely located at the postsynaptic site as in healthy rats. These results indicate a time window (1-2 weeks) where intervention might be beneficial for more versatile treatment options which finally might result in a more satisfactory outcome for stroke survivors.

Disclosures: **A. Luft:** None. **M. Rioult-Pedotti:** None.

Poster

114. Pre- and Postsynaptic Mechanisms in Long-Term Plasticity

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 114.14

Topic: B.05. Synaptic Plasticity

Support: Fellowship 725800 (LAM) from Consejo Nacional de Ciencia y Tecnología, México.
Fellowship 727269 (EG) from Consejo Nacional de Ciencia y Tecnología, México.

Title: Transient hypofunction of NMDA receptors impairs the induction of synaptic plasticity at the Mossy Fiber - CA3 synapse

Authors: *L. A. MÁRQUEZ, E. GRIEGO, C. LOPEZ-RUBALCAVA, E. J. GALVÁN; Farmacobiología, Ctr. de Investigación y de Estudios Avanzados, Mexico City, Mexico

Abstract: Growing evidence indicates that electrophysiological properties and synaptic plasticity of hippocampal cells are compromised in multiple psychiatric disorders and that transient hypofunction of NMDA receptors during early brain development is central to this dysregulation. Despite the relevance of this tenet, little is known about the changes endured by granule cells axons, the mossy fibers, and contacting CA3 pyramidal cells (MF-CA3 synapse). In this study, we present experimental evidence that male rats (postnatal day P, P35-P45) transiently treated with the NMDA receptor antagonist MK-801 (0.2 mg/kg subcutaneously injected at P7-P11) exhibit altered biophysical properties and reduced synaptic plasticity capabilities as revealed with whole-cell patch-clamp recordings and extracellular recordings from the MF-CA3 synapse. A reduction in the MF field Excitatory Postsynaptic Potential (MF fEPSP) amplitude was systematically observed in MK-801 slices compared to control slices. Also, increased MF PPR (determined with paired pulses with 60 ms ISI) was observed in acute slices from MK-801 treated animals, suggesting presynaptic dysregulation of glutamate release. Consistent with this finding, tetanic stimulation of the MF bundle, situated in the stratum lucidum (100 Hz, 1 s; repeated 3 times at 10 s) elicited blunted post-tetanic potentiation and reduced MF LTP in the slices of MK-801 treated animals. Whole-cell patch-clamp recordings revealed decreased AMPA/NMDA current ratio in CA3 pyramidal cells and increased output discharge without changes in passive electrophysiological properties. Although induction and expression of MF LTP are independent events of NMDA receptor activity, our data indicate that transient hypofunction of NMDARs during early postnatal development dysregulates the intracellular control of glutamate release from dentate gyrus granule cells and modifies the AMPA/NMDA current ratio of CA3 pyramidal cells. These changes may explain the reduced levels of MF LTP and partially explain, the cognitive impairment associated with transient hypofunction of NMDA receptors.

Disclosures: L.A. Márquez: None. **E. Griego:** None. **C. Lopez-Rubalcava:** None. **E.J. Galván:** None.

Poster

114. Pre- and Postsynaptic Mechanisms in Long-Term Plasticity

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 114.15

Topic: B.05. Synaptic Plasticity

Support: NIH Grant R37NS045876
Yale Wu Tsai Institute

Title: Mitochondrial basis for hippocampal learning and memory formation

Authors: A. SHTEYMAN, S. SUBRAMANIAN, H. ROLYAN, *E. A. JONAS;
Yale Univ. Sch. Med., Yale Univ. Sch. Med., New Haven, CT

Abstract: Uncovering the neural basis behind learning and memory formation is crucial to developing therapies for neurological and psychiatric illnesses that result from improper neuronal interactions. Long-term potentiation (LTP) is considered to be a crucial mechanism underlying learning and memory formation and leads to stronger and more enduring interactions between neurons. LTP stimulation at the hippocampal CA3 to CA1 synapse results in the opening of NMDA receptor channels in dendritic spines and causes a cascade of physiological changes, including post-synaptic spine remodeling. Our previous studies have shown that stimuli that produce LTP cause a rapid decrease followed by a persisting, long lasting increase in ATP levels in dendritic spines. The mechanism involves an increase in ATP production efficiency by mitochondrial ATP synthase. ATP synthase is located on mitochondrial cristae and helps determine cristae structure. Although previous reports have suggested that mitochondrial remodeling is necessary for LTP to occur, the role of cristae in LTP is not well understood. The purpose of our experiments was to track cristae changes that occur as a result of LTP stimulation of neurons. Novel high resolution confocal microscopy with Nonyl Acridine Orange dye (NAO) as well as traditional transmission electron microscopy were used to investigate the dynamic dendritic mitochondrial cristae changes during post-LTP synaptic remodeling. Though average cristae area initially decreased from baseline levels during the LTP stimulation, at 50 min after stimulation there was an overall increase in the average area of mitochondrial cristae compared to the pre-stimulation baseline, with no change in cristae number detected. The high energy demand accompanying LTP stimulation in neurons likely results in cristae remodeling, and these changes correlate with increased ATP production efficiency by mitochondria. These findings help elucidate the mitochondrial mechanisms underlying LTP. Future research based on these cristae morphology findings may help identify treatment targets for neurodevelopmental and degenerative pathologies.

Disclosures: A. Shteyman: None. **S. Subramanian:** None. **H. Rolyan:** None. **E.A. Jonas:** None.

Poster

114. Pre- and Postsynaptic Mechanisms in Long-Term Plasticity

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 114.16

Topic: B.05. Synaptic Plasticity

Support: NINDS, NIH Intramural Research Program

Title: Rhythmic GABAergic Synaptic Plasticity across Sleep and Wake

Authors: K. WU[1], W. HAN[2], ***W. LU**[1];
[1]NINDS/NIH, NINDS/NIH, Bethesda, MD; [2]NINDS/NIH, NIH, Natl. Inst. of Neurolog. Disorders & Stroke (NINDS), Bethesda, MD

Abstract: It is widely believed that sleep is a critical physiological process that consolidates memories through altering synaptic connections. Although modulation of excitatory synapses across sleep and wake has been extensively studied, less is known about how inhibitory synapses are regulated by sleep. As synaptic excitation and inhibition are balanced to stabilize neuronal and circuit function, and modulation of inhibitory transmission plays a critical role in learning and memory, it is crucial to understand the impact of sleep on inhibitory synapses and plasticity. In this study, we have employed a real-time, non-invasive sleep tracking system to monitor sleep/wake states and recorded GABAergic transmission in hippocampal CA1 neurons under basal conditions and during synaptic plasticity. We show that GABAergic synapses in hippocampal CA1 pyramidal neurons undergo daily rhythmic alterations. Specifically, wake inhibits phasic inhibition whereas it promotes tonic inhibition compared to sleep. We further utilize a model of chemically induced inhibitory long-term potentiation (iLTP) to examine inhibitory plasticity. Intriguingly, while CA1 pyramidal neurons express iLTP in both wake and sleep mice, wake mice have a much higher magnitude. Importantly, we employ optogenetics and observe that inhibitory inputs from parvalbumin (PV)-, but not somatostatin (SOM)-, expressing interneurons onto pyramidal neurons contribute to dynamic iLTP expression during sleep and wake. Finally, we show that synaptic insertion of α5-$GABA_A$ receptors underlies the wake-specific enhancement of iLTP at PV synapses, providing a mechanistic understanding of dynamic modulation of inhibitory synaptic plasticity by sleep and wake. Taken together, our work reveals a previously uncharacterized daily oscillation of inhibitory synaptic plasticity in hippocampal neurons that is dependent on sleep and wake states, identifies a novel sleep-dependent, input-specific GABAergic plasticity, demonstrates how a specific $GABA_A$ receptor subunit, α5, interacts with sleep. These data will form an important foundation for understanding how sleep contributes to memory.

Disclosures: K. Wu: None. **W. Han:** None. **W. Lu:** None.

Poster

114. Pre- and Postsynaptic Mechanisms in Long-Term Plasticity

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 114.17

Topic: B.05. Synaptic Plasticity

Support: R01 NS104829-01

Title: Divergent synaptic changes of superficial and deep CA1 pyramidal neurons in response to in vivo activity

Authors: *M. BERNDT[1], M. TRUSEL[2], T. F. ROBERTS[1], B. E. PFEIFFER[3], L. J. VOLK[4]; [1]UT Southwestern Med. Ctr., Dallas, TX; [2]Neurosci., UT Southwestern, Dallas, TX; [3]Neurosci., Univ. of Texas Southwestern Med. Ctr., Dallas, TX; [4]Neurosci., Southwestern Med. Ctr., Dallas, TX

Abstract: Divergent synaptic changes of superficial and deep CA1 pyramidal neurons in response to *in vivo* activityMarcus Berndt[1,2], Massimo Trusel, Ph.D.[2], Todd Roberts Ph.D.[2,4] , Brad E. Pfeiffer, Ph.D.[2,4], Lenora J. Volk, Ph.D.[2,3,4],[1]Neuroscience Graduate Program, [2]Department of Neuroscience, [3]Department of Psychiatry, [4]Peter O'Donnell Jr. Brain Institute Investigator, UT Southwestern Medical Center, Dallas, TXThe synaptic mechanisms through which experience modifies circuit behavior to form memories is poorly understood. Place cells in the hippocampus fire action potentials in a spatially tuned manner, encoding sequential information with behaviorally relevant temporal and spatial components. Evidence suggests that place cell activity during active navigation, even activity from a single traversal of a path, produces synaptic plasticity across the hippocampal network. However, the extent and details of such plastic changes *in vivo* remain unclear due to the technical challenges of identifying active vs. inactive neurons during brief (seconds to minutes) epochs of movement. CaMPARI is a green fluorescent protein fused to a Ca2+ sensor which, when bound to calcium, will undergo an irreversible photoconversion from green to red in the presence of blue light. We expressed CaMPARI in dorsal hippocampal area CA1 of adult male and female rats and photolabeled neurons during active exploration of a novel linear track. Two-photon imaging revealed 54 out of 101 CA1 pyramidal cells were photoconverted (active) during exploration of a novel track, compared to 10 of 103 cells photoconverted in the home cage. Almost no photoconversion was observed in the absence of blue light regardless of the animal's experience, demonstrating the utility of this tool for labeling hippocampal neurons activated by novel exploration. In subsequent experiments we prepared acute slices immediately following labeling during 30 min of novel spatial exploration and quantified cellular and synaptic differences between labeled cell populations. Converted cells in the superficial sublayer of *stratum pyramidale* had larger post-synaptic responses to CA3 input with no significant change to cortical input, consistent with activity dependent potentiation of those synapses. In contrast, photoconverted place cells in the deep sublayer had weaker pre-synaptic and post-synaptic function in response to both CA3 and entorhinal cortex input. Taken together these findings indicate that deep and superficial CA1 pyramidal cells are differentially affected by experience, suggesting that *in vivo* activity produces divergent synaptic changes based on specific excitatory neuron populations.

Disclosures: M. Berndt: None. **M. Trusel:** None. **T.F. Roberts:** None. **B.E. Pfeiffer:** None. **L.J. Volk:** None.

Poster

114. Pre- and Postsynaptic Mechanisms in Long-Term Plasticity

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 114.18

Topic: B.05. Synaptic Plasticity

Support: KBRI Grant 22-BR-02-02
KBRI Grant 22-BR-03-04
WISET Grant 2021-000

Title: Modulation of synaptic plasticity and social decision via serotonin receptor 4 activity in the lateral habenula during acute social isolation

Authors: *M. KANG, S. SONG, B. KIM, S. CHAE, J. KIM;
Korea brain research institude, Korea Brain Res. Inst. (KBRI), Daegu, Korea, Republic of

Abstract: The lateral habenula (LHb) is an essential hub brain region that modulates monoamine systems, such as dopamine and serotonin systems. LHb hyperactivity has implications for psychiatric disorders, such as depression, anxiety, and schizophrenia, which are commonly associated with social dysfunction. However, the role of the LHb in social behavior remains unclear. Here we investigated how acute social isolation influences subsequent social behavior such as social preference by mediating synaptic, molecular changes in lateral habenula using behavioral, electrophysiological, immunohistochemical, and molecular analyses such as qRT-PCR, ELISA, bulk-RNAseq. We found that acute social isolation affects synaptic function in LHb and social behavior. After acute social isolation, long-term depression (LTD) in the LHb is impaired and rescued by activating the 5-HT_4 receptor (5-HT_4R). Moreover, *htr4* expression in the LHb was upregulated following acute social isolation. Finally, acute social isolation enhanced the social preference for familiar mice, such as housing-mates, over stranger conspecifics. Consistent with the electrophysiological findings, pharmacological 5-HT_4R activation in the LHb restored innate social preference. In conclusion, acute social isolation influences social decisions via 5-HT_4R-dependent synaptic modifications in the LHb.

Disclosures: **M. Kang:** None. **S. Song:** None. **B. Kim:** None. **S. Chae:** None. **J. Kim:** None.

Poster

114. Pre- and Postsynaptic Mechanisms in Long-Term Plasticity

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 114.19

Topic: B.05. Synaptic Plasticity

Support: T32 Training Program in Integrative Membrane Biology 5T32GM008181-34

Title: Serotonergic modulation of the claustrum

Authors: *M. MADDEN[1], B. N. MATHUR[2];
[1]Univ. of Maryland Sch. of Med. Program In Neurosci., Baltimore, MD; [2]Univ. of Maryland Sch. of Med., Baltimore, MD

Abstract: Cognitive flexibility deficits are a major contributor to diminished life and therapeutic outcomes across myriad neuropsychiatric disorders including Alzheimer's, depression, and

schizophrenia. The classical psychedelic, psilocybin, induces long-lasting improvement of cognitive flexibility, but the mechanisms of this action are unknown. The claustrum, a subcortical nucleus, connects frontal cortical and parietal cortical network nodes and is required for optimal task performance in cognitively demanding tasks. Both the claustrum and cortical networks are disrupted by psilocybin; psilocybin challenge both depresses claustrum activity and disrupts functional connectivity between the claustrum and cortical networks. Thus, we hypothesize that psilocybin targets the claustrum. To test this, we employ whole-patch clamp electrophysiology and pharmacology in mouse claustrum slices to assess the serotonin receptors subtypes involved in psilocybin action on claustrum function. These data provide avenues toward understanding the subjective and therapeutic effects of psychedelic drug treatment.

Disclosures: **M. Madden:** None. **B.N. Mathur:** None.

Poster

114. Pre- and Postsynaptic Mechanisms in Long-Term Plasticity

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 114.20

Topic: B.05. Synaptic Plasticity

Title: A GluN2A PAM enhances neural synaptic plasticity in vitro and meta-plasticity ex vivo in rat hippocampus

Authors: *K. NAKASHIMA[1], A. HARADA[1], Y. TOMIMATSU[1], A. NAKATANI[1], T. HASUI[1], T. YAMASHITA[1], E. BETTINI[2], A. UGOLINI[2], M. CORSI[2], H. IWASHITA[1]; [1]Takeda Pharmaceut. Co. Limited / NS-DDU, Takeda Pharmaceut. Co., Fujisawa C. / Kanagawa-Ken, Japan; [2]Aptuit (Verona) Srl, an Evotec Co., Verona, Italy

Abstract: Neural synaptic plasticity has been recognized as a biological basis of cognitive function in the brain. In addition, a form referred to the meta-plasticity is presumed to be a shared mechanism among several clinically effective therapies for the treatment-resistant depression (TRD). The activation of N-methyl-D-aspartate (NMDA) receptors plays an important physiological role in the regulation of synaptic plasticity. Among NMDA receptors, GluN2A (NR2A)-containing NMDA receptors (GluN2A-NMDARs) are predominantly expressed in postsynaptic membranes and involved in postsynaptic calcium influx, which results in the synaptic plasticity including meta-plasticity. However, over-activation of the NMDA receptors is also well known as a trigger of neuronal cell death. Therefore, designed modulation of GluN2A-containing NMDA receptors without excessive effects may be a potential therapeutic approach for cognitive impairment and TRD. Given that the deactivation kinetics of NMDA currents affects the excitatory postsynaptic current decay and that the deactivation kinetics of GluN2A-NMDARs is the fastest among NMDA receptors, we hypothesized that selective positive modulation of GluN2A-NMDARs without affecting its deactivation kinetics is important to enhance the synaptic plasticity measured as the long-term potentiation (LTP) and avoiding the cell death. To identify selective positive allosteric modulators of GluN2A-

NMDARs (GluN2A PAMs), we performed a calcium influx-based compound screen and channel kinetics studies using CHO cells expressing GluN2A-NMDARs, along with *in vitro* selectivity assays. Next, the effect of identified GluN2A-PAMs on the LTP was evaluated in both *in vitro* and *ex vivo*. We found that GluN2A PAMs that maintained the deactivation kinetics enhanced *in vitro* LTP in acute hippocampal slices of rats, but ones that delayed the deactivation kinetics did not. An orally available and selective GluN2A PAM that maintained the deactivation kinetics enhanced *in vitro* LTP in acute hippocampal slices, and also enhanced the hippocampal LTP recorded 24 hours after oral administration in rats, an indicator of meta-plasticity, without any apparent adverse effects. These data suggest that the well-designed modification of the GluN2A-NMDARs can enhance neural plasticity, including meta-plasticity, that may be beneficial to treat cognitive dysfunction and TRD.

Disclosures: K. Nakashima: None. **A. Harada:** None. **Y. Tomimatsu:** None. **A. Nakatani:** None. **T. Hasui:** None. **T. Yamashita:** None. **E. Bettini:** None. **A. Ugolini:** None. **M. Corsi:** None. **H. Iwashita:** None.

Poster

114. Pre- and Postsynaptic Mechanisms in Long-Term Plasticity

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 114.21

Topic: B.05. Synaptic Plasticity

Support: NIH Grant 1R15 AG060461-(01)

Title: Expression of hippocampal chimeric GluN2 subunits promotes a greater CA1 EPSP selectively after the third postnatal week and influences plasticity dynamics

Authors: *R. KEITH[1], T. C. DUMAS[2];
[1]Col. of Sci., George Mason Univ., Fairfax Station, VA; [2]Psychology, George Mason Univ., Fairfax, VA

Abstract: Hippocampal NMDA receptors (NMDARs) play a key role in modulating Schaffer collateral synaptic transmission and plasticity. Beginning at the end of the second postnatal week, NMDARs undergo a change in GluN2 subunit composition from predominantly GluN2B to predominantly GluN2A. This GluN2 subunit switch is associated with a reduction in the generation of new synapses and modulation of the ability of patterned activity to induce synaptic plasticity. However, the GluN2 subunit switch alters both NMDAR channel kinetics and intracellular signaling. As such, it is unknown how the channel kinetics vs the intracellular signaling of the NMDAR separately affect Schaffer collateral synapses across hippocampal development. To study the influence of these signaling streams on hippocampal synapses, we utilized transgenic mice which express chimeric GluN2 subunits. Specifically, the ABc line expresses the amino terminal domain (ATD) and transmembrane domains (TMDs) of GluN2A subunits coupled with the carboxy terminal domain (CTD) of GluN2B, and the BAc line

expresses the ATD and TMDs of GluN2B coupled to the CTD of GluN2A.
By studying these mice across hippocampal development and comparing them to age-matched wildtype littermates, it is possible to elucidate the effects of specific NMDAR functional domains on Schaffer collateral electrophysiology, providing an indication of whether the channel kinetics or intracellular dynamics principally influences synaptic signaling. Animals were studied just prior to the third postnatal week (P17 - P19), just after the third postnatal week (P22 - P24) and in young adulthood (P30 - P60). Results revealed a selective and transient increase in Schaffer collateral synaptic strength in ABc mice at P22 - P24, with no change in paired-pulse facilitation, suggesting a postsynaptic modification. In addition, preliminary plasticity data suggests that there is no effect of ABc subunit expression on the magnitude of 40 Hz LTP. By contrast, there are age-dependent effects on BAc subunit expression on the magnitude of 40 Hz LTP.

Disclosures: R. Keith: None. **T.C. Dumas:** None.

Poster

114. Pre- and Postsynaptic Mechanisms in Long-Term Plasticity

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 114.22

Topic: B.05. Synaptic Plasticity

Support: NIH Grant R01NS111749
UIC Honors College Research Grant

Title: Group II mGluR Liberated Gβγ Modulates Insertion of AMPA Receptors in the Postsynaptic Membrane During Long Term Potentiation

Authors: *S. HUYNH[1], C. DELBOVE[2], Z. ZURAWSKI[1], A. CABALLERO[1], K. Y. TSENG[1], S. ALFORD[1];
[1]Univ. of Illinois at Chicago, Chicago, IL; [2]Univ. of Chicago, Chicago, IL

Abstract: Long term potentiation (LTP) is a form of synaptic plasticity that represents a critical step in learning and memory. Following LTP induction, the density of AMPA receptors (AMPARs), which mediate synaptic transmission and are located postsynaptically in synapses, increases, resulting in an increased excitatory postsynaptic current (EPSC). The two main types of AMPARs are calcium permeable (CP), which are inwardly rectifying, and calcium impermeable (CI) AMPARs. The insertion of AMPARs is necessary for maintaining LTP, and recent research suggests an especially important role of CP-AMPARs insertion in LTP. AMPAR insertion is mediated through the fusion of trafficking vesicles with the postsynaptic plasma membrane, a type of exocytosis. The exocytosis of AMPARs is facilitated by SNARE protein complexes consisting of proteins such as SNAP-25. Gβγ, as liberated by Gi/o-coupled G-protein coupled receptors (GPCRs), such as Group II metabotropic glutamate receptors (mGluRs), can inhibit exocytosis through binding to SNAREs such as SNAP-25, competing with fusogenic

calcium sensors. These interactions have mainly been studied presynaptically. The effect of Gβγ on the exocytosis and insertion of AMPARs, especially CP-AMPARs, into the postsynaptic membrane is unknown.
By comparing the effects of LTP on wild type (WT) mice vs SNAP-25Δ3 mice, whose mutant SNAP-25 protein is unable to bind Gβγ, we can test whether Gβγ can regulate the exocytosis of AMPAR bearing vesicles through binding to the SNAP-25 t-SNARE complex. In extracellular field recordings, a Group II mGluR agonist inhibits LTP in WT mice but not SNAP-25Δ3 mice. Using iGluSnFR imaging, we show that the Group II mGluR agonist does not affect presynaptic glutamate release. From whole cell recordings, we show that LTP increases the amplitude of post LTP mini EPSCs (mEPSCs) while having no effect in WT mice. Finally, we show that the Group II mGluR agonist increases the ratio of CI-AMPARs to inwardly rectifying CP-AMPARs in WT mice but not SNAP-25Δ3 mice.
Thus, we show that Gβγ from Group II mGluRs can inhibit LTP through inhibiting the insertion of AMPA receptor-bearing vesicles with the postsynaptic plasma membrane by binding to the SNAP-25 t-SNARE complex. Additionally, the insertion of CP-AMPAR might be driven by the SNAP-25 t-SNARE complex.

Disclosures: **S. Huynh:** None. **C. Delbove:** None. **Z. Zurawski:** None. **A. Caballero:** None. **K.Y. Tseng:** None. **S. Alford:** None.

Poster

114. Pre- and Postsynaptic Mechanisms in Long-Term Plasticity

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 114.23

Topic: B.05. Synaptic Plasticity

Support: Flagship ERA-NET Joint Transnational Call JTC 2019 in synergy with the Human Brain Project Grant No. S-FLAG-ERA-20-1/2020-PRO-28, Research Council of Lithuania
Agence Nationale de la Recherche (France)
EU Horizon 2020 Framework Program for Research and Innovation (Specific Grant 945539, Human Brain Project SGA3)
Specific Grant Agreement No. 800858 (Human Brain Project ICEI)
Grant from the Swiss National Supercomputing Centre (CSCS) under project ID ich011

Title: Altered synaptic plasticity at hippocampal CA1-CA3 synapses in Alzheimer's disease: integration of Amyloid precursor protein intracellular domain and Amyloid beta effect into computational models

Authors: *A. SAUDARGIENE[1], J. J. DAINAUSKAS[1,2], S. MORENO[3], H. MARIE[3], M. MIGLIORE[4];
[1]Neurosci. Inst., Lithuanian Univ. of Hlth. Sci., Kaunas, Lithuania; [2]Dept. of Informatics,

Vytautas Magnus Univ., Kaunas, Lithuania; [3]Inst. de Pharmacologie Moleculaire et Celluaire (IPMC), Inst. de Pharmacologie Moleculaire et Celluaire (IPMC), Valbonne, France; [4]Natl. Res. Council, Natl. Res. Council, Palermo, Italy

Abstract: Alzheimer's disease (AD), a degenerative and irreversible brain disorder, is the leading cause of dementia worldwide. Although the population of AD patients is growing, no breakthrough therapies have been proposed in the recent years. Therefore, a new multidisciplinary approach is needed to shed light on the complex molecular, synaptic, cellular, neuronal and network level mechanisms of impaired learning and memory in the AD pathology. We apply the integrated experimental and computational modelling approach to understand the AD-related peptide-induced impairment in synaptic plasticity at hippocampal CA1-CA3 synapses in early pathology of AD. In early AD, the alterations in amyloid precursor protein (APP) processing and clearance of APP peptides are observed, and this leads to the altered production of AD related peptides such as Amyloid beta (Aβ), Amyloid eta (Aη) and the Amyloid APP intracellular domain (AICD). In hippocampal CA1 pyramidal neurons, Aβ inhibits long-term potentiation (LTP) and enhances long-term depression (LTD), while high concentrations of AICD lead to LTP disruption and leave LTD intact at glutamatergic synapses (Pousinha et al., 2019; Opazo et al., 2018). The aim of this study is to investigate the joint effect of AICD and Aβ on LTP and LTD at hippocampal CA1-CA3 synapses. We used a detailed compartmental model of a CA1 pyramidal neuron (Migliore et al., 2018) and a newly developed NMDAr-dependent voltage-based model of synaptic plasticity. The influence of the elevated AICD levels was included by modifying the conductances of SK channels, L-type calcium channels, and the contribution of GluN2B-containing NMDA receptor. The effect of the elevated levels of Aβ was modeled as the increased extracellular glutamate concentration, endocytosis of synaptic AMPA receptors, reduced synaptic density, altered GluN2B-containing NMDA receptor-mediated activation of calcium/calmodulin-dependent kinase II. The modeling results support the experimental evidence that pathological concentration of AICD lead to the LTP disruption leaving LTD intact, and elevated concentration of Aβ cause LTP impairment and LTD enhancement. The joint effect of AICD and Aβ was expressed as the loss of synapse ability to potentiate its weight, and strongly depended on the NMDAR GluN2B receptor-gated channel functioning. Computational modeling study sheds light on the AICD- and Aβ-induced complex processes and their interactions in shaping synaptic plasticity at the hippocampal synapses.

Disclosures: A. Saudargiene: None. **J.J. Dainauskas:** None. **S. Moreno:** None. **H. Marie:** None. **M. Migliore:** None.

Poster

114. Pre- and Postsynaptic Mechanisms in Long-Term Plasticity

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 114.24

Topic: B.05. Synaptic Plasticity

Title: Biophysical and synaptic properties of hippocampal CA3 interneurons of aged rats

Authors: *E. GRIEGO, E. J. GALVAN;
Dept. de Farmacobiología, Ctr. de Investigación y Estudios Avanzados, Mexico City, Mexico

Abstract: Neuronal processing from the dentate gyrus to the hippocampus is critical for storage and recovery of new memory traces. In area CA3, GABAergic interneurons form a strong barrage of inhibition that modulates the network activity. A well-established feature of aging is decreased GABAergic inhibition, a phenomenon that contributes to the exacerbated excitability of aged pyramidal cells. In hippocampal slices of aged rats (25 ± 3 months old) we analyzed the properties of regular spiking CA3 interneurons with patch-clamp whole-cell recordings. We found enhanced firing discharge of aged regular spiking interneurons. In the mossy fibers (MF) to interneurons synapse, a switch in the AMPA receptor subunit composition was found in aged interneurons. Young regular spiking interneurons predominantly express CP-AMPA receptors and MF LTD. In sharp contrast, regular spiking interneurons of aged rats contain a higher proportion of CI-AMPA receptors and express MF LTP. In this work, we provide evidence for the first time that the specialized MF terminals contacting interneurons retain plastic capabilities and provide a novel insight of the interneuron's function during aging.

Disclosures: E. Griego: None. **E.J. Galvan:** None.

Poster

114. Pre- and Postsynaptic Mechanisms in Long-Term Plasticity

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 114.25

Topic: B.05. Synaptic Plasticity

Support: NIMH R00MH109626
NIMH R01MH124997

Title: The mitochondrial calcium uniporter regulates mitochondrial mass, dendritic localization and synaptic plasticity in distinct hippocampal circuits

Authors: *K. PANNONI, Q. S. FISCHER, D. GIL, S. FARRIS;
Fralin Biomed. Res. Inst., Virginia Tech., Roanoke, VA

Abstract: Hippocampal area CA2 is essential for social memory, or the ability to recognize a familiar conspecific. In our effort to understand the molecular basis of CA2's unique capacity to encode social memory, we identified multiple components of the mitochondrial calcium uniporter (MCU) complex as selectively enriched in CA2 compared to neighboring subregions. The MCU complex regulates calcium entry into mitochondria, which in turn regulates mitochondrial transport and localization to active synapses. We found that MCU is strikingly enriched in CA2 distal apical dendrites, precisely where CA2 neurons receive entorhinal cortical input carrying social information. MCU-enriched mitochondria in CA2 distal dendrites are also larger compared to mitochondria in CA2 proximal apical dendrites and CA1 apical dendrites. The distal and proximal dendrites of CA2 receive distinct inputs and have distinct plasticity

profiles. We hypothesize that the distinct mitochondrial properties in distal dendrites of CA2 promote LTP there. We confirmed with extracellular recordings in acute hippocampal slices that synapses onto the proximal dendrites, which receive input from CA3, are resistant to high frequency stimulation-induced LTP, while synapses in the distal dendrites, which receive input from the entorhinal cortex, readily express high frequency stimulation-induced LTP. In CA2 specific MCU-knockout mice, these plasticity profiles were differentially altered, suggesting that MCU plays a role in regulating circuit-specific synaptic plasticity. Ongoing studies are looking at the impact of MCU loss on mitochondrial mass and localization in CA2 distal dendrites. To test whether MCU uniquely impacts CA2 neurons or plays a broader role in regulating mitochondria in the hippocampus, we overexpressed MCU in CA1 neurons with adeno-associated virus, which led to an increase in mitochondrial size in CA1 dendrites, indicating that MCU expression regulates mitochondrial mass. In contrast to CA2, MCU overexpression in CA1 led to larger mitochondria preferentially in proximal dendrites compared to distal dendrites and GFP controls, reflecting cell-specific differences in dendritic localization of mitochondria. Collectively, our findings demonstrate that mitochondria are molecularly and structurally diverse across hippocampal cell types and circuits, and that MCU expression plays a role in plasticity, as well as regulating mitochondrial mass and dendritic localization. Our data suggest that mitochondrial diversity in CA2 may confer unique synaptic and circuit properties underlying CA2 function in social memory.

Disclosures: **K. Pannoni:** None. **Q.S. Fischer:** None. **D. Gil:** None. **S. Farris:** None.

Poster

114. Pre- and Postsynaptic Mechanisms in Long-Term Plasticity

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 114.26

Topic: B.05. Synaptic Plasticity

Support: NSERC
Canada Research Chair program

Title: Reversal of age-related susceptibility to depotentiation in mouse CA1 through noradrenaline

Authors: P. KARIMI TARI[1], *S. CONNOR[2];
[1]Biol., [2]York Univ., Toronto, ON, Canada

Abstract: Long-term potentiation (LTP), an activity-dependent increase in synaptic strength, shares considerable mechanistic overlap with processes associated with memory. Similar to many aspects of memory, including encoding and retrieval, LTP is subject to the effects of neuromodulators including noradrenaline. Noradrenaline engages neuromodulatory receptors that increase synaptic flexibility during learning and memory events. In parallel with some aspects of age-dependent memory loss, LTP is more readily reversed in aged neural circuits

which can be examined using “depotentiation”. Shortly after induction of LTP, synaptic strength gains can be reversed using low-frequency stimulation. Here, we report that susceptibility to depotentiation is increased in aged mouse hippocampus slices, at area CA1 glutamatergic inputs. Induction of robust (4x100Hz) LTP could be reversed in aged but not young mice using a low-frequency depotentiating stimulus. In hippocampus slices from aged mice, depotentiation was blocked by the noradrenaline when applied prior to the de-potentiating stimulus. Further testing revealed that reversal of exaggerated depotentiation required beta-1 but not alpha-1-adrenergic receptors. These results indicate a functional dissociation between noradrenergic receptor subtypes in rendering LTP resistant to depotentiation in the aged hippocampus. These findings have implications for preserving memory formation and limiting memory loss associated with aging and neurodegenerative disorders.

Disclosures: **P. Karimi Tari:** None. **S. Connor:** None.

Poster

114. Pre- and Postsynaptic Mechanisms in Long-Term Plasticity

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 114.27

Title: WITHDRAWN

Poster

114. Pre- and Postsynaptic Mechanisms in Long-Term Plasticity

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 114.28

Topic: B.05. Synaptic Plasticity

Support: NIH Grant T32 5T32NS061788-13
NIH Grant R01NS113948 (JIW)
NIH Grant R01NS064025 (LOW)
NIH Grant R01NS064025 (LOW)

Title: $GABA_A$ receptor-mediated inhibition suppresses long-term potentiation in adult-born dentate granule cells

Authors: *W. M. KENNEDY, H. LEE, J. I. WADICHE, L. OVERSTREET-WADICHE; Neurobio., Univ. of Alabama at Birmingham, Birmingham, AL

Abstract: Neurogenesis occurs in the dentate gyrus of adult rodents, leading to a heterogeneous population of dentate granule cells (GCs) in the granule cell layer. Adult-born GCs (abGCs)

transiently show both a greater magnitude and lower threshold for long term potentiation (LTP) in response to high frequency stimulation of the perforant path (Schmidt-Hieber et al., 2004; Ge et al., 2007). Inhibition has been shown to increase in strength during abGC maturation, suggesting less inhibition in young abGCs facilitates LTP (Snyder et al., 2001; Wang et al., 2000, Saxe et al., 2006). However, the contribution of GABAergic inhibition to LTP differences between adult-born and mature GCs has not been well defined. To address whether inhibition suppresses LTP in abGCs, we compared LTP using gramicidin A perforated patch recordings with inhibition intact. First, we characterized the morphological and intrinsic characteristics of abGCs at 4-, 6-, and 8-weeks after tamoxifen induction using Ascl1-CreER mice. Consistent with previous studies, we found higher input resistance and slower excitatory post synaptic potentials in young abGCs. To induce LTP, we applied a theta-burst stimulation paradigm to the perforant path while pairing postsynaptic depolarization sufficient to generate a spike. As anticipated, LTP success was greatest in 4- and 6-week-old abGCs and significantly less in 8-week-old and unlabeled (mature) GCs. To test the role of $GABA_A$ receptor-mediated inhibition, we assessed LTP in mature and 4-week-old abGCs in the presence of GABAzine (10 μm). Surprisingly, young abGCs showed a greater increase in LTP than mature GCs, suggesting that inhibition strongly suppresses plasticity despite the delayed development of inhibitory synaptic connectivity (Dieni et al., 2013; Groissman et al., 2020; Remmers et al., 2020). These results expand on the idea that young abGCs express a period of enhanced plasticity yet also illustrate the role of GABAergic inhibition in restricting plasticity once the developmental switch in $GABA_A$ receptor polarity has occurred.

Disclosures: W.M. Kennedy: None. **H. Lee:** None. **J.I. Wadiche:** None. **L. Overstreet-Wadiche:** None.

Poster

114. Pre- and Postsynaptic Mechanisms in Long-Term Plasticity

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 114.29

Topic: B.05. Synaptic Plasticity

Support: NIH R01 grant MH116673
NIH R01 grant MH125772
NIH R01 grant NS 113600
Postdoctoral Fellowship for a research abroad/Fondation pour la Recherche Medicale
Prix pour les jeunes chercheurs 2016/Bettencourt Schueller Fondation
Postdoctoral Research Fellowship/ American Epilepsy Society

Title: Novel retrograde adenosine/A2A receptor signaling in the hippocampus

Authors: *K. NASRALLAH[1], C. BERTHOUX[2], Y. HASHIMOTODANI[5], A. E. CHAVEZ[6], M. GULFO[3], R. LUJAN[7], P. E. CASTILLO[4];

[2]Dominick P. Purpura Dept. of Neurosci., [3]Neurosci., [4]Dominick P Purpura Dept. of Neurosci., [1]Albert Einstein Col. of Med., Bronx, NY; [5]Grad. Sch. of Brain Sci., Doshisha Univ., Kyoto, Japan; [6]Neurosci., Univ. De Valparaiso, Valparaiso, Chile; [7]Univ. Castilla-La Mancha, 02006 Albacete, Spain

Abstract: Retrograde signaling at the synapse is a common mechanism mediating long-term presynaptic plasticity. Here, a messenger released from the postsynaptic neuron upon activity modifies neurotransmitter release in a long-term manner by targeting a presynaptic receptor. In the dentate gyrus (DG), the main input area of the hippocampus, granule cells (GCs) and mossy cells (MCs) form a recurrent excitatory circuit that is critically involved in DG function and epilepsy. MC-GC synapses express a robust activity-dependent long-term potentiation (MC-GC LTP) which can be induced in vivo with optogenetic stimulation, by enriched environment exposure, and following experimental epileptic activity. Uncontrolled strengthening of MC-GC transmission promotes seizures and likely contribute to the pro-epileptic role of MCs in early epilepsy. In this study, we sought to determine the molecular mechanism underlying MC-GC LTP in the rodent hippocampus. To our surprise, we discovered that retrograde adenosine/A2A receptor (A2AR) signaling mediates presynaptic LTP at MC-GC synapses. Taking advantage of single-cell manipulations and selective pharmacology, we showed that activation of Gs-coupled adenosine A2A receptors (A2ARs) are necessary and sufficient to induce MC-GC LTP. Interfering with adenosine release from a single GC abolished LTP, and immunoelectron microscopy revealed A2ARs at MC axon terminals. Using the genetically encoded sensor for adenosine $GRAB_{Ado1.0m}$, we found that neuronal activity triggered phasic, postsynaptic TrkB-dependent release of adenosine. Lastly, epileptic seizures released adenosine in vivo, while removing A2ARs from DG decreased seizure susceptibility. To our knowledge, we provide first evidence for adenosine/A2AR retrograde signaling in the brain. By mediating presynaptic strengthening of MC-GC synaptic transmission, adenosine/A2AR retrograde signaling may contribute to DG-dependent learning and promote epilepsy.

Disclosures: K. Nasrallah: None. **C. Berthoux:** None. **Y. Hashimotodani:** None. **A.E. Chavez:** None. **M. Gulfo:** None. **R. Lujan:** None. **P.E. Castillo:** None.

Poster

114. Pre- and Postsynaptic Mechanisms in Long-Term Plasticity

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 114.30

Topic: B.05. Synaptic Plasticity

Support: ERC Dyn-Syn-Mem

Title: Role of AMPAR intracellular trafficking during LTP

Authors: C. BONNET[1], V. PECORARO[2], J. CHARPENTIER[2], D. CHOQUET[3], ***F. COUSSEN**[4];

[1]Interdisciplinary Inst. for Neuoscience, CNRS -Bordeaux univ, Bordeaux, France; [3]CNRS Univ. Bordeaux, [2]Interdisciplinary Inst. for Neurosci., Bordeaux, France; [4]CNRS - Bordeaux Univ., Interdisciplinary Inst. of Neurosci. (IINS), Bordeaux Cedex, France

Abstract: Abundance of AMPA receptors (AMPAR) at synapse is essential for the establishment and maintenance of synaptic function. Their synaptic localization is dependent on a highly dynamic exocytosis, endocytosis and plasma membrane mobility events. Using our new biochemical tool combined with photonic live imaging, we controlled and followed the intracellular transport of tagged GluA1 containing receptors in cultured rat hippocampal neurons. Analyzes are performed for GluA1 WT and mutants of GluA1 C-terminus domain in basal condition and during LTP. In organotypic hippocampal slices we combine imaging and electrophysiology experiments to analyze the impact of intracellular transport of AMPAR on LTP. Localization of AMPAR is regulated by their intracellular trafficking thru interaction of their C-terminus domains with different intracellular partners. These interactions play a major rule in the exocytosis and localization of the receptor at the plasma membrane both in basal condition of during cLTP. In hippocampal slice intracellular transport of AMPAR plays a major role during LTP.

Disclosures: C. Bonnet: None. **V. Pecoraro:** None. **J. Charpentier:** None. **D. Choquet:** None. **F. Coussen:** None.

Poster

115. Neural Plasticity

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 115.01

Topic: B.05. Synaptic Plasticity

Support: Association Syndrome de Wolfram
Région Occitanie
The Snow Foundation
Eye Hope Foundation

Title: Sigma-1 receptor is critical for mitochondrial activity and unfolded protein response in larval zebrafish

Authors: *T. MAURICE, L. CROUZIER, M. DENUS, E. M. RICHARD, A. TAVERNIER, C. DIEZ, N. CUBEDO, B. DELPRAT;
MMDN, Univ. Montpellier, EPHE, INSERM, Montpellier Cedex 5, France

Abstract: The sigma-1 receptor (S1R) is a highly conserved transmembrane protein highly enriched in mitochondria-associated endoplasmic reticulum (ER) membranes, where it interacts with several partners involved in ER-mitochondria Ca^{2+} transfer, activation of the ER stress pathways, and mitochondria function. S1R can be activated, inactivated or modulated by small molecules and accumulating data show that the so-called S1R agonists are protectants in

neurodegenerative diseases such as Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease and Parkinson's disease. Zebrafish-based models are becoming increasing popular as they allow pertinent description of pathological process combined with facility of pharmacological as well as genetic approaches. We therefore established a new S1R deficient zebrafish line and analyzed first the impact of S1R deficiency on the visual, auditory and locomotor functions. The $s1r^{+25/+25}$ mutant line showed impairments in visual and locomotor functions compared to $s1r^{WT}$. The locomotion of the $s1r^{+25/+25}$ larvae, at 5 days post-fertilization, was increased in the light and dark phases of the visual motor response. No deficit was observed in acoustic startle response. As a critical role of S1R was shown in ER stress pathways and mitochondrial activity, we then analyzed to analyze the unfolded protein response genes by qPCR and observed that loss of S1R led to decreased levels of IRE1 and PERK related effectors and increased over-expression of most of the effectors after a tunicamycin challenge. Finally, S1R deficiency led to alterations in mitochondria bioenergetics with decreased in basal, ATP-linked and non-mitochondrial respirations and following tunicamycin challenge. In conclusion, this new S1R KO zebrafish model confirmed that S1R activity plays an important role in the physiopathological regulation of mitochondrial bioenergetics and confirmed the potentialities of the zebrafish model to further analyze the physiopathological roles of S1R.

Disclosures: T. Maurice: None. **L. Crouzier:** None. **M. denus:** None. **E.M. Richard:** None. **A. Tavernier:** None. **C. Diez:** None. **N. Cubedo:** None. **B. Delprat:** None.

Poster

115. Neural Plasticity

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 115.02

Topic: B.05. Synaptic Plasticity

Support: FNRS Grant 34959817

Title: Is the homeostatic reset an artefact or a feature of synaptic plasticity rules for sleep-dependent memory consolidation?

Authors: *K. JACQUERIE, C. MINNE, G. DRION;
Neuroengineering, Univ. of Liege, Liege, Belgium

Abstract: Brains comprise well-defined circuits responsible for our behavior. Nonetheless, they are not rigidly wired and are adaptable by experience, a process critical for memory and learning. Neurons adapt their connections with each other thanks to *synaptic plasticity*. Simultaneously, brains process incoming information through fluctuations in neuronal rhythmic activities, each defining *brain states*. Switches in brain states during wake-sleep cycle are described by a neuronal population shift from active to oscillatory state, at the network level. Zooming at the cellular level, it corresponds to a transition from *tonic to burst*. *Neuromodulators* orchestrate the switch. They refer to signaling molecules that reversibly change the functional properties of

neurons or synapses.
Altogether, memory is impacted during sleep through a phenomenon called *sleep-dependent memory consolidation*. Experimental results show a down-selection mechanism ie. strong (resp. weak) connections established during wakefulness are preserved (resp. decreased) during sleep. However, its underlying physiological mechanisms remain unclear.
We built a cortical network to study the evolution of synaptic weights during switches in brain states, by using a conductance-based model. The synaptic weights are modified by a synaptic plasticity rule. We have shown that maintaining a synaptic rule parametrized on experimental data acquired in spiking regime leads to a *homeostatic reset* during burst. All the connectivity strengths converge towards the same basal value meaning that strong weights acquired during learning are converging at the same stable fixed point as weak weights. The reset occurs whatever the rule category, ie. spike-time dependent plasticity rules (such as STDP or triplet) and calcium-based rules [Graupner,2016].
Here, we developed an innovative sleep-dependent plasticity rule. It governs long-lasting change such as the number of AMPA receptors (AMPAr) available. We take advantage of the homeostatic reset. In the beginning of the night, AMPAr *changes with a rate proportional to the synaptic weight acquired during the learning phase*: strong (resp. weak) weights increase (resp. decrease) the number of AMPAr. Reaching the end of the night, the synaptic weight has converged towards its reset value stabilizing the change in AMPAr. Learning is well transferred, and the network can encode new information. This creative sleep-dependent plasticity rule avoids brain saturation. It is compatible with homeostasis and synaptic drift observed in memory engram.

Disclosures: **K. Jacquerie:** None. **C. Minne:** None. **G. Drion:** None.

Poster

115. Neural Plasticity

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 115.03

Topic: B.05. Synaptic Plasticity

Support: NIH Grant R01NS099245
NIH Grant R01NS069568

Title: Cgrp release from parabrachial neurons potentiates post-synaptic response in central amygdala and bed nucleus of the stria terminalis, and activates glia in insula

Authors: *R. LORSUNG[1], J. KOENIG[1], H. LAUB[2], N. CRAMER[2], Y. JI[3], R. A. MASRI[3], A. KELLER[2];
[1]MD UM at Baltimore, Univ. of Maryland Sch. of Med. Program In Neurosci., Baltimore, MD; [2]MD UM at Baltimore, Univ. of Maryland Sch. of Med. Dept. of Anat. and Neurobio., Baltimore, MD; [3]MD UM at Baltimore, Univ. of Maryland Sch. of Dentistry, Dept. of Oral Sci. and Therapeut., Baltimore, MD

Abstract: Despite its prevalence, chronic pain remains largely resistant to therapy. Treatments targeting aversive-affective processing of pain, centered around the parabrachial nucleus (PB), may prove promising. Calcitonin gene-related peptide (CGRP)-expressing PB neurons densely project to several brain structures implicated in aversive-affective pain processing, including the insula, central amygdala (CeA), and the bed nucleus of the stria terminalis (BNST). We are testing the overarching hypothesis that CGRP-expressing PB projections to these brain structures is causally involved in driving the affective component of chronic pain. The first aim of this project is to test whether CGRP release from PB potentiates post-synaptic responses. To test this, we performed whole-cell, voltage-clamp recordings in insula, CeA, and BNST slices from $CGRP^{Cre}$ mice. Endogenous, optogenetically-evoked CGRP release from PB terminals in CeA and BNST potentiated evoked excitatory post synaptic currents in a subpopulation of neurons. This potentiation lasted several minutes and was blocked by a CGRP-antagonist, but not a NMDA antagonist. However, in the insula, neither endogenous nor bath applied CGRP potentiated evoked EPSCs. Additionally, neither manipulation affected the amplitude or frequency of spontaneous synaptic inputs to insula neurons, suggesting CGRP does not have a direct effect on insula neurons. RNAscope established that CGRP receptor expression in the insula is restricted to glia and vascular endothelium. In insula neurons in animals with persistent pain there is an increased occurrence of extrasynaptic slow transient currents, thought to arise from astrocytic glutamate release, suggesting an upregulation in glial activation or receptor expression in the insula in chronic pain. These data suggest that PB CGRP release can either alter downstream affective signaling directly through activation of neuronal CGRP receptors as seen in the CeA or BNST, or cause more subtle shifts in activity via glial activation.

Disclosures: R. Lorsung: None. **J. Koenig:** None. **H. Laub:** None. **N. Cramer:** None. **Y. Ji:** None. **R.A. Masri:** None. **A. Keller:** None.

Poster

115. Neural Plasticity

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 115.04

Topic: B.05. Synaptic Plasticity

Support: Monash-Newcastle PVCRRI grant

Title: Tissue type plasminogen activator induces conditioned receptive field plasticity in the mouse auditory cortex

Authors: C. SMART[1], A. MITCHELL[1], F. MCCUTCHEON[1], *R. MEDCALF[1], **A. THIELE**[2]; [1]Monash Univ., Monash Univ., Melbourne, Australia; [2]Newcastle Univ., Newcastle Univ., Newcastle upon Tyne, United Kingdom

Abstract: Tissue-type plasminogen activator (tPA) is a serine protease that is expressed in various compartments in the central nervous system. It has important roles in neuronal plasticity

in relation to learning and memory, and addiction. How these plasticity effects manifest at the neuronal level *in vivo* is poorly understood. Here, we evaluated whether tPA, exogenously applied, could influence neuroplasticity within the mouse auditory cortex. We used a frequency pairing paradigm to determine whether neuronal best frequencies shift following the pairing protocol. On a given recording day we either injected vehicle or tPA (1ug in ~280nl) into the auditory cortex prior to electrode insertion. Thereafter, we initially determined neuronal best frequencies presenting pure tones ranging from 1-32kHz at 1/4 octave intervals and intensities of 50,60,70 and 80dB[SPL]. Thereafter, a conditioning stimulus was presented 30 times at 30 sec interval which was close to the neural best-frequency. This was followed by another determination of neural best frequency (frequency tuning). tPA administration significantly affected the best frequency after pairing, whereby this depended on the pairing frequency relative to the best frequency. When the pairing frequency was above the best frequency, tPA caused a best frequency shift away from the conditioned frequency. tPA significantly widened auditory tuning curves. tPA also influenced the strength of the response to the post-conditioning best frequency, relative to the pre-conditioning best frequency, but only in the higher pairing condition. Our data show that tPA is capable of changing the tuning of neurons within the auditory cortex. These findings indicate that regional changes in proteolytic activity within the auditory cortex modulates the fine-tuning of auditory neurons, supporting the function of tPA as a modulator of neuronal plasticity.

Disclosures: C. Smart: None. **A. Mitchell:** None. **F. McCutcheon:** None. **R. Medcalf:** None. **A. Thiele:** None.

Poster

115. Neural Plasticity

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 115.05

Topic: B.05. Synaptic Plasticity

Support: NIH Grant R01MH12435101
NIH Grant R01ES031823
NIH Grant U18DA052504

Title: Bdnf regulation of the voltage-gated sodium channel complex via differential kinase activity

Authors: *N. GOODE, P. WADSWORTH, A. SINGH, F. LAEZZA;
Pharmacol. & Toxicology, Univ. of Texas Med. Br., Galveston, TX

Abstract: Neuroadaptive changes in intrinsic firing of medium spiny neurons (MSNs) in the nucleus accumbens (NAc) are a form of structural and functional plasticity that depends on brain-derived neurotrophic factor (BDNF)/tropomyosin receptor kinase B (TrkB) signaling. Suppression of BDNF/TrkB signaling in MSNs promotes a resilient phenotype, whereas

prolonged local stimulation of this pathway in the NAc leads to susceptibility. Yet, how changes in BDNF/TrkB signaling confer vulnerability and resilience in these cells is still poorly understood. Previous studies identified glycogen-synthase kinase 3β (GSK3β), a downstream effector of BDNF/TrkB signaling, and voltage-gated Na^+ channel Nav1.6 as regulators of neuroplasticity induced by environmentally enriched (EC) or isolated (IC) conditions-models for resilience and vulnerability. Here, we sought to determine whether Nav1.6 and its accessory protein fibroblast growth factor 14 (FGF14) are converging sites for BDNF/TrkB signaling via GSK3β downstream regulation. We used the split-luciferase complementation assay (LCA) to screen the Broad and UT kinase libraries of >1,400 kinase inhibitors against 3 pairwise LCA complexes (FGF14:Nav1.6, GSK3β:Nav1.6 and GSK3β:FGF14) under 3 conditions (no BDNF, 10ng/ml and 75ng/ml BDNF) in TrkB stably expressing HEK293 cells (384-well plate including 320 kinase inhibitors, n=8 positive controls and n=56 negative controls (0.3% DMSO), each condition tested in duplicate). We observed that compounds targeting the PI3K/Akt pathway reversed luminescence signal from cells treated with low BDNF, while compounds targeting Src and GSK3β blocked the effect of high BDNF. We also used immunohistochemistry combined with laser scanning confocal imaging to characterize the expression pattern of Nav1.6, FGF14 and GSK3β in the NAc in response to BDNF stimulation. Our results showed that BDNF stimulation increased the localization of Nav1.6 channels and FGF14 to the action potential initiation site in MSNs. Our results support the existence of distinct mechanisms downstream of BDNF/TrkB that converge on the Nav1.6 channel macromolecular and might confer resilience and vulnerability via changes in MSN firing as part of structural and functional plasticity.

Disclosures: **N. Goode:** None. **P. Wadsworth:** None. **A. Singh:** None. **F. Laezza:** None.

Poster

115. Neural Plasticity

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 115.06

Topic: B.05. Synaptic Plasticity

Support: NIH Grant KL2TR001432

Title: Neuronal Membrane Proteasome (NMP) degrades nascent proteins in the optic tectum of Xenopus laevis tadpoles during enhanced visual experience

Authors: A. S. AHSAN[1], R. BERA[1], *H. HE[2];
[1]Biol. Dept., Georgetown Univ., WASHINGTON, DC; [2]Biol. Dept., Gorgetown Univ., Washington, DC

Abstract: Proteostasis plays critical roles in synaptic plasticity, the ability of neurons to modify synaptic connections in response to changes in activity. However, our understanding of the cellular machinery and mechanisms underlying activity-dependent proteostasis remains incomplete, as highlighted by the discovery of the neuronal membrane proteasome (NMP).

Unlike the well-known intracellular 26S proteasome which targets misfolded or other unwanted proteins through the UPS pathway, NMPs were found to specifically degrade nascent proteins in response to elevated activity in mouse neuronal cultures, and may be involved in regulating neuronal activity. We have investigated NMP functions *in vivo* using Xenopus laevis tadpoles. Our prior data showed that NMPs degrade nascent proteins in live tadpole brain under both basal and pharmacologically stimulated (PS) conditions, albeit at distinct levels. Intriguingly, NMP inhibition rapidly increases neuronal activity *in vivo*. Moreover, inhibiting NMP activity during visual training abolishes learning-induced behavioral plasticity, suggesting NMP function may be required for experience-dependent circuit plasticity. To further test if NMPs also degrade pre-existing proteins, we utilized the bio-orthogonal non-canonical amino acid tagging (BONCAT) method to time-stamp pre-existing proteins in the brain. Inhibiting NMP activity did not change the level of time-stamped pre-existing proteins under either basal or PS conditions, confirming that NMPs do not degrade pre-existing proteins, but preferentially target nascent proteins *in vivo*. To study the proteolytic function of NMPs in response to physiologically-relevant stimulation, we employed an enhanced visual experience (VE) paradigm that is known to induce experience-dependent plasticity in the developing retinotectal circuit. We examined the level of nascent CAMKII, a key plasticity-related protein degraded by NMPs *in vivo*, in the optic tectum during 30 minutes of VE. VE significantly upregulated CaMKII synthesis, consistent with previous reports. Importantly, NMP inhibition during the same period resulted in a significant increase in nascent CaMKII, suggesting that part of VE--induced nascent proteins was actively degraded by NMPs. These results further characterized the proteolytic activity of NMPs *in vivo*, and shed light on the temporal dynamics of the proteostasis of activity-induced nascent proteins in intact brain. Plasticity-inducing activities are predicted to induce multiple waves of protein synthesis. NMP-mediated degradation of nascent proteins may serve as a novel mechanism for activity-dependent proteostasis in neurons.

Disclosures: **A.S. Ahsan:** None. **R. Bera:** None. **H. He:** None.

Poster

115. Neural Plasticity

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 115.07

Topic: B.05. Synaptic Plasticity

Title: Cholinergic adaptive learning for robust cortex-wide networks

Authors: *M. FILIPOVICA, R. PONTE COSTA, W. GREEDY, H. ZHU, K. NEJAD; Univ. of Bristol, BRISTOL, United Kingdom

Abstract: The cholinergic system has been associated with learning, but also with cognitive decline in dementia and aging. Yet, to date no computational models have been put forward to explain how the cholinergic system contributes to both learning and cognitive decline.To investigate this we developed a cortex-wide computational model of Cholinergic-modulated

learning. To explore these questions we built on a recently introduced cortex-wide computational model, which includes excitatory and inhibitory cell populations and approximates hierarchical credit assignment in the cortex. We combined this model with an adaptive learning module that mimics the cholinergic system, using cortical prediction errors to produce a signal that modulates the learning rate in both pyramidal and inhibitory interneurons. We considered three levels of spatial specificity at which the cholinergic system could act: local (cell assembly/ cortical column), cortical area-wise, and global, producing a modulation factor for the corresponding level of specificity.The models were trained on an image recognition task (MNIST). Networks trained with adaptivemethods learned faster and reached higher accuracy on the task at all modulation levels. Area-wisemodulation led to the most consistent improvement in learning. We then compared the robustnessof networks by performing a simulated ablation experiment in which 0-70% of neurons were removed. We observed a more rapid decline in accuracy in networks without cholinergic modulation with lesions of the same severity, similarly to what has been observed in lesions with cholinergic depletion. In networks trained with adaptive methods, each subsequent cortical area becomes more specialized and predictive of the output, as reflected by increasing mutual information between neuronal activity and the output. This could act as cognitive reserve, as units that contain more information about the task on average could provide enough information even with neuronal loss. In summary, we show that all levels of Cholinergic modulation can facilitate learning. However local modulation can provide additional robustness in cortical networks, when measured via neuronal ablation. These results provide a framework by which Cholinergic function in cortical networks can be linked to learning and cognitive decline.

Disclosures: **M. Filipovica:** None. **R. Ponte Costa:** None. **W. Greedy:** None. **H. Zhu:** None. **K. Nejad:** None.

Poster

115. Neural Plasticity

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 115.08

Topic: B.05. Synaptic Plasticity

Support: HHMI
Allen Institute
Google Deepmind

Title: Optical brain computer interface for measuring circuit plasticity during learning

Authors: *K. DAIE[1], M. ROZSA[1], P. HUMPHREYS[2], T. P. LILLICRAP[2], C. CLOPATH[3], A. GRABSKA-BARWINSKA[2], M. KULKARNI[1], L. KINSEY[1], M. M. BOTVINICK[2], K. SVOBODA[1];
[1]Allen Inst. for Neural Dynamics, Seattle, WA; [2]Google Deepmind, London, United Kingdom; [3]Imperial Col. London, London, United Kingdom

Abstract: Learning a new task or skill involves plasticity in neural circuits. Our goal is to understand how neural activity triggers synaptic plasticity, which in turn causes learning-related changes in neural activity. However, in most behavioral tasks, learning-related changes in activity are wide-spread; it is often not clear if changes in activity in a particular group of neurons is causally related to behavior and if changes in synapses impinging on these neurons is involved. Another difficulty in linking synaptic plasticity and learning is measuring synaptic connections on neurons that show changes in spiking. To overcome these challenges, we developed a robust optical brain computer interface (BCI) task that results in learning-related changes in activity in a sparse subset of neurons. Combined with all-optical circuit mapping, this platform will enable us to link changes in circuit connectivity and learning-related changes in activity.Mice control the position of a motorized reward port using the activity of a single, 'conditioned neuron' (CN) in layer 2/3 of primary motor cortex, recorded with two-photon calcium imaging. At the start of a trial, the port is positioned out of reach. Activity in the CN drives approach of the port with a 10 s integration time. Naive mice exhibit task-related neural activity during the first day of training, with 10-20 % of neurons reliably modulated after trial start, and these dynamics are stable across days and we refer to them as a stable activity manifold. Each day a new CN is chosen outside of this manifold. Mice improve the rate of rewarded trials to 75 % within the first 25 trials (5 minutes), driven by an increase in CN activity. The learning-related changes in CN activity are almost entirely along directions orthogonal to this stable activity manifold. These results demonstrate the ability of a neural circuit to rapidly learn off-manifold patterns of activity. Learning was remarkably sparse: Only about 3% of imaged neurons increased their activity on the same level as the CN. To probe network connectivity, we use holographic photostimulation to activate ensembles of neurons and observe their effective connections with the surrounding network. Photostimulation of groups containing 10 randomly chosen neurons caused significant changes in the activity of 25 non-stimulated neurons. Most of these connections were inhibitory (66%) and were strongest between nearby neurons with similar activity during the BCI task. Combining rapid BCI learning and all-optical circuit mapping will allow us to link synaptic plasticity and learning-related changes in activity.

Disclosures: K. Daie: None. **M. Rozsa:** None. **P. Humphreys:** None. **T.P. Lillicrap:** None. **C. Clopath:** None. **A. Grabska-Barwinska:** None. **M. Kulkarni:** None. **L. Kinsey:** None. **M.M. Botvinick:** None. **K. Svoboda:** None.

Poster

115. Neural Plasticity

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 115.09

Topic: B.05. Synaptic Plasticity

Title: Synaptopodin is a target of TNFα-mediated synaptic plasticity

Authors: *D. KLEIDONAS[1,2,3], M. KIRSCH[1,4], A. VLACHOS[1,4,5];
[1]Dept. of Neuroanatomy, Inst. of Anat. and Cell Biology, Fac. of Medicine, Univ. of Freiburg,

Freiburg, Germany; [2]Spemann Grad. Sch. of Biol. and Medicine, Univ. of Freiburg, Freiburg, Germany; [3]Fac. of Biology, Univ. of Freiburg, Freiburg, Germany; [4]Ctr. BrainLinks-BrainTools, Univ. of Freiburg, Freiburg, Germany; [5]Ctr. for Basics in Neuromodulation (NeuroModulBasics), Fac. of Medicine, Univ. of Freiburg, Freiburg, Germany

Abstract: The proinflammatory cytokine tumor necrosis factor α (TNFα) is a key mediator of synaptic plasticity. Although its role in modulating neurotransmission has been thoroughly studied, the neuronal targets through which TNFα exerts its synaptic effects remain not well understood. Here, we theorized that synaptopodin, an essential component of the spine apparatus organelle (SA), could be involved in mediating TNFα-dependent synaptic plasticity. Using mouse organotypic entorhino-hippocampal tissue cultures prepared from mice of both sexes, we found that TNFα induces the insertion of GluA1-only-containing AMPA receptors into the postsynaptic membrane without affecting baseline excitatory neurotransmission. This effect of TNFα required the presence of synaptopodin and the SA. Moreover, TNFα increased the number of synaptopodin clusters as well as the number of spine apparatus organelles in the CA1 region of the hippocampus. These results provide new mechanistic insight into TNFα-mediated synaptic plasticity, thereby identifying synaptopodin and the SA as major targets of TNFα-dependent neuronal signaling pathways.

Disclosures: D. Kleidonas: None. **M. Kirsch:** None. **A. Vlachos:** None.

Poster

115. Neural Plasticity

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 115.10

Topic: B.05. Synaptic Plasticity

Support: CONACyT grant FOINS 474
DGAPA-PAPIIT-UNAM grant IN212919 for FB-R

Title: The effect of optogenetic-induced synaptic plasticity in LC-CA1pathway on memory

Authors: *A. S. VAZQUEZ, D. K. GÁLVEZ, F. BERMÚDEZ-RATTONI;
Inst. de Fisiología Celular, UNAM, Ciudad DE Mexico, Mexico

Abstract: Learning is the process of acquiring new information through experience, while memory is the encoding and storage of this information for later recall. Both processes allow the adaptation, storage of new information, and updating of previous knowledge. The formation of a new memory involves changes in the strength of the synapses, called synaptic plasticity. The most accepted model for synaptic plasticity is long-term potentiation (LTP), which is proposed to be one of the mechanisms that underlie learning and memory. The hippocampus is critical for memory encoding and consolidation and contains place cells that encode spatial locations. Furthermore, some studies demonstrate that it is essential in novelty detection and contextual encoding. It has been demonstrated by in vivo microanalysis that mice performing an object

location memory (OLM) task show an increase in dopamine (DA) and norepinephrine (NE) release in the dorsal hippocampus. They also demonstrated that depletion of the catecholaminergic terminals in the dorsal hippocampus impairs OLM, indicating their essential role in contextual memory. The dorsal hippocampus receives many catecholaminergic terminals from the Locus coeruleus (LC). LC optogenetic stimulation can induce LTP in the dentate gyrus and CA1. Nevertheless, so far, it is unclear if there is a relation between induced LTP through activation of catecholaminergic terminals from LC to CA1 and the behavioral outcome of mice in a memory task. Thus, we propose that optogenetic-induced LTP in the LC-CA1 pathway will improve hippocampus-dependent memory consolidation. We selectively activate LC catecholaminergic terminals inflicting a Cre-inducible virus in TH-Cre mice that express a light-activated protein channel, rhodopsin (ChR2). We found that optical stimulation of LC terminals to CA1 can induce LTP. After Morris water maze (MWM) and Barnes maze (BM) standardization, we found that mice tested ten days after the last training session had a poor performance in both tasks, indicating that the memory trace at this time is not easily retrieved. However, mice that received the Opto-LTP induction protocol significantly improved their memory performance, as shown by parametric statistics. In conclusion, this project provides direct evidence that hippocampal LTP induced by optogenetic activation of LC catecholaminergic terminals to CA1 enhances the memory trace evaluated by MWM and BM.

Disclosures: **A.S. Vazquez:** None. **D.K. Gálvez:** None. **F. Bermúdez-rattoni:** None.

Poster

115. Neural Plasticity

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 115.11

Topic: B.05. Synaptic Plasticity

Support: Korea Brain Research institute funded by the Ministry of Science and ICT (22-BR-01-02)
National Research Foundation of Korea (NRF) Grants NRF-2017M3C7A1048086

Title: Electrophysiological characterization of PPC-PFC connectivity

Authors: *H. LEE[1], J.-C. RAH[2,3], H. PARK[1,3];
[1]Res. group for Neurovascular unit, [2]Res. group of Sensory & Motor Syst., Korea Brain Res. Inst., Daegu, Korea, Republic of; [3]Dept. of Brain Sci., DGIST, Daegu, Korea, Republic of

Abstract: Short-term memory (STM) information lasting for seconds to minutes is thought to be stored in the prefrontal cortex (PFC). Sustained firing of PFC neurons may encode STM information, but underlying mechanisms for sustained firing of PFC neurons remain to be elusive. Because a line of evidence showed that neuronal activity in the posterior parietal cortex (PPC) well correlates with working memory information, it is possible that changes in PPC-PFC

connectivity are involved in STM-associated sustained firing of PFC neurons. To address this possibility, we tested whether either neuronal or synaptic properties of PFC neurons correlates with connectivity with the PPC neurons. PFC neurons with or without PPC connectivity were differentially labeled by injecting anterograde trans-synaptic viral vector, AAV1-hSyn-Cre, into the presynaptic PPC area and the AAV containing (flox) mCherry-(STOP)-EGFP cassette into the postsynaptic PFC. In this condition, PPC-connected PFC cells ((+) PPC) could express EGFP due to the Cre-induced inversion of (flox) mCherry-(STOP)-EGFP cassette, whereas PFC cells with no PPC connectivity ((-) PPC) would express mCherry. AAV with Cre-dependent ChR2-EYFP (AAV5-EF1a-cDIO-hChR2(H134R)-EYFP) was also co-injected with AAV1-hSyn-Cre into the presynaptic PPC, to test synaptic connectivity between PPC-PFC areas by optogenetic stimulation. Since 72% of (+) PPC in the PFC showed optogenetic synaptic responses, our anatomical labeling of synaptic connectivity achieved significant connectivity-based labeling of PFC cells. When overall cell properties of (+) PPC and (-) PPC neurons were compared, there are no significant differences, except the lower excitability of (+) PPC than that of (-) PPC. When the basal synaptic connectivity was measured by recording spontaneous excitatory and inhibitory postsynaptic currents (sEPSC and sIPSC, respectively) from the PFC neurons, both (+) PPC and (-) PPC cells displayed comparable sEPSC and sIPSC responses. Our results suggest that cellular and synaptic properties of PFC cells are not correlated with connectivity with the PPC, and STM-related sustained firing of PFC neurons may depend on changes in excitability of PPC-connected PFC neurons rather than basal synaptic strength between PPC and PFC.

Disclosures: H. Lee: None. **J. Rah:** None. **H. Park:** None.

Poster

115. Neural Plasticity

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 115.12

Topic: B.05. Synaptic Plasticity

Title: Nuclear morphology of cortical excitatory neurons is regulated by visual experience and aging

Authors: *T. M. FREY[1], T. MURAKAMI[2], K. OHKI[3], Y. GOTOH[2], Y. KISHI[4];
[1]Grossman Sch. of Med., New York Univ., New York, NY; [3]Dept. of Physiology, Grad. Sch. of Med., [4]Inst. for Quantitative Biosci., [2]The Univ. of Tokyo, Tokyo, Japan

Abstract: Our nervous system can adapt to external stimuli and dynamically adjust patterns of neuronal activity. Neuronal activity and sensory experience are important for the functional maturation of the mammalian brain- and the cerebral cortex in particular- partially via changes in transcription and epigenetic regulation. However, recent work has revealed that neuronal activity can impact nuclear morphology as well (Wittman, 2009; Feurle, 2020). This morphological change might reflect or have effects on chromatin reorganization and gene expression. To

examine how sensory experience leads to changes in single-cell nuclear morphology, we performed *in vivo* time-lapse imaging by the 2-photon microscopy for layer 2/3 excitatory neurons within the mouse visual cortex in response to light exposure. We developed the *Nex-Cre;SUN1-GFP* mouse to allow us to visualize the nuclear shape of neurons and recorded the nuclear shape under non-stimulated or stimulated conditions by showing a black or stripe image, respectively, on a monitor placed in front of them. Our data show that the nuclear shape changes over the time of visual stimulation in two months old mice (N=5 mice). This reveals a link between neuronal activity and nuclear morphology in the visual system. Additionally, we found that inhibiting neuronal activity prevented the change in the nuclear shape, suggesting that nuclear infolding in neurons is a dynamic and reversible process. We examined changes in nuclear morphology over the course of aging. In contrast to young mice, the nuclear shape of neurons in aged mice (more than two years old) was less dynamic upon light stimulation. This suggests that the natural aging process is associated with the alteration of nuclear dynamics. Taken together, we propose the role of regulation of nuclear shape in the regulation of gene expression upon neuronal activity and over the lifespan.

Disclosures: **T.M. Frey:** None. **T. Murakami:** None. **K. Ohki:** None. **Y. Gotoh:** None. **Y. Kishi:** None.

Poster

115. Neural Plasticity

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 115.13

Topic: B.05. Synaptic Plasticity

Support: NIH Grant MH126534
NIH Grant MH116900
NIH Grant HD097088

Title: Role for histone serotonylation in regulating neurodevelopment

Authors: *J. CHAN[1], M. CHEN[1], E. BALJINNYAM[1], A. RAMAKRISHNAN[1], L. SHEN[1], M. BEDFORD[2], S. MARRO[1], H. LI[3], I. MAZE[1];
[1]Mount Sinai Sch. of Med., New York, NY; [2]The Univ. of Texas MD Anderson Cancer Ctr., Houston, TX; [3]Tsinghua Univ., Beijing, China

Abstract: Brain development is a complex organizational process that can be altered by genetic variants, environmental perturbations, aberrant monoaminergic signaling, and more. In particular, dysregulation of serotonin (5-HT) has been implicated in the pathophysiology of neurodevelopmental disorders including autism spectrum disorders (ASD), yet the molecular mechanisms underlying 5-HT contribution to neurodevelopment remains unclear. Recently, our lab identified a novel epigenetic role for 5-HT, whereby this biogenic monoamine can be transamidated to glutamine 5 of histone H3 (H3Q5). Deposition of 5-HT at this site stabilizes

neighboring H3K4me3, resulting in the combinatorial H3K4me3Q5ser that recruits regulatory machinery to increase permissive transcription. Interestingly, an additional role of H3K4me3 'broad' domains has been described. Broad H3K4me3 peaks enhance transcriptional activation and associate with cell-specific processes, such as synaptic signaling in neurons. In postmortem brains from ASD patients, aberrant spreading of H3K4me3 domains has been observed, though how this dysregulation occurs is unclear. Our current studies examine histone serotonylation involvement in the organization of H3K4me3 spreading to impact neurodevelopment. To determine whether H3Q5 serotonylation associates with broad H3K4me3 peaks, we performed ChIP-sequencing of H3K4me3Q5ser in mouse embryonic forebrain tissues. Indeed, H3K4me3 peaks also exhibit broad patterning in combination with H3Q5ser, occupying 4-to-35 kb across the genome. Moreover, broad H3K4me3Q5ser domains associate with loci that enrich for neurodevelopment-associated pathways. Spreading of H3K4me3 peaks is regulated, in part, by the enzyme Lysine methyltransferase 2e (Kmt2e). To determine whether H3Q5 serotonylation influences Kmt2e recruitment, we used a high-throughput methyl domain reader array that evaluates binding between recombinant chromatin reader domains and modified histone tail peptides. Along with peptide immunoprecipitation studies, we show that the Kmt2e PHD finger binds H3K4me3Q5ser more extensively than H3K4me3 alone, suggesting H3Q5 serotonylation may enhance Kmt2e recruitment to regulate H3K4me3 spreading. We also validated Kmt2e-PHD interactions with H3K4me3Q5ser using X-ray crystallography and isothermal calorimetry. Ongoing experiments using viral and CRISPR/Cas9 strategies will interrogate Kmt2e involvement in H3K4me3Q5ser domain patterning and neurodevelopmental regulation. These studies offer a novel role for histone serotonylation that, if disrupted, may contribute to the etiology of neurodevelopmental disorders.

Disclosures: **J. Chan:** None. **M. Chen:** None. **E. Baljinnyam:** None. **A. Ramakrishnan:** None. **L. Shen:** None. **M. Bedford:** None. **S. Marro:** None. **H. Li:** None. **I. Maze:** None.

Poster

115. Neural Plasticity

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 115.14

Topic: B.05. Synaptic Plasticity

Support: MH116900
HD097088

Title: The long-term effects of reproductive experience on the maternal brain

Authors: *G. DI SALVO[1,2], J. CHAN[1], A. CUNNINGHAM[1], I. S. MAZE[1,3];
[1]Dept. of Neurosci., Icahn Sch. of Med. At Mount Sinai, New York, NY; [2]Maastricht Univ., Maastricht, Netherlands; [3]Howard Hughes Med. Inst., New York, NY

Abstract: Reproductive experiences, such as pregnancy, exert long-lasting effects on structural and functional organization of the maternal brain. However, there is limited knowledge on the molecular mechanisms that mediate long term pregnancy-dependent brain adaptations. The study of epigenetic mechanisms and their roles in modulating gene expression might offer insights into the mechanisms involved. First, to explore the long-term effects of reproductive experience on behavioral outcomes, we performed open field, elevated plus maze, novel object recognition and location tasks, and fear conditioning on nulliparous (NP), reproductive experienced (RE) and stressed RE (SRE) C57BL/6J mice at 49 days postpartum. We found that RE mice display robust behavioral plasticity in tasks related to spatial memory. Next, to identify potential transcriptomic changes associated with this behavioral outcome, we analyzed the transcriptome of dorsal (dH) and ventral hippocampus (vH), as well as medial prefrontal cortex (mPFC), regions known to underlie spatial memory tasks; additional brain regions were also examined that are not thought to contribute to spatial memory. We found that the majority of differentially expressed genes between NP and RE mice occurring in dH and vH were involved in modulation of synaptic vesicle regulation and learning or memory via Gene Ontology analyses. This suggests that hippocampal gene expression patterns might have a critical role in mediating these long-term behavioral adaptations. Changes in metabolic states observed throughout pregnancy and postpartum periods affect the availability of important substrates for chromatin modifications, with resulting impacts on the modulation of gene expression. Thus, we performed metabolomics analysis on the serum of RE and NP mice. Global untargeted metabolomics revealed increased levels of peripheral serotonin (5-HT) both during and long after the pregnancy experience in RE *vs* NP mice. Interestingly, our lab recently demonstrated that 5-HT can be transamidated to glutamine 5 of histone H3 in brain, a process known as histone serotonylation. Therefore, we hypothesize that changes in 5-HT levels in brain may play a role in histone PTM-mediated chromatin remodeling and downstream gene expression. Ongoing research will investigate the relationship between peripheral and central 5-HT in the regulation of histone serotonylation contributing to maternal brain adaptations. This study constitutes an important step in understanding the molecular mechanisms that underlie the long-term effects of reproductive experience on the maternal brain, an underrepresented field in neuroscientific research.

Disclosures: G. Di Salvo: None. **J. Chan:** None. **A. Cunningham:** None. **I.S. Maze:** None.

Poster

115. Neural Plasticity

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 115.15

Topic: B.05. Synaptic Plasticity

Title: Histone serotonylation: a novel regulator of stress-induced neuroplasticity

Authors: *A. AL-KACHAK[1], S. L. FULTON[1], L. FARRELLY[1], R. M. BASTLE[1], A. LEPACK[1], F. CATHOMAS[1], E. L. NEWMAN[2], H. E. COVINGTON, III[3], C. MENARD[1], A. RAMAKRISHNAN[1], Y. LYU[1], S. J. RUSSO[1], L. SHEN[1], I. S. MAZE[1];

[1]Neurosci., Icahn Sch. of Med. At Mount Sinai, New York, NY; [2]Tufts Univ., Somerville, MA; [3]Psychology, Tufts Univ., Medford, MA

Abstract: The field of neuroepigenetics has implicated chromatin phenomena in the etiology of major depressive disorder (MDD). While it has been demonstrated that dysregulation of histone posttranslational modifications may be involved in the deleterious transcriptional processes that promote physiological maladaptations in MDD, the field has only a limited understanding of the underlying mechanisms that contribute to this disorder. Data from our laboratory suggest alternative mechanisms of action for monoamines, where the presence of serotonin in the dorsal raphe nucleus (DRN) may directly mediate transcriptional responses related to various forms of serotonergic plasticity, and the subsequent mediation of mood, via histone serotonylation. In our studies, mice were subjected to chronic social defeat stress (CSDS) and were behaviorally classified as either stress-susceptible or resilient. Defeated mice were 1) sacrificed 48h post-CSDS, 2) subjected to 30 days of fluoxetine vs. water treatment post-CSDS, or 3) underwent viral surgeries intra-DRN to block serotonylation pre-CSDS. Human MDD DRN tissues were also obtained from a brain bank. We detected decreases in H3 serotonylation in DRN from both MDD patients and susceptible male and female mice 48h post-CSDS. These changes in global levels of H3 serotonylation were accompanied by robust alterations in genomic enrichment of the mark, as well as related gene expression patterns, implicating aberrant transcriptional regulation of neural plasticity related ontologies. Interestingly, serotonylation levels were significantly increased in susceptible male mice given water for 30 days post-CSDS *vs.* resilient animals, an effect reversed in susceptible mice treated with fluoxetine for 30 days, which corresponded to behavioral rescue of stress phenotypes. These data suggest that the chronic nature of stress susceptibility in mice following CSDS may be controlled by elevated H3 serotonylation in DRN. Finally, intra-DRN knockdown of serotonylation resulted in significantly greater social interaction after CSDS, indicating that preventing aberrant accumulation of H3 serotonylation in this brain region promotes a pro-resilient behavioral response compared to controls. Further RNA sequencing on virally infected tissue highlighted changes in serotonergic plasticity via knockdown of serotonylation, which may contribute importantly to antidepressant responses. In sum, this work implicates histone serotonylation in DRN as an important mediator of stress vulnerability via alterations in serotonergic signaling dynamics and related gene expression programs.

Disclosures: A. Al-Kachak: None. **S.L. Fulton:** None. **L. Farrelly:** None. **R.M. Bastle:** None. **A. Lepack:** None. **F. Cathomas:** None. **E.L. Newman:** None. **H.E. Covington:** None. **C. Menard:** None. **A. Ramakrishnan:** None. **Y. Lyu:** None. **S.J. Russo:** None. **L. Shen:** None. **I.S. Maze:** None.

Poster

115. Neural Plasticity

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 115.16

Topic: B.05. Synaptic Plasticity

Title: Identification of N-ribosyldihydronicotinamide: quinone reductase 2 (NQO2) as a novel reader of histone H3 serotonylation that contributes to neural gene expression

Authors: *M. CHEN[1], I. MAZE[1], H. LI[2];
[1]Icahn Sch. of Med. at Mount Sinai, New York, NY; [2]Tsinghua Univ., Beijing, China

Abstract: Aberrant regulation of neuronal gene expression promotes physiological alterations implicated in a wide variety of developmental and adult neurological disorders; however, our understanding of how these mechanisms may mediate life-long alterations in neural plasticity remains limited. Monoaminergic neurotransmission in the central nervous system (CNS) plays a critical role in brain development and function, with alterations in monoamine production/signaling implicated in the development and treatment of many neurological diseases, including substance use disorders, mood syndromes and neurodegeneration. Although vesicular packaging of monoamines is essential for numerous aspects of motor function, affect and reward, recent findings demonstrated the presence of non-vesicularized pools of monoamines in the nucleus and soma of monoaminergic neurons. Serotonin - as well as other monoamines - had previously been shown to form covalent bonds with certain cytoplasmic proteins, catalyzed by the Transglutaminase 2 enzyme, and our group recently identified histone proteins as robust substrates for monoaminylation in brain (specifically histone H3 at position glutamine 5 - H3Q5ser). Our data indicate that histone serotonylation acts to alter the binding of histone/DNA modification interacting proteins and plays direct roles in neuronal transcription, particularly during periods of increased cellular activity. Furthermore, we have uncovered pathophysiological associations between altered levels of H3 monoaminylations and behavioral deficits observed in rodent models of disease. Importantly, however, the field has yet to uncover H3Q5ser specific 'readers' that may contribute to transcriptional plasticity in brain. As such, we recently profiled H3Q5ser interacting proteins in cellular nuclear extracts via immunoprecipitations using biotinylated chemically modified H3 peptides, followed by LC-MS/MS mass spectrometric identification. In doing so, we found N-ribosyldihydronicotinamide: quinone reductase 2 (NQO2) to be robustly increased in its binding to H3 in the presence of Q5ser, an interaction that was subsequently validated using both biophysical and X-ray crystallography-based approaches. Now, employing a wide variety of biochemical, genome-wide and protein engineering strategies, we are assessing functional roles for NQO2-H3Q5ser interactions in the regulation of permissive gene expression in neurons. In sum, our work has identified a previously uncharacterized, *bona fide* 'reader' of novel H3Q5ser, which likely contributes significantly to H3 serotonylation mediated gene expression in the CNS.

Disclosures: **M. Chen:** None. **I. Maze:** None. **H. Li:** None.

Poster

115. Neural Plasticity

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 115.17

Topic: C.08. Ischemia

Support: NS106901
GM109089

Title: Detrimental effects of spreading depolarization in metabolically-compromised brain: contribution of synaptic Zn^{2+}

Authors: *M. BENNETT[1], R. A. MORTON[1], A. CARLSON[2], C. W. SHUTTLEWORTH[1]; [1]Neurosciences, [2]Neurosurg., Univ. of New Mexico HSC, Albuquerque, NM

Abstract: Introduction: Spreading depolarization (SD) has been implicated as a key contributor to progression of ischemic infarction. We have previously shown that SD is accompanied by a massive release of Zn^{2+} from presynaptic stores, but it is unknown whether this Zn^{2+} contributes to neuronal injury in vulnerable tissue. We tested here whether targeting Zn^{2+} accumulation can reduce the damaging consequences of SD in metabolically compromised brain slices. **Methods:** SD was induced in the hippocampal CA1 region of murine brain slices, and SD progression and swelling monitored with intrinsic optical signals (IOS), extracellular recordings of DC potential shifts and field excitatory postsynaptic potentials (fEPSPs). Responses in control conditions were compared with metabolically compromised conditions, using flow restriction as previously described (Exp Neurol 305 (2018) 121-128). Zn^{2+} transients were monitored using FluoZin-3 fluorescence. **Results:** As previously reported, slices recovered rapidly from SD in control conditions, but severe impairment occurred when SD was generated in slices with reduced metabolic substrate availability. SD in control conditions led to transient (~10min) synaptic silencing followed by full recovery and full recovery of IOS transients. In metabolically compromised slices, SD led to persistent inhibition of synaptic potentials (fEPSPs, 51.8% recovery at 20 mins post-SD) and evidence of structural disruption (27.8% decrease in IOS signals at 10 mins post-SD). A Zn^{2+} chelator with slow kinetics (CaEDTA; 100mM) did not prevent detrimental effects of SD (23.95% decrease in IOS at 10 mins, P=0.9147; 36.7% fEPSP recovery at 20 mins, P=0.4756). Other studies have shown that the extracellular chelator ZX1 is sufficiently rapid to sequester synaptically released Zn^{2+} before postsynaptic actions. ZX1 (100μM) completely prevented IOS decreases after SD in compromised tissues ($P<0.0001$, n=6) and almost fully restored fEPSP recovery (95.3% recovery at 20 mins, $P<0.04$). ZX1 effectively reduced Fluozin-3 transients after SD, consistent with the SD-induced wave of synaptic Zn^{2+} release being responsible for detrimental effects of SD. Likewise, tissues from ZnT3 knockout animals showed similar protection against SD-induced disruption (7.8% increase in IOS signal at 10 mins). **Conclusions:** These results indicate a significant contribution of synaptic Zn^{2+} accumulation to detrimental effects of SD in compromised brain slices. Preventing post-synaptic uptake and Zn^{2+} related receptor modulation could provide a useful additional approach to limit damaging consequences of SD in stroke and other injuries.

Disclosures: M. Bennett: None. **R.A. Morton:** None. **A. Carlson:** None. **C.W. Shuttleworth:** None.

Poster

115. Neural Plasticity

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 115.18

Topic: C.08. Ischemia

Support: NS106901
GM109089

Title: Involvement of gluN2A-containing NMDA receptors in spreading depolarization

Authors: *J. WEISEND[1], A. CARLSON[2], C. W. SHUTTLEWORTH[1];
[1]Neurosciences, [2]Neurosurg., Univ. of New Mexico HSC, Albuquerque, NM

Abstract: Spreading depolarizations (SDs) are now recognized as a principal source of repetitive episodes of excessive glutamate accumulation in stroke (Exp Neuro 267 (2015) 243-53). The contributions of different NMDA receptor (NMDAR) subtypes to progression and/or damaging effects of SD in vulnerable tissues are not fully understood. We examined possible contributions of GluN2A- and GluN2B-containing NMDARs to SDs in healthy tissues and in a model of metabolic compromise. Focal microinjection of KCl was used to initiate SDs in the hippocampal CA1 subregion of murine brain slices. Intrinsic optical signals (iOS) were recorded to monitor SD propagation and tissue swelling. Extracellular potential changes ("DC shifts") were used to examine prolonged depolarizations previously linked to neuronal injury (J Physiol 590 (2012) 5877-93). Field excitatory postsynaptic potentials (fEPSPs) provided an additional measure of functional recovery. As reported previously, iOS and fEPSPs were fully recoverable after SD in control recording conditions, but were both persistently suppressed in vulnerable tissues where metabolic substrate supply was reduced by flow restriction (Exp Neuro 305 (2018) 121-128). Non-selective inhibition of NMDARs (MK801 or APV) caused concentration-dependent inhibition of SD initiation/propagation and reduced the duration of SD shifts. Selective inhibition of GluN2A-containing NMDARs (NVP-AAM077, 300nM) slowed SD propagation (4.2±0.8 vs. 3.4±0.8 mm/min, control vs NVP-AAM077, $P<0.05$, n=7), while GluN2B inhibition (Ro 25-6981, 1μM) was without effect. Likewise, GluN2A inhibition significantly reduced the late phase of the DC shift (52.2±3.5, 45.5±1.2, control vs NVP-AAM077, $P<0.05$, n=4) with no effect of GluN2B inhibition. Neither GluN2A- nor GluN2B- antagonism affected fEPSP recovery rate in healthy tissues (n=4-6, $P=0.38$). In vulnerable tissues, GluN2B-antagonism did not protect tissues from SD induced injury, as observed by unaltered fEPSP and tissue swelling recovery rates. These results are consistent with prior evidence for NR2-A involvement in SD propagation (Sci Rep 6 (2016) 23576) and suggest that GluN2A-contining receptors activated by the dramatic increases in extracellular glutamate caused by recurrent SD events may be more likely to contribute to detrimental effects of SD. Selective targeting of these receptor subtypes during SD events may provide an adjunct approach to limiting progression of acute brain injuries.

Disclosures: J. Weisend: None. **A. Carlson:** None. **C.W. Shuttleworth:** None.

Poster

115. Neural Plasticity

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 115.19

Topic: B.09. Glial Mechanisms

Support: EU Horizon 2020 Grant 764860

Title: Parameters of cortical spreading depolarization in adult rat are controlled by three galanin receptors

Authors: F. GIMENO-FERRER[1], A. EITNER[1], R. BAUER[1], A. LEHMENKUHLER[2], H.-G. SCHAIBLE[1], ***F. RICHTER**[1];
[1]Univ. Hosp. Jena, Univ. Hosp. Jena, Jena, Germany; [2]Pain Inst., Pain Inst., Duesseldorf, Germany

Abstract: We have previously shown that topical application of Galanin on cortex dose-dependently lowered amplitudes, slowed velocities of cortical spreading depolarization (CSD), reduced the number of propagating CSD and increased the threshold to ignite a CSD by KCl. We interpreted this as a decrease in brain excitability. Here, we investigated the location of the Galanin receptors 1/2/3 (GalR1/2/3) in cerebral cortex and the effects of their blockade on neuronal excitability represented in parameters of the CSD. Brain slices from naïve rats were stained for Galanin and GalR1/2/3 localization. In spontaneously breathing anesthetized adult rats (sodium thiopentone, 100 mg/kg, i.p.) we recorded the electrocorticogram at cortical depths of 400 and 1200 µm with arrays of glass microelectrodes in two brain areas: treated and untreated (separated by a wall made from dental acrylic). CSD was induced by KCl microinjection. CSD-related direct current (DC) potential shifts, changes in extracellular potassium concentration and in regional cerebral blood flow were continuously monitored. We applied either M40, a pan GalR antagonist with preferential effects on GalR1 at 3 nM, or the GalR2 antagonist M871 at 3 nM, or the GalR3 antagonist SNAP 37889 at 30 nM for 2 h as pretreatment, followed by 2 h application of Galanin at 100 nM, or in co-application with Galanin at 100 nM for 4h. Galanin is expressed by all cortical neurons. The three GalRs were stained in cortical neurons with a different pattern: GalR1 in 50% neurons of layer IV/V; GalR2 and GalR3 in all neurons and all layers. Blocking the GalR2 prevented the Galanin effects on CSD amplitude and on threshold of CSD elicitation both in pretreatment and in coapplication protocols, but not the effects on CSD velocity (coapplication: reduction from 2.79±0.13 to 2.42±0.14 mm/min). Blockade of GalR3 prevented the effects of Galanin on CSD amplitude, but SNAP 37889 in pretreatment still did not prevent the increase of threshold of CSD elicitation (4.5 fold) neither the slowing of CSD propagation (from 2.63±0.13 to 2.24±0.11 mm/min) by Galanin. Using M40 all Galanin effects on CSD were prevented: amplitudes, propagation velocity and threshold did not change during protocol thus indicating an effect on all three GalR. We conclude that all three GalRs modify parameters of CSDs elicited by KCl microinjection. The formation and propagation of CSD is preferentially controlled by GalR2 and GalR3. Both GalR2 and GalR3 determine the Galanin effect on CSD amplitudes, thus indicating a cooperation, whereas the effect on CSD threshold is mediated by GalR2 but not by GalR3. The decay in velocity by Galanin is only prevented if all three GalRs are blocked by M40.

Disclosures: **F. Gimeno-Ferrer:** None. **A. Eitner:** None. **R. Bauer:** None. **A. Lehmenkuhler:** None. **H. Schaible:** None. **F. Richter:** None.

Poster

116. Oscillations and Synchrony: LFP and Unit Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 116.01

Topic: B.07. Network Interactions

Support: National Research Foundation of Korea grant (NRF-2022R1A2C3003901)
KIST Intramural grant (2E31511)

Title: The emergence of worker from mouse groups in a reward-threat conflict situation is related with their mPFC-BLA-NAc activity

Authors: *J. LEE[1], S. KIM[1], G.-H. LEE[1,2], D. JUNG[1,3], J. H. CHOI[1];
[1]Brain Sci. Inst., Korea Inst. of Sci. and Technol., Seoul, Korea, Republic of; [2]Dept. of Linguistics, Seoul Natl. Univ., Seoul, Korea, Republic of; [3]Korea Univ., Seoul, Korea, Republic of

Abstract: Despite the well-known notion that mice are social animals, whether or not a group of a mouse living together establishes a clear division of labor and if so, how the division temporally evolves, is largely unknown. Here we set up an ecological foraging experiment under which a mouse group is subjected to a reward-threat conflict situation. We used the CBRAIN (Collective Brain Research Aided by Illuminating Neural activities) telemetry system (Kim et al., Sci Adv, 2020) to track brain activities in the basolateral amygdala (BLA), nucleus accumbens (NAc), and medial prefrontal cortex (mPFC) of individual mice. Two types of individuals with distinct behavior repertoires were identified under behavioral analysis on more than 60 group foraging trials: workers and free-riders. Workers were the individuals that actively engaged in the foraging, while free-riders were the individuals who did not themselves bring the food, but took it from the workers. Moreover, behavioral patterns of mice became more solidified as foraging continued over days. Analysis of neural dynamics has found that the rate of oscillatory bursts in the beta (24 - 32 Hz) and gamma (40 - 70 Hz) frequency bands were significantly elevated in the workers compared to the free-riders. The information on individuals' positions and brain activities at each time allowed us to compare the dynamics within the mPFC-BLA-NAc network of worker and free-rider mice. Our findings provide evidence of the dynamic establishment of the social division of labor within a mouse society, composed of individuals that vary in mPFC-BLA-NAc regulation depending on their social role.

Disclosures: **J. Lee:** None. **S. Kim:** None. **G. Lee:** None. **D. Jung:** None. **J.H. Choi:** None.

Poster

116. Oscillations and Synchrony: LFP and Unit Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 116.02

Topic: B.07. Network Interactions

Support: NRF-2022R1A2C3003901
The KIST Intramural grant 2E31511

Title: Changes of individual sleep pattern to group-level sleep pattern in freely-moving mice group

Authors: *B. KIM, J. CHOI;
Korea Inst. of Sci. and Technol., Seoul, Korea, Republic of

Abstract: As a social animal, mice naturally show huddling behavior during sleep and influence each other conspecifics' sleep patterns. Accordingly, group-level sleep pattern is observed in group hosing; however, it remains to be investigated how individual sleep patterns change and what factors influence the formation of group-level sleep patterns. Due to the limitation of the experimental setup, sleep studies were mainly conducted in individual mice. Also, it requires a lot of labor to compare video and sleep states in a group of mice. Here, we developed the algorithm of CBRAIN (Collective Brain Research Aided by Illuminating Neural activity) system for wireless real-time sleep monitoring. Briefly, EEG and EMG signals were acquired at 256 Hz, and real-time analysis of the 2-s signals was performed in every 10 sample updates for wake / NREM sleep / REM sleep classification by a microprocessor. The classified sleep and wake states were indicated by the color of the LED attached in CBRAIN. Using this system, we measured sleep patterns in a small group of mice (n=4) and measured them again individually. We found that Group-level sleep patterns are adjusted to those of individuals who slept shorter. During group sleep, the overall sleep time tends to decrease, and the subjects with longer sleep times decrease to the amount of those with shorter sleep durations. Also, the sleep states were more synchronized, and REM sleep was rich when mice huddled together. These results showed that the amount of individual sleep could be maintained internally as well as flexibly changed according to the group sleep pattern under the naturalistic environment.

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

Poster

116. Oscillations and Synchrony: LFP and Unit Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 116.03

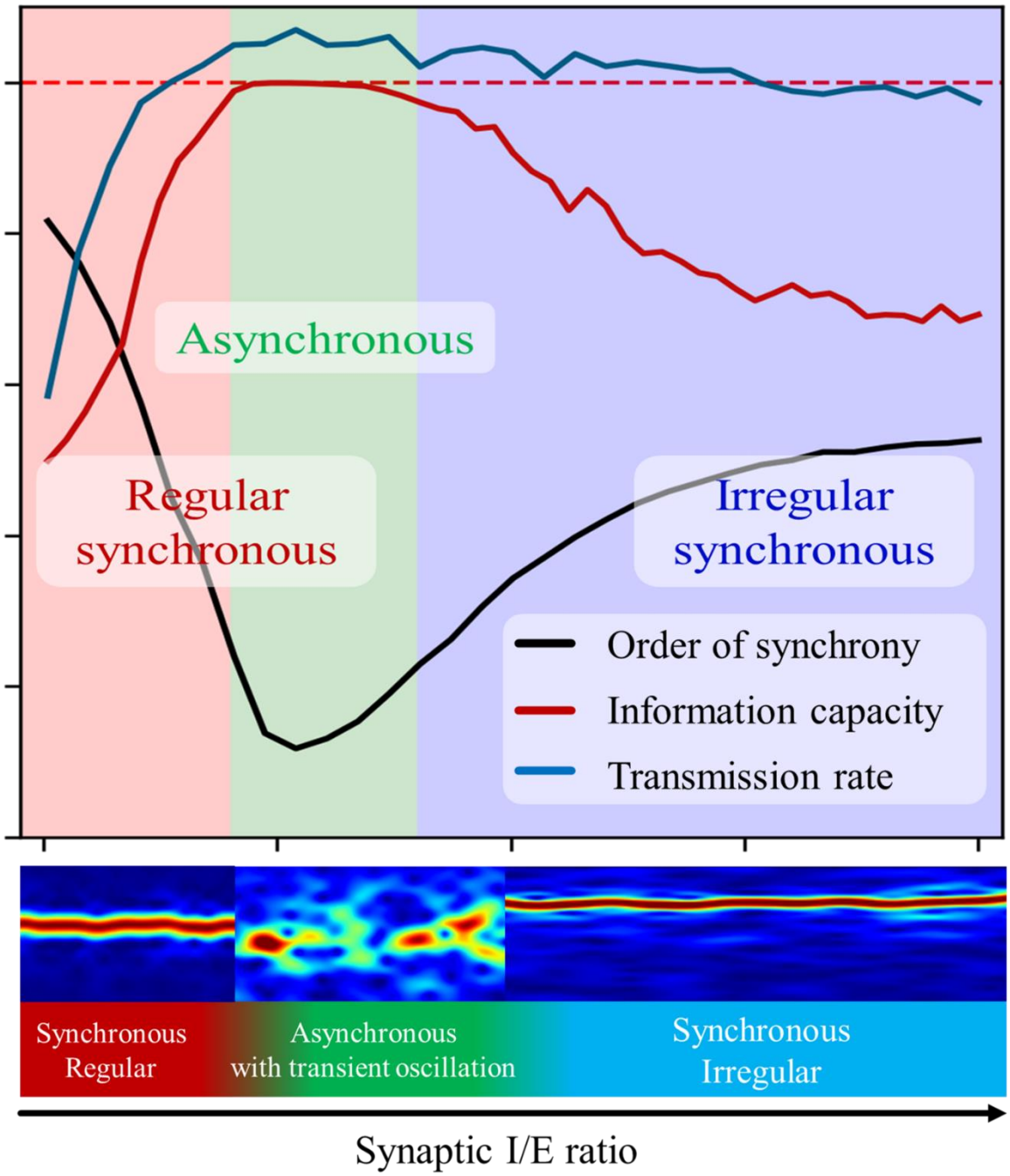
Topic: B.07. Network Interactions

Support: National Research Foundation of Korea grant (NRF-2022R1A2C3003901)
KIST Intramural grant (2E31511)
ETRI grant funded by the Korean government (21YB3210)

Title: Significance of transient oscillation in maximizing information capacity and transmission

Authors: *J. KIM[1,2], S.-H. YOOK[3], J. CHOI[1,4];
[1]Korea Inst. of Sci. and Technol., Seoul, Korea, Republic of; [2]Physics, [3]Kyung Hee Univ., Seoul, Korea, Republic of; [4]Univ. of Sci. and Technol., Daejeon, Korea, Republic of

Abstract: Transient oscillatory bursts in nervous system are short-lived oscillation occurring suddenly at the specific frequency and have come to fore of the questions about their role in neural computation and/or information presentation. To investigate the role of transient bursts in information level, we built a randomly coupled Izhikevich neuronal model with time-delayed synapses and induced the burst generation by tuning the excitatory and inhibitory (E/I) balance. The local field potential (LFP) was determined by averaging the membrane potentials of excitatory neurons. We conducted simulation by varying E/I balance based on the knowledge that synaptic E/I balance is critical for efficient neural computation. We quantified the order of synchrony to determine the status of oscillation with respect to E/I ratio using the coherence of the membrane potentials and the Kuramoto order parameter (a scale of synchrony based on rhythmic spiking). We found that there was an asynchronous activity in the intermediate E/I ratio between a regular and an irregular synchronous state. In the regular synchronous state, both the coherence and Kuramoto order parameter were high, while in the irregular synchronous state, the Kuramoto order parameter was low. In the asynchronous state, isolated events of oscillatory bursts were observed in the time-frequency map, similar to the physiological observation. Next, we investigated state-dependency of information capacity by calculating information entropy. The capacity was maximized in asynchronous state then decreased as the E/I balance far from the state. Lastly, we investigated the efficiency of information transmission between the neurons along the E/I balance using the probability of post-synaptic neuron activating to the spike of pre-synaptic neuron. We found that also this transmission rate was maximized in the asynchronous state. These results show that the transient oscillations generated in the intermediate range of E/I balance contribute to maximize not only the information capacity but also the transmission rate.



Disclosures: **J. Kim:** None. **S. Yook:** A. Employment/Salary (full or part-time):; Kyung Hee University. **J. Choi:** A. Employment/Salary (full or part-time):; Korea Institute of Science and Technology.

Poster

116. Oscillations and Synchrony: LFP and Unit Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 116.04

Topic: B.07. Network Interactions

Support: The National Research Foundation of Korea grant (NRF-2022R1A2C3003901)
KIST Intramural grant (2E31511)

Title: Ultrasound vocalization syllable-shape specific neural activity modulations found within cortico-limbic areas

Authors: *G.-H. LEE[1,2], J. LEE[1], J. H. CHOI[1];
[1]Brain Sci. Inst., Korea Inst. of Sci. and Technol., Seoul, Korea, Republic of; [2]Dept. of Linguistics, Seoul Natl. Univ., Seoul, Korea, Republic of

Abstract: It is known that mice produce ultrasonic vocalizations (USVs) under several social contexts comprising syllables with different lengths and shapes. Although it is documented that USVs have certain communicative functions (Portfors and Perkel, Curr Opin Neurobiol, 2014), the neural correlates and social meanings of different syllable morphologies remain unexplored. At the same time, there is a lack of understanding of activities in the cortico-limbic areas related to USV production, although some correlated activity was found in lower thalamic and medullary regions. In this study, we let pairs of a male and a female mouse freely interact while using the CBRAIN telemetry system (Kim et al., Sci Adv, 2020) to record activities in the nucleus accumbens (NAc), medial prefrontal cortex (mPFC), and basolateral amygdala (BLA) regions. Over 20,000 distinct USV syllable contours were extracted from the recordings through an optimized USV detection and purification algorithm. Through analysis of USV frequency contour patterns together with oscillatory activities synchronized to the USV production time, we identified syllable-shape specific modulations in the recorded areas, where the strongest were found in the NAc region. Current study's findings suggest a possibility of dynamic activities in the higher brain regions of the mouse influencing lower motor regions, enabling the mouse to produce a larger repertoire of sounds that could convey different social values.

Disclosures: G. Lee: None. **J. Lee:** None. **J.H. Choi:** None.

Poster

116. Oscillations and Synchrony: LFP and Unit Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 116.05

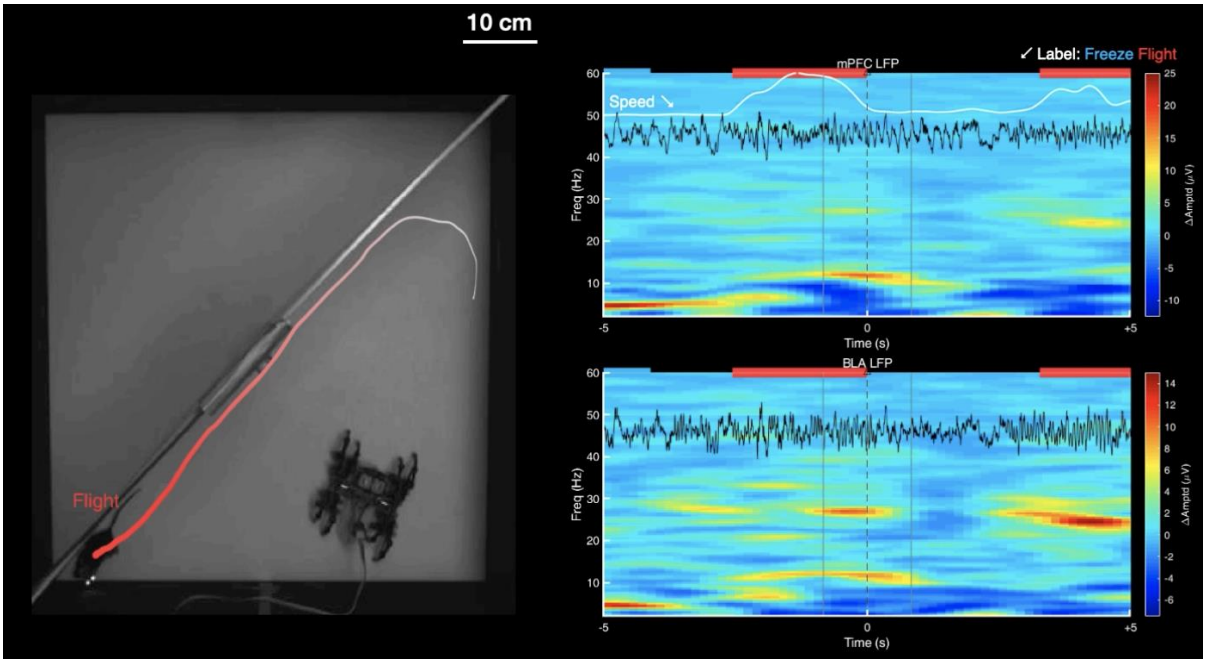
Topic: B.07. Network Interactions

Support: NRF Korea NRF-2022R1A2C3003901
KIST Intramural grant 2E31511

Title: Dynamic switching between distinct oscillatory rhythms in prefrontal-amygdala circuits across diverse behaviors under natural threats

Authors: *H.-B. HAN[1], H.-S. SHIN[2], Y. JEONG[3], J. CHOI[1];
[1]Brain Sci. Inst., Korea Inst. of Sci. and Technol., Seoul, Korea, Republic of; [2]Inst. for Basic Sci., Daejeon, Korea, Republic of; [3]Bio and Brain Engin., Korea Advanced Inst. in Sci. and Technol., Daejeon, Korea, Republic of

Abstract: The prefrontal cortex and amygdala are involved in the regulation of defensive behavior under threat, but how they are engaged in flexible shift among behaviors remain unclear. Recent reports from the Pavlovian fear conditioning experiments have indicated that a long-range synchrony in the prefrontal-amygdala network is crucial for a representative type of defensive behavior, i.e., freezing; however, its role with respect to a vast repertoire of naturalistic threat-induced behaviors remains unknown. We used a predatory robot and investigated the rhythmic activities in the network of the prefrontal cortex (PFC) and basolateral amygdala (BLA) during natural behavior of mice. We found that mice exhibited freezing or flight in react to the threat of robot, and both regions increased low theta (3-7 Hz, PFC→BLA) during freezing, and high theta (8-14 Hz, BLA→PFC) and high beta (22-34 Hz, PFC→BLA) during flight. Similar to how freezing and flight cannot coexist, the coexistence of freeze- and flight-related oscillatory states in PFC-BLA network was rarely found. Trajectory analysis of flight showed that the prefrontal-to-amygdala beta bursts were prominent during flights with intention (e.g., flight towards the gate to the safe-zone) and suppressed but temporally coordinated fast gamma activities (60-120 Hz) in the amygdala, suggesting its role in the top-down processing. These results demonstrate a neurodynamic substrate of the prefrontal-amygdala circuits to freeze-or-flight under a naturalistic threat and provide a unified understanding of neural dynamics underlying flexible selection of behaviors.



Disclosures: **H. Han:** None. **H. Shin:** None. **Y. Jeong:** None. **J. Choi:** None.

Poster

116. Oscillations and Synchrony: LFP and Unit Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 116.06

Topic: B.07. Network Interactions

Support: NRF Grant 2020R1A2C4002156
ETRI Grant (Collective Brain-Behavioral Modelling in Socially Interacting Group, 21YB1500)
PCoE DGIST Grant 22-CoE-BT-03

Title: Interbrain broadband modulation of local field potential in the dorsomedial prefrontal cortex of a group of mice in a naturalistic, task-free social environment

Authors: *J. LEE[1], D. KWAK[2], G. LEE[2], C. KIM[2], J. CHOI[3], S. LEE[4], H. CHOE[2];
[1]Brain Sci. Res. Ctr., [2]Dept. of Brain Sci., Daegu Gyeongbuk Inst. of Sci. and Technol., Daegu, Korea, Republic of; [3]Korea Inst. of Sci. and Technol., Seoul, Korea, Republic of; [4]Electronics and Telecommunications Res. Inst., Daejeon, Korea, Republic of

Abstract: The Great Coronavirus Pandemic has reminded us how valuable social interaction is. The research on social behavior and its neural correlates is gaining traction; however, with a few exceptions, a majority of research focuses on how a single brain responds to and processes social information rather than investigating how multiple brains interact with each other in a social context. In this study, we simultaneously recorded local field potential (LFP) signals in the dorsomedial prefrontal cortex (dmPFC) from up to four mice. The brain activities of the mice were measured in two contradicting conditions - freely interacting with each other or being individually separated. We found that social context and the activeness states predominately modulate the entire LFP structure. Power spectral density (PSD) estimate and spectrogram of LFP signals showed a broadband modulation; lower frequency bands—delta (<4Hz), theta (4-7Hz), alpha (8-12Hz), and low beta (13-20Hz) power were highly correlated to each other, while weakly correlated with high beta (21-30HZ) and anti-correlated with gamma (>30Hz) power. We calculated the Gamma-to-Low-power Ratio (GLR) and found that GLR was higher when the mice were in a group than were separated. The GLR was also higher when they were active—whether or not they were moving. The mice in the group showed higher GLR in any activeness states. However, the group/single GLR disparity disappeared when the mice were huddling (gathering together), suggesting the importance of social aggregation. Time series analysis of GLR indicated that the mice in the group displayed high cross-correlation to each other, indicating interbrain synchrony. Then we examined whether there is any directional causal relationship between a pair of mice. A particular mouse in the group showed unilateral temporal precedence of the GLR by Granger causality analysis, implying a directed influence among the group of mice. The relationship between the temporal dynamics of GLR and the social hierarchy

based on behaviors is discussed. Overall, this study shows the importance of the naturalistic, task-free social environment and simultaneous multi-brain recording for researching social behavior and its neural correlates in mice.

Disclosures: **J. Lee:** None. **D. Kwak:** None. **G. Lee:** None. **C. Kim:** None. **J. Choi:** None. **S. Lee:** None. **H. Choe:** None.

Poster

116. Oscillations and Synchrony: LFP and Unit Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 116.07

Topic: B.07. Network Interactions

Support: Massachusetts Life Sciences Center (MLSC)

Title: VTA coordination of BLA and mPFC network states and impact on motivated behaviors

Authors: *B. T. STONE[1], P. ANTONOUDIOU[2], J. L. MAGUIRE[2];
[1]Tufts Med. Univ., Tufts Med. Ctr., Boston, MA; [2]Neurosci., Tufts Med. Univ., Boston, MA

Abstract: Motivated behaviors, such as social encounters, depend largely on reliable interactions between neural reward systems (e.g. ventral tegmental area; VTA), limbic structures (e.g. basolateral amygdala; BLA), and cerebral regions (e.g. medial prefrontal cortex; mPFC). Dysregulation of interactions between such networks severely disrupts reward valuation and, thus, motivation, which can contribute to pathology. This type of maladaptive signaling can impair both life quality and survival and has been linked to the etiology and symptomology of several psychiatric disorders (e.g. substance use disorders). While it has been demonstrated that the VTA projects to both the BLA and mPFC and that the BLA->mPFC plays a critical role in social interaction, the influence of the VTA on BLA-mPFC network communication underlying behavioral states remains unknown. To assess the strength of functional connectivity within this circuit, we employed a series of *in vivo* optogenetic, electrophysiology, and imaging approaches in freely moving C57BL/6 male mice, activating either VTA terminals in the BLA (VTA_{BLA}) or mPFC (VTA_{mPFC}) at various (5, 10, 20, and 40Hz) frequencies. Channelrhodopsin-2 (ChR2)-mediated VTA_{BLA} activation had the strongest power elevation during 20Hz photo-stimulation, where it also robustly increased the BLA-mPFC spectral coherence from baseline. A similar effect was observed during VTA_{mPFC} activation, however, the strongest power elevation occurred at 40Hz photo-stimulation. Furthermore, we tested whether VTA_{BLA} and VTA_{mPFC} activation impacted social interaction. We show that 20Hz stimulation in either region facilitated interaction with a female conspecific, with no discernable difference amongst stimulated regions. These results suggest a bidirectional, functional relationship between VTA-mediated activity in the BLA-mPFC pathway which may be necessary for motivated behaviors (such as social interaction). These results provide a framework to investigate how dysregulation of this network

may impair healthy handling of external stimuli (e.g. alcohol, stressors), which could manifest in substance use and/or major depressive disorders.

Disclosures: **B.T. Stone:** None. **P. Antonoudiou:** None. **J.L. Maguire:** None.

Poster

116. Oscillations and Synchrony: LFP and Unit Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 116.08

Topic: B.07. Network Interactions

Support: R01MH128235
P50MH122379

Title: Observational stress impairs neurosteroid signaling in the BLA

Authors: *A. EVANS-STRONG[1], N. L. WALTON[1], A. ROPER[2], T. DONALDSON[2], J. L. MAGUIRE[1];
[1]Neurosci., Tufts Univ., Boston, MA; [2]Psychology, Univ. of Massachusetts, Boston, Boston, MA

Abstract: Behavioral and physiological responses to stress can be socially transmitted, which is thought to be an adaptive way to communicate a threat without direct exposure. However, witnessing a traumatic event has been shown to lead to the development of post-traumatic stress disorder (PTSD). Previous research has implicated deficits in 5α-reduced neurosteroids in the development of PTSD. To better understand the role that 5α-reduced neurosteroids play in the development of PTSD associated with witnessing a traumatic event, we used an observational fear model in which an observer mouse witnesses a demonstrator mouse experience a series of footshocks. Results from these studies demonstrate increased freezing in observer mice compared to naive controls upon contextual recall. This suggested to us that neural circuits involved in fear learning, such as the basolateral amygdala (BLA), may be involved in observational fear. We quantified transcript levels of 5α-reductase type 1 and 2 (Srd5a1&2), the rate-limiting enzymes involved in neurosteroidogenesis, and the $GABA_A$ receptor δ subunit (Gabrd), the primary site of action for 5a-reduced neurosteroids, and demonstrated that expression of Srd5a2 and Gabrd is reduced in both demonstrator and observer mice compared to naive controls. Notably, the decrease in observer expression was comparable to that of demonstrators. We then administered a synthetic neurosteroid analog (SGE-516) which significantly decreases freezing upon recall compared to vehicle mice. Conversely, we administered Finasteride, a 5α-reductase inhibitor, which significantly increased freezing in mice during the recall session. Taken together, this data demonstrates a role for endogenous neurosteroidogenesis in the BLA in the behavioral outcomes of observational fear and suggests that targeting endogenous neurosteroidogenesis may be a useful therapeutic intervention for PTSD, including cases resulting from witnessing a trauma.

Disclosures: **A. Evans-Strong:** None. **N.L. Walton:** None. **A. Roper:** None. **T. Donaldson:** None. **J.L. Maguire:** F. Consulting Fees (e.g., advisory boards); SAGE Therapeutics.

Poster

116. Oscillations and Synchrony: LFP and Unit Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 116.09

Topic: B.07. Network Interactions

Support: NIH R01MH128235
NIH P50MH122379

Title: Locus coeruleus-derived norepinephrine shapes BLA rhythmic inhibitory activity and promotes negative valence assignment through interneuronal α1A signaling.

Authors: *E. TEBOUL[1,2], G. WEISS[2], P. ANTONOUDIOU[2], J. MAGUIRE[1,2];
[1]Neurosci., Tufts Univ. Grad. Sch. of Biomed. Sci., Boston, MA; [2]Neurosci., Tufts Univ. Sch. of Med., Boston, MA

Abstract: The basolateral amygdala (BLA) is well recognized as a critical node involved in emotional processing. Mounting evidence highlights the central role of the BLA in assigning binary emotional valuation, either positive or negative, to an experience, termed 'valence assignment'. This process involves the activation of distributed networks associated with either positive or negative valence processing. While the specific BLA output pathways underlying valence assignment have been well studied, we lack understanding of how output specific circuitry is engaged, governing the directionality of valence assignment. Interneurons in the BLA have been shown to play a role in coordinating network states associated with negative affective behaviors. We propose neuromodulation of BLA interneurons differentially shapes local oscillatory networks to preferentially engage target-specific cell assemblies, directing valence assignment. Initial findings suggest PV and CCK interneurons drive norepinephrine-induced gamma (40-120 Hz) and theta (2-12 Hz) activity changes via α1A adrenergic signaling, respectively. Additionally, we illustrate that tonically stimulating locus coeruleus noradrenergic projections in the BLA promotes real time negative valence assignment and similarly reorganizes local oscillatory activity in mice. These data demonstrate a novel mechanism involving circuit-specific, neuromodulatory control over BLA network states driving negative valence assignment.

Disclosures: **E. Teboul:** None. **G. Weiss:** None. **P. Antonoudiou:** None. **J. Maguire:** None.

Poster

116. Oscillations and Synchrony: LFP and Unit Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 116.10

Topic: B.07. Network Interactions

Support: NIH Grant K00MH130162-03
NIH Grant R01MH128235
NIH Grant P50MH122379

Title: Basolateral amgydala parvalbumin-expressing interneurons mediate goal-directed behaviors

Authors: *K. A. AMAYA, P. ANTONOUDIOU, J. L. MAGUIRE;
Tufts Univ., Boston, MA

Abstract: Survival for many species depends on effective decision-making, where outcomes produced by one's actions are evaluated for their usefulness. When considering future courses of action, decision-making relies on outcome value representations that are dependent on the basolateral nucleus of the amgydala (BLA). While studies of BLA microcircuitry have identified parvalbumin-expressing (PV) interneurons as key governors of fear behaviors, strikingly little is known about how BLA microcircuitry works to govern appetitive learning, even though it is well established that the BLA is involved in both positive and negative valence processing. Therefore, we conducted a series of experiments targeting BLA PV interneurons to interrogate their role in mediating goal-directed behaviors. We found that inhibition of PV interneurons rendered animals insensitive to satiety-induced outcome devaluation. Separately, during reversal testing, PV inhibition had no effect on the rate at which animals acquired a new action-outcome association but did impact how quickly animals ceased performing an action once it was no longer rewarded. Together, these results describe a new, critical role for PV interneurons in the BLA as regulators of goal-directed behaviors.

Disclosures: K.A. Amaya: None. **P. Antonoudiou:** None. **J.L. Maguire:** None.

Poster

116. Oscillations and Synchrony: LFP and Unit Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 116.11

Topic: B.07. Network Interactions

Support: NIH R01MH128235
NIH P50MH122379

Title: Circuit mechanisms mediating pro-safety network states in rodent affective networks

Authors: *P. ANTONOUDIOU, B. T. STONE, G. L. WEISS, E. TEBOUL, J. MAGUIRE;
Tufts Univ., Tufts Univ. Sch. of Med., Boston, MA

Abstract: Allopregnanolone (allo) has been recently approved as the first drug for the treatment of postpartum depression and has demonstrated promise in the treatment of major depressive disorder. We have previously demonstrated that 5α-reduced neurosteroids, including allo, increase high theta (6 - 12 Hz) and beta (15 - 30) band oscillatory power in the basolateral amygdala (BLA), a network state that has been associated with the pro-safety behavioral state in mice. Here we sought to further understand the network mechanisms that give rise to the pro-safety state by employing LFP/EEG recordings in affective networks (BLA, ventral hippocampus (vHPC), and frontal cortex (FC)) and by utilizing calcium imaging in BLA. We find that allo application increases high theta and beta power across brain regions (BLA, vHPC and FC), whereas the coherence between BLA and FC decreased and remained unchanged between vHPC and FC—suggesting that the routing of information could be altered during high neurosteroid tone. In agreement with our previous findings, changes in oscillatory power and coherence were absent in mice lacking the delta containing $GABA_A$ receptors. Calcium imaging during allo application in wild-type mice revealed a large population of BLA principal cells that decreased their activity. This finding is unexpected given that allo acts through delta containing $GABA_A$ receptors to increase tonic inhibition on BLA GABAergic interneurons in the BLA, which would theoretically result in principal cell disinhibition. These results suggest that the main effect of allo is to promote circuit synchronization rather than dis-inhibition and begin to uncover circuit mechanisms of pro-safety switching, relevant to understanding the antidepressant effects of these compounds and the episodic nature of depression.

Disclosures: P. Antonoudiou: None. **B.T. Stone:** None. **G.L. Weiss:** None. **E. Teboul:** None. **J. Maguire:** F. Consulting Fees (e.g., advisory boards); Sage Therapeutics.

Poster

116. Oscillations and Synchrony: LFP and Unit Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 116.12

Topic: B.07. Network Interactions

Support: R01MH128235
P50MH122379

Title: Effects of Corticotropin Releasing Hormone on Stress Induced Network States in Basolateral Amygdala

Authors: *G. L. WEISS, G. B. SCARPA, J. L. MAGUIRE;
Neurosci., Tufts Univ. Sch. of Med., Boston, MA

Abstract: Corticotropin releasing hormone (CRH) projections from the hypothalamus to the pituitary have long been established as the apical controller of stress induced glucocorticoid release, which is the neuroendocrine component of the stress response that is dysfunctional in disorders involving anxiety and depression. However, CRH release has been more recently found

in many extrahypothalamic regions including many limbic regions, revealing a possible direct role of CRH in anxiety and depression independent of glucocorticoid release. We recently reported that network activity in basolateral amygdala (BLA) is affected by acute and chronic stress. Given the role of the amygdala in emotional processing in both mice and humans, we examined the impact of CRH signaling in the BLA on network and behavioral states. Here we demonstrate that exogenous CRH dampens the acute stress induced suppression of 2-12 Hz (Theta) oscillations in the BLA. Interestingly, previous exposure to chronic stress impacted the ability of acute stress to alter BLA network states in a modality dependent manner. Further, previous exposure to chronic stress occluded the effects of exogenous CRH on BLA network states. Labeling of CRH neurons in the BLA and their presynaptic projections revealed only a sparse population of local CRH neurons in the BLA, but retrograde labeling of CRH neurons projecting to the BLA revealed several brain regions with CRH projections to the BLA. Finally, we further investigated the nuance in network state shifting by stressing the animal with a perceived areal predator via looming-disk. Preliminary data show differences in power in several frequency bands depending on behavioral response. These data help to further understand the role of CRH in neuromodulation of network states of anxiety.

Disclosures: **G.L. Weiss:** None. **G.B. Scarpa:** None. **J.L. Maguire:** None.

Poster

116. Oscillations and Synchrony: LFP and Unit Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 116.13

Topic: B.07. Network Interactions

Support: I01 BX04500 (JMM)
I01 BX002774 (RES)
IK6 BX005714 (RES)
R21 MH125242 (JTM/JMM)
NRF-2021R1A6A3A03044041 (JYC)

Title: The olfactory bulb drives default mode network-like activity in basal forebrain of mice

Authors: J. CHOI[1], B. KOCSIS[2], R. E. STRECKER[1], J. T. MCKENNA[1], ***J. MCNALLY**[1]; [1]VABHS, Harvard Med. Sch., West Roxbury, MA; [2]Psychiatry, Beth Israel Deaconess Med. Ctr., Boston, MA

Abstract: The neural mechanisms which support consciousness and our engagement with the external world remain poorly understood. Such processes necessitate the precise cooperation of specialized functional networks, which must dynamically coordinate their activity and interactions as a function of task performance and cognitive demand. One such functional network that has garnered significant interest over the last few decades is the default mode network (**DMN**), a large-scale brain circuit that is activated during quiet wakefulness and

deactivated during goal-directed tasks which evoke cognitive load. Abnormalities in DMN functional connectivity and activation appear across many neuropsychiatric disorders, including schizophrenia. Recent evidence suggests the basal forebrain is functionally and structurally important for regulation of DMN activity. Here, we attempt to test and extend this hypothesis using multisite local field potential (**LFP**) recording techniques. Adult mice (n = 4) were implanted with LFP electrodes targeting up six distinct brain regions: several associated with DMN (Basal Forebrain, Prefrontal Cortex, Posterior Parietal Cortex) and several not (Primary Visual Cortex, CA1 and Olfactory Bulb). Spontaneous LFP activity was recorded from freely behaving animals in a home cage, to promote DMN-like activity, and a novel environment. In our experimental work, we have been able to recapitulate prior findings showing pronounced gamma activity in both the basal forebrain and prefrontal cortex during quiet wakefulness in the home cage and suppression of this activity during active exploration of a novel environment. Surprisingly, DMN-like activity was also observed in the olfactory bulb. As expected, this effect was not observed in visual cortex or CA1. However, the posterior parietal cortex, which has been identified as a likely-DMN node, also did not exhibit DMN-like activity. Finally, granger causality analysis of our data shows that gamma activity in the olfactory bulb drives gamma activity in the BF. This finding suggests the functional importance of respiratory-entrained neural activity in the modulation of DMN neural network activity. Overall, this research provides valuable insight into the brain regions that comprise functional networks such as DMN, and their properties. The mechanisms which regulate their function can provide novel targets for therapeutic interventions for cognitive deficits associated with a number of neurological and psychiatric disorders.

Disclosures: **J. Choi:** None. **B. Kocsis:** None. **R.E. Strecker:** None. **J.T. McKenna:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Merk MISP. **J. McNally:** None.

Poster

116. Oscillations and Synchrony: LFP and Unit Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 116.14

Topic: B.07. Network Interactions

Title: Characterization of local field potential activity in a cell-based neuronal assay for neurotoxicity and disease modeling

Authors: P. J. ELLINGSON[1], D. D. SULLIVAN[1], H. B. HAYES[2], *D. MILLARD[1]; [1]Axion Biosystems, Atlanta, GA; [2]Axion Biosystems, Inc., Atlanta, GA

Abstract: The flexibility and accessibility of induced pluripotent stem cell (iPSC) technology has allowed complex human biology to be reproduced *in vitro* at high throughput scales. Indeed, rapid advances in stem cell technology have led to widespread adoption for the development of

in vitro models of neuron electrophysiology to be used in screening applications in drug discovery and safety. Furthermore, advanced cells preparations, such as spheroids or organoids, are under intense investigation with aims towards establishing mature human phenotypes *in vitro*. As *in vitro* neuronal models become more mature, the functional electrophysiological activity may begin to reproduce low-frequency brain rhythms, in addition to the spiking, bursting, and synchronization already observed. The objective of this work is to develop and validate a functional neuronal assay that quantifies the relationship between spiking activity of individual neurons and the network activity embedded in the local field potential (LFP). A planar grid of microelectrodes embedded in the substrate of each well of a culture plate interfaces with cultured cellular networks to continuously monitor broadband (0.1 - 5000 Hz) electrophysiological data from rodent and human iPSC-derived neuronal networks. The spectral power within the LFP was correlated with the emergence of bursting activity within the rodent cortical and human iPSC-derived neurons when monitored over 28 days in culture. LFP events were detected spontaneously and also extracted as network burst triggered averages. The LFP event frequency, amplitude, and power spectrum were quantified and compared across the rodent and human iPSC-derived models over the culture period. Known reference compounds were then added to the cultures and the change in LFP features were quantified and compared with more traditional functional endpoints based in spiking activity. For example, Carbachol increased the burst duration and mean firing rate, while decreasing the LFP power in the theta, alpha, and delta bands. These results support the continued development and use of human iPSC-derived neural assays for high throughput drug discovery and safety assessment.

Disclosures: **P.J. Ellingson:** A. Employment/Salary (full or part-time):; Axion Biosystems. **D.D. Sullivan:** A. Employment/Salary (full or part-time):; Axion Biosystems. **H.B. Hayes:** A. Employment/Salary (full or part-time):; Axion Biosystems. **D. Millard:** A. Employment/Salary (full or part-time):; Axion Biosystems.

Poster

116. Oscillations and Synchrony: LFP and Unit Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 116.15

Topic: B.07. Network Interactions

Support: NIH Grant 5R01GM124023
NIH Grant 5R01NS113366
NIH Grant 1F31NS118808-01A1

Title: Local cortical activity state fluctuations in anesthetized rats have weak, region- and layer-dependent coupling despite a low-dimensional global state space

Authors: *E. B. BLACKWOOD[1], B. P. SHORTAL[1], A. PROEKT[2];
[1]Neurosci., [2]Anesthesiol. and Critical Care, Univ. of Pennsylvania, Philadelphia, PA

Abstract: Abrupt switches between global cortical activity patterns within a low-dimensional state space occur during both recovery from anesthesia and maintenance of a fixed dose. While global state switches, such as sleep/wake transitions, are often thought to be driven by modulation from the thalamus and other subcortical structures, the potential role of cortico-cortical connectivity is not well understood. If subcortical inputs directly drove activity state switches throughout the cortex, we would expect state switches at different recording sites, even across different regions, to be highly synchronized. In contrast, these subcortical inputs may drive only some cortical columns to switch states, which then propagate the signal to other columns via local connections. Then we would expect higher state synchrony within regions than between them. To differentiate these hypotheses, we recorded local field potential (LFP) from either the right primary visual (V1) and motor (M1) cortices (n = 3) or left and right V1 (n = 4) in rats breathing 1% isoflurane for 4-7.25 hours. We computed spectrograms using the multitaper method, then reduced dimensionality using non-negative matrix factorization (NMF). We then identified a set of states for each channel based directly on its NMF components. By both inspecting raw data and analyzing the composition of states identified from pooled data, we validated that this method produces states that classify activity patterns in a consistent and relevant manner. We then computed state transition synchrony, normalized mutual information (NMI) of states, and canonical correlation of NMF scores between each pair of channels. According to all three measures, coupling of both activity and transitions was significantly higher than with a null model in most channel pairs at the corrected $p < 0.05$ level, but was nevertheless weak. Specifically, coupling was weaker for pairs that spanned both recorded regions than for those within a region ($p < 10^{-6}$ in all cases), supporting the hypothesis that local connections participate in coupling. Also, in V1 recordings, the thalamic input layer IV was consistently less coupled to other channels than others were to each other ($p < 0.05$ in all cases), which suggests that other layers do exhibit activity that is not conducted by the thalamic inputs. Our findings impose a limit on the view that state transitions during anesthesia are tightly synchronized at the level of individual columns, despite the emergence of global synchronization when many recording sites are considered. Future research should record from more regions and use interventions, such as chemogenetics, to probe specific circuit mechanisms.

Disclosures: **E.B. Blackwood:** None. **B.P. Shortal:** None. **A. Proekt:** None.

Poster

116. Oscillations and Synchrony: LFP and Unit Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 116.16

Topic: B.07. Network Interactions

Support: NIH MH122023
NSF OAC-1730655

Title: Computational model provides a key role for chandelier interneurons in generation of sharp wave ripples in the CA1 Hippocampus

Authors: *D. DOPP[1], G. GLICKERT[3], B. LATIMER[1], M. BHAGAVATHI PERUMAL[4], P. SAH[5], S. S. NAIR[2];
[2]Electrical & Computer Engin., [1]Univ. of Missouri, Columbia, MO; [3]Neural Engin., Univ. of Missouri, Columbia, Wildwood, MO; [4]Queensland Brain Insititute, Brisbane, Australia; [5]The Univ. of Queensland Queensland Brain Inst., St Lucia, Australia

Abstract: Sharp waves (less than 20Hz) and ripples (200 Hz) (SWRs) oscillations in the local field potential reflect large-scale synchronized activity in neural circuits that mediate memory consolidation. SWRs have been extensively investigated in the CA1 region of the hippocampus for their role in spatial memory. However, neural circuit mechanisms in the CA1 that generate SWRs especially ripples remain contentious and unresolved. Previous models have proposed feedback inhibition from basket type interneurons (INs) to pace spiking of principal cells (PNs) that rely on extrinsic excitation from the CA3 hippocampus. However, both *in vitro* and *in vivo* evidence indicate CA1 contains necessary circuit motifs to generate SWRs without input from the CA3. We recently showed chandelier interneurons, a rare subset of INs, drive microcircuit modules to generate SWRs in the amygdala using experimental and computational methods. Here, we present an experimental data driven model of CA1 circuits motifs that generate SWRs spontaneously and with extrinsic inputs reproducing cellular, synaptic, and field potential properties of physiological SWRs. In contrast to previous models, here we demonstrate a central role for chandelier INs in the CA1 circuit motifs for generating SWRs.

Disclosures: D. Dopp: None. **G. Glickert:** None. **B. Latimer:** None. **M. Bhagavathi Perumal:** None. **P. Sah:** None. **S.S. Nair:** None.

Poster

116. Oscillations and Synchrony: LFP and Unit Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 116.17

Topic: B.07. Network Interactions

Support: USIAS-Fellows 20-D Battaglia

Title: Structure or dynamics? On the role of the canonic circuit in the emergence of cortical multi-frequency oscillations and multiplexed routing

Authors: *S. CASTRO[1,2], M. HELMER[4], R. HERZOG[5], F. WOLF[6], D. BATTAGLIA[7,3];
[1]Inst. for Advanced Studies (USIAS), [2]Lab. de Neurosciences Cognitives et Adaptatives (LNCA), [3]Univ. of Strasbourg Inst. for Advanced Studies (USIAS), Univ. de Strasbourg, Strasbourg, France; [4]Yale university, New Heaven, CT; [5]Univ. de Valparaiso, Valaparaiso, Chile; [6]MPI Dynamics & Self-Organization, MPI Dynamics & Self-Organization, Goettingen, Germany; [7]INS, Univ. Aix-Marseille, INS, Univ. Aix-Marseille, Marseille, France

Abstract: Bottom-up and top-down functional connectivity (FC) between cortical regions are mediated by faster and slower frequency oscillations. Eventually, different cortical layers also

oscillate at different frequencies. Therefore, it has been proposed that FC in different directions operates at different frequencies because of the distinct resonance frequencies of the source and target layers. Based on a systematic modelling analysis, we propose here on the contrary that the frequency specialization of directed FC stems as an emergent by-product of self-organized collective dynamics rather than of hardwired anatomy and interneuronal diversity. Specifically, we analyze rate models of coupled cortical regions embedding a realistic multi-layer anatomical organization. Every layer includes an excitatory and a unique inhibitory population of the fast-spiking type, resonating at a fast gamma-range frequency. Despite this intrinsic resonance, we can obtain a great diversity of possible dynamical states as a function of contextual inputs and the relative strength of excitation and inhibition. Regimes in which faster and slower frequency oscillations predominate respectively in superficial or deeper layers arise spontaneously and robustly due to non-linear inter-layer interactions. However, we also find that the strength and the dominant frequencies of directed FC can be flexibly adjusted by modulating the dynamical regime of the network, without the need of structural changes and in a context-dependent way. We furthermore show that dynamical regimes allowing such a multi-frequency adaptivity of directed functional interactions are extremely unlikely to arise in randomized networks. We thus speculate that the canonic circuit wiring may be optimized to favour the frequency multiplexing of inter-regional information routing, which we show being a mechanism to maximize high-order interactions and synergies.

Disclosures: S. Castro: None. **M. Helmer:** None. **R. Herzog:** None. **F. Wolf:** None. **D. Battaglia:** None.

Poster

116. Oscillations and Synchrony: LFP and Unit Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 116.18

Title: WITHDRAWN

Poster

116. Oscillations and Synchrony: LFP and Unit Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 116.19

Topic: B.07. Network Interactions

Support: R01MH112143

Title: Optogenetic Mapping of Cerebellar Cortical Modulation of Cerebral Cortical Coherence

Authors: *M. B. FOX[1], B. L. CORREIA[1], M. DHAMALA[2], R. V. SILLITOE[3], Y. LIU[1], D. H. HECK[1];
[1]Univ. of Tennessee Hlth. Sci. C Neurosci. Grad. Program, Memphis, TN; [2]Georgia State Univ., Atlanta, GA; [3]Pathology & Immunol., Baylor Col. of Med., Houston, TX

Abstract: The cerebellum has been linked to motor, cognitive, and emotional processes and is historically known for coordination and temporal control, particularly in motor tasks. There is general agreement that cerebellar involvement in cognitive tasks requires cerebrocerebellar interactions. We recently published evidence supporting a role for the cerebellum as a coordinator of neuronal communication in the cerebral cortex through the modulation of coherence of neuronal oscillations. We have shown that optical stimulation of cerebellar lobulus simplex alters coherence between the prefrontal cortex and hippocampus, two regions crucially involved in spatial working memory. Others have shown that coherence of gamma oscillations between the primary sensory and motor cortices in mice depend on the cerebellum. However, there is no systematic evaluation of which areas of the cerebellar cortex modulate coherence between areas of cerebral cortex and possibly subcortical structures. This study involved mapping the cerebellar influence on coherence of neuronal oscillations between the prefrontal cortex (mPFC), hippocampus (dCA1), mediodorsal thalamus (MDt) and the basolateral amygdala (BLA) in awake, head-fixed mice by applying optogenetic activation or inhibition to cerebellar Purkinje cells while recording local field potential (LFPs) activity from the aforementioned structures. Ai32(RCL-ChR2(H134R)/EYFP) and Ai40(RCL-ArchT/EGFP)-D mice were crossed with $L7^{Cre}$ mice to create a transgenic model that expressed channelrhodopsin or archerhodopsin, respectively, in cerebellar Purkinje cells. Craniotomies were made over the vermis, lobulus simplex, and Crus I. Mice were able to walk on a treadmill (Speedbelt, Phenosys, Germany) whose movements were registered together with neuronal data. Optogenetic stimulation (30 stimuli, 25 sec. ISI, at 470 nm and 520 nm) was applied over the lobulus simplex, Crus I, or the vermis via an optical fiber. All animal experimental procedures were approved by the University of Tennessee Health Science Center Animal Care and Use Committee. Time resolved coherence analysis showed that photoactivation to any single region of the cerebellum differentially modulated coherence between mPFC and dCA1, mPFC and BLA, and PFC and MDt. Hippocampal and MDt coherence, however, was only affected by Crus I and vermis stimulation. While stimulation in lobulus simplex and Crus I affected coherence in multiple frequency bands, activation of the vermis appears to affect coherence predominantly in the beta band. These findings further support a possible role of the cerebellum in the coordination of coherence in forebrain structures.

Disclosures: M.B. Fox: None. **B.L. Correia:** None. **M. Dhamala:** None. **R.V. Sillitoe:** None. **Y. Liu:** None. **D.H. Heck:** None.

Poster

116. Oscillations and Synchrony: LFP and Unit Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 116.20

Topic: B.07. Network Interactions

Title: Modulation of beta and gamma frequency oscillations in the rat anterior cingulate cortex (ACC) in vitro by the mGlu2 metabotropic glutamate receptor

Authors: B. H. DENNIS[1], ***S. A. NEALE**[2,1], F. E. LEBEAU[1], T. E. SALT[2,3,1];
[1]Biosci. Inst., Newcastle Univ., Newcastle upon Tyne, United Kingdom; [2]Neurexpert Limited, Neurexpert Limited, Newcastle Upon Tyne, United Kingdom; [3]Inst. of Opthalmology, Univ. Col. London, London, United Kingdom

Abstract: The anterior cingulate cortex (ACC) plays a role in remote spatial memory, attention and executive functions. These functions are associated with network oscillations in the beta (20-30 Hz) and gamma (30-80 Hz) range. We have demonstrated that both beta and/or gamma oscillations can be recorded in vitro in the deep and superficial layers of ACC (Adams et al 2017 DOI: https://doi.org/10.1523/ENEURO.0313-16.2017). Changes in cortical beta and gamma frequency activity occur in patients in a range of neuropsychiatric and neurodegenerative diseases, and Group II mGlu receptors (mGlu2 & mGlu3) have been suggested as targets for diseases of both types. Therefore, it is important to determine whether these receptors affect cortical network oscillations. ACC slices (450 µm) were prepared following transcardial sucrose perfusion in anaesthetised rats. Slices were transferred to an interface chamber for recording. Network oscillations were evoked using bath application of kainate (800 nM) for 1-3 hours until oscillation magnitude stabilised.Following application of kainate, beta activity (assessed over the 20-33 Hz frequency band) and gamma activity (assessed over the 33-80 Hz frequency band) were observed in ACC slices. Both beta and gamma activity were attenuated in the presence of the mGlu2/3 receptor agonist LY354740 in a concentration dependent manner. Following 60 mins application, LY354740 reduced the area under the curve of beta and gamma activity, with the top concentration (3 µM) reducing beta and gamma area power by 52±5 and 66±9%, respectively. The effects of LY354740 were occluded by bath application of the antagonist LY341495 (300 nM). To distinguish between mGlu2 and mGlu3 activation, the mGlu2-agonist/mGlu3-antagonist LY541850 (1 µM) was applied, and this was found to reduce beta and gamma oscillations by 38±9 and 58±8%, respectively. Cognitive and network dysfunction can be modelled in rodents using phencyclidine (PCP). Application of PCP (10 µM) to a stable kainate-evoked oscillation induced a significant increase in beta frequency oscillations (216±23%). Subsequent application of LY354740 (3 µM) or LY541850 (1 µM) significantly reduced this effect, returning oscillation power to levels not significantly different from pre-PCP application. Our results show that Group II mGlu receptors modulate network oscillations and point to an involvement of mGlu2 receptors. In addition, attenuation of the effect of PCP points to a mechanism by which mGlu2 receptors may stabilise aberrant network activity. These results underline the importance of mGlu2 receptors as targets for the treatment of neuropsychiatric and neurodegenerative diseases.

Disclosures: **B.H. Dennis:** None. **S.A. Neale:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neurexpert Limited. **F.E. LeBeau:** None. **T.E. Salt:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neurexpert Limited.

Poster

116. Oscillations and Synchrony: LFP and Unit Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 116.21

Topic: B.07. Network Interactions

Support: ISF-NSFC joint research program (grant No. 3459/20)
BSF grant No. 2019186

Title: Neural correlates of social behaviour during affiliative and aversive behavioural states in SD rats

Authors: *S. R. JOHN, S. NETSER, S. WAGNER;
Sagol Dept. of Neurobio., Univ. of Haifa, Haifa, Israel

Abstract: Adaptive social behaviour is a natural phenomenon exhibited across all animal kingdom. Depending on the positive or negative valence of a conspecific, the subject will decide whether to approach or avoid it. Despite the importance of social behaviour, many fundamental questions remain unanswered in our understanding of its underlying brain circuits and neural mechanisms. Previous studies have shown that a complex assemblage of brain regions, termed the Social Brain, is involved in supporting different types of social interactions. Our main working hypothesis is that coordinated neuronal activity distributed across the social brain reflects differential behavioural response of social approach or avoidance. To test this hypothesis, we chronically implanted custom-made multiunit electrode array probes in adult male SD rats. We have recorded electrophysiological activity from multiple brain regions simultaneously, while the subject animals performed the Social Preference task, using novel social stimuli. We have analysed both multiunit spiking activity (MUA) and local field potential (LFP) signals recorded from the various brain regions. Specifically, we recorded signals from various areas of the amygdaloid complex, which is considered as a central hub for driving emotional behaviours.We found that specific changes in power of the LFP frequencies depend on the valence of the stimulus, as reflected by subject's behaviour towards the social stimulus. For example, approach or avoidance behaviours were found to be differentially correlated with a clear change in power of Theta (4-12 Hz) and Gamma (30-80 Hz) oscillations in specific areas of the amygdaloid complex, such as the medial (MeA), central (CEM), stria terminalis (STIA), and anterior amygdala (AA). In contrast, MUA in the social brain regions did not show significant changes except in brain areas of AA and STIA during appetitive and aversive states. Also, Theta and Gamma oscillations showed differential pattern of coherence between the social brain regions during affiliative and aversive social encounters. We observed changes in vocalization as well, when the subject rat interacts with a stimulus of varied emotional state. They produce more calls in ultrasonic range (~50kHz) when they are happy and long 22kHz calls when in stress.We revealed neural correlates of both affiliative and aversive social behaviours in several regions of the social brain, which provides insight into the mechanisms underlying socio-emotional internal states of rats. This insight might help us to understand changes in brain activity involved in brain pathologies associated with atypical social behaviour.

Disclosures: **S.R. John:** None. **S. Netser:** None. **S. Wagner:** None.

Poster

116. Oscillations and Synchrony: LFP and Unit Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 116.22

Topic: B.07. Network Interactions

Support: EU MSCA-ITN "iConn"

Title: Large-scale dynamic network and information theory analyses of coherent activity during a working memory task

Authors: *V. LIMA CORDEIRO[1], S. J. HOFFMAN[2], N. DOTSON[3], C. M. GRAY[2], A. BROVELLI[4], D. BATTAGLIA[1,5];
[1]Aix-Marseille University, INS, Marseille, France; [2]Montana State Univ. Bozeman, Bozeman, MT; [3]SNL-R, Salk Inst. for Biol. Studies, LA JOLLA, CA; [4]Aix-Marseille University, INT, Marseille, France; [5]Univ. of Strasbourg Inst. for Advanced Studies, Strasbourg, France

Abstract: Working memory requires large-scale coordination among widespread cortical and subcortical brain regions. Long-range coherence between the oscillatory activity of cortical regions, arising in multiple frequency bands, may be a mechanism supporting information routing and integration across distributed multi-regional networks. In line with this hypothesis, the strength of coherence links between frontal and parietal regions is consistently modulated by the specific identity of a visual stimulus held in working memory. Is content-specific synchronization limited to the frontoparietal network or do large-scale networks of coherent oscillations support working memory?
Here, we perform a time-resolved network coherence analysis of local field potentials recorded simultaneously from dozens of cortical areas in non-human primates performing a visual delayed match-to-sample task. Preliminary results indicate that networks in multiple frequency bands are not only structured in space, but also in time. Indeed, the bursting dynamics of different links are not independent but often coordinated to the fluctuation of other links, as we reveal through a brain-wide, edge-centric functional connectivity analysis. The consequence of these coordinated coherence fluctuations is that "network bursts" emerge spontaneously during the delay period, superimposed on a sustained network scaffold, visible also through static network analyses.
We then compute the mutual information between stimulus identity and a variety of node- and link-level features for different frequency bands, comparing their relative encoding, such as node power, node strength within static functional connectivity, link coherence and link "entanglement" (dynamic coupling to other links). We then discuss the results in the context of dynamic mechanisms for stimulus-biased sampling of different classes of network bursts.

Disclosures: **V. Lima Cordeiro:** None. **S.J. Hoffman:** None. **N. Dotson:** None. **C.M. Gray:** None. **A. Brovelli:** None. **D. Battaglia:** None.

Poster

116. Oscillations and Synchrony: LFP and Unit Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 116.23

Topic: B.07. Network Interactions

Title: Local field potentials in the BNST in patients with OCD: acute effects of DBS after symptom provocation

Authors: H. HEYLEN[1,2,4], C. BERVOETS[3,4], B. NUTTIN[3,5], M. MC LAUGHLIN[3];
[1]Circuits & Systems for Hlth., imec, Leuven, Belgium; [2]Dept. of Electrical Engin. (ESAT), KU Leuven, KU Leuven, Belgium; [3]Neurosciences, KU Leuven, Leuven, Belgium; [4]UPC KU Leuven, Leuven, Belgium; [5]UZ Leuven, Leuven, Belgium

Abstract: *Introduction:* Obsessive-compulsive disorder (OCD) is a disabling psychiatric disorder that affects 2-3% of the population. Pharmacological or cognitive behavioral therapy can reduce symptoms. Deep brain stimulation is emerging for treatment-resistant patients.
Objectives: We measured neuronal activity in two patients with treatment-resistant OCD, who had DBS electrodes implanted bilaterally in the BNST. Local field potentials were recorded directly from the BNST during and without symptom provocation and without electrical stimulation.
Methods: In two patients with a diagnosis of treatment resistant OCD (TR-OCD) local field potentials (LFP) were recorded as part of their clinical follow up post-implantation. In both patients, the diagnosis of TR-OCD was confirmed by a neuropsychiatric examination and a multidisciplinary committee comprising both experienced psychiatrists and neurosurgeons from different medical centers in Belgium. We used BrainSense recording technology in the Percept PC to record the LFPs. The LFP recordings in the first patient were acquired on the 15th day after DBS surgery. In the second patient, the interval between implantation and recording was 18 days. Symptom provocation was performed using the MOCCS image set, developed by Mataix-Cols.
Results: At rest, relative power peaks in the BNST were highest in the theta (4-8 Hz) frequency band for both patients. In both patients switching DBS ON during provocation images appears to cause the LFP signal to closely resemble that recorded during neutral images.
Conclusions: The main finding of this pilot study is that switching stimulation ON in the BNST during provocation images causes the LFP signal to more closely resemble the LFP recorded during neutral images. Switching stimulation ON alters the brain state more closely to pre-provocation.

Disclosures: H. Heylen: ; Funded by Research Foundation - Flanders (FWO): PhD Fellowship fundamental research 11K1922N. **C. Bervoets:** None. **B. Nuttin:** None. **M. Mc Laughlin:** None.

Poster

116. Oscillations and Synchrony: LFP and Unit Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 116.24

Topic: B.07. Network Interactions

Title: Nmda and sigma-1 receptor modulation of network oscillations and neuroinflammation in the rodent hippocampus and anterior cingulate cortex

Authors: *B. DENNIS[1], R. S. PAXMAN[1], O. J. BADDELEY[1], S. A. NEALE[1,2], T. E. SALT[1,2], G. J. CLOWRY[1], F. E. N. LEBEAU[1];
[1]Biosci. Inst., Newcastle Univ., Newcastle upon Tyne, United Kingdom; [2]Neurexpert Limited, Neurexpert Limited, Newcastle Upon Tyne, United Kingdom

Abstract: Aberrant beta and gamma frequency oscillations are reported in patients with schizophrenia, alongside impaired working memory and attention. Additionally, increased neuroinflammation is reported in human *post-mortem* tissue. Beta (20-30Hz) and gamma (30-80Hz) frequency oscillations can be recorded from the rat anterior cingulate cortex (ACC) and hippocampus (HPC) in vitro. Cognitive and network dysfunction can be modelled in rodents using the N-methyl-D-aspartate (NMDA) receptor antagonist phencyclidine (PCP) and in vivo studies suggest sigma-1 receptor (σ1R) activation may reverse these deficits. However, the mechanism by which PCP causes disruption of oscillations, and the effects of PCP and σ1R modulation on network activation and neuroinflammation are unknown. Rat ACC/HPC slices were prepared by standard methods and transferred to an interface chamber for electrophysiological recording. Network oscillations were evoked using bath-applied kainate. PCP was bath-applied to stable beta and gamma oscillations for 1 hour followed by 1 hour co-application of σ1R agonist PRE-084. Effects on peak frequency and area power were measured. In the ACC, PCP significantly increased the power of stable beta oscillations (216±23%) and caused gamma oscillations to switch to a beta frequency (41±1.3 to 27±1.5 Hz). In contrast, PCP had little effect on HPC beta/gamma oscillations. The σ1R agonist PRE-084 had no effect on network oscillations in either brain region. To assess the effect of PCP and σ1R activation on glial activation ACC/HPC slices were transferred to an interface chamber and incubated for 4 hours with KA and/or PCP, or pre-incubated for 30 minutes with PRE-084 and incubated for 4 hours with KA and/or PCP. Slices were then fixed, re-sectioned and immunohistochemistry was conducted using the reactive astrocyte marker GFAP and reactive microglia marker IBA1. The %area stained in the different conditions was then determined. Reactive astrocyte expression in HPC slices exposed to KA alone was 6.78 ± 1.3%, which significantly increased to 8.93 ± 0.92% when exposed to KA and PCP ($p = 0.022$). Interestingly our preliminary data suggests this PCP-evoked neuroinflammatory response was reduced by pre-incubation with the σ1R agonist PRE-084 (6.08 ± 1.17%; $p = 0.025$). Our data suggests that the NMDA receptor antagonist PCP induces an abnormally large beta oscillation in rat ACC, but not the HPC, and increases neuroinflammation, whilst the σ1R agonist PRE-084 reduces PCP's neuroinflammatory effect. Further investigation is required to better understand the interplay between these two receptors and their effects on cognitive impairment.

Disclosures: **B. Dennis:** None. **R.S. Paxman:** None. **O.J. Baddeley:** None. **S.A. Neale:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neurexpert Limited. **T.E. Salt:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neurexpert Limited. **G.J. Clowry:** None. **F.E.N. LeBeau:** None.

Poster

116. Oscillations and Synchrony: LFP and Unit Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 116.25

Title: WITHDRAWN

Poster

116. Oscillations and Synchrony: LFP and Unit Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 116.26

Topic: B.07. Network Interactions

Support: R01-NS101108
I01RX002705

Title: Changes in CA1 physiology following theta stimulation of the medial septum in sham and TBI rats

Authors: *C. ADAM[1], E. MIRZAKHALILI[2], A. D. ANDREWS[2], J. A. WOLF[2,3];
[1]Univ. of Pennsylvania Neurosci. Grad. Group, Philadelphia, PA; [2]Univ. of Pennsylvania, Philadelphia, PA; [3]Corporal Michael J. Crescenz VA Med. Ctr., Philadelphia, PA

Abstract: Cognitive deficits are often reported following traumatic brain injury (TBI) and occur when resulting pathologies disrupt neuronal circuits that normally support cognition. Learning and memory deficits are especially common following TBI, especially when the hippocampus or its afferent/efferent pathways are directly affected by injury. In the rat lateral fluid percussion injury (FPI) model of TBI, previous studies have reported that theta stimulation of the medial septum (MS) or fornix can rescue TBI-associated spatial learning deficits; however, the mechanisms underlying this restoration of function are not well understood. We recently discovered a layer-specific loss of oscillatory power and theta-gamma phase amplitude coupling in the hippocampal area CA1 in injured rats using the same FPI model. Additionally, we found disrupted sharp-wave ripple generation, changes in single unit entrainment to theta, and

remapping deficits in TBI rats that correlated with decreased spatial memory. In the present study, we are investigating whether these TBI-associated physiological deficits are rescued with theta stimulation. To this end, rats were subjected to an FPI (1.8atm) or sham injury and implanted with high-density, laminar electrodes bilaterally in CA1 and a stimulating electrode in the MS. Recordings were obtained 1-week post-injury while rats ran on a linear track both before and immediately after 1 minute of 80 or 800uA theta (7.7Hz) stimulation. In both injured and sham injured rats, we found that individual MS stimulation pulses elicit a transient (~80ms) gamma oscillation in CA1. The power of this stimulation-evoked gamma oscillation changes as a function of stimulation intensity and varies along the laminar profile of CA1. This suggests that stimulating at theta frequency can artificially create theta-gamma phase amplitude coupling which we previously showed to be drastically reduced in TBI rats. Preliminary results show that individual units can change their firing rate and bursting properties post-stimulation, and that place fields on the linear track can reorganize following theta stimulation. Additionally, we found that CA1 theta power on the linear track decreases in the post-stimulation session compared to the pre-stimulation session when the rat is moving, but not when the rat is still. These results suggest that effects of stimulation can have a lasting effect on the circuit which is important for potential future clinical translation of this therapy.

Disclosures: C. Adam: None. **E. Mirzakhalili:** None. **A.D. Andrews:** None. **J.A. Wolf:** None.

Poster

116. Oscillations and Synchrony: LFP and Unit Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 116.27

Topic: B.07. Network Interactions

Support: NIH Grant R01NS054281

Title: Fast spiking interneurons generate high frequency gamma oscillations in the medial entorhinal cortex

Authors: *B. D. WILLIAMS[1], F. R. FERNANDEZ[1], C. C. CANAVIER[2], J. A. WHITE[1]; [1]Dept. of Biomed. Engineering, Ctr. for Systems Neuroscience, Neurophotonics Ctr., Boston Univ., Boston, MA; [2]Cell Biol. and Anat., LSU Hlth. New Orleans, New Orleans, LA

Abstract: Many neurons in layer II of the medial entorhinal cortex (mEC) display spatially tuned firing rates that generate a grid-like (‘grid cells’) pattern when navigating an open field. A theta (4-12 Hz) frequency network-wide oscillation modulates the firing rates of these grid cells. Additionally, higher frequency gamma (40-140 Hz) oscillations are nested within the network theta oscillation and are hypothesized to increase the synchrony of grid cell firing (Hafting et al. 2008 Nature 453:1248-52; Reifenstein et al. 2012 PNAS 109:6301-6306). Two different (but not mutually exclusive) mechanisms have been proposed to generate gamma oscillations. In the pyramidal-interneuron network gamma (PING) model, pyramidal cells excite local interneurons

which provide inhibitory feedback. Alternatively, the interneuron network gamma (ING) model proposes that inhibition between interneurons can become synchronous. To investigate the mechanisms of theta-nested gamma oscillations, we used intracellular recordings in acute slices to measure excitatory and inhibitory post synaptic currents in stellate, pyramidal, and fast spiking cells during optogenetic stimulation of thy1 expressing neurons. No differences were observed in the gamma frequency, theta phase or maximum power of the inhibitory gamma oscillations among the main cell types in the mEC. Excitatory gamma oscillations were observed in fast spiking interneurons, but not excitatory cells, consistent with the low degree of recurrent excitatory connections (Fuchs et al. 2016 Neuron 89:194-208). Interestingly, inhibitory gamma oscillations remained after the pharmacological blockade of AMPA/kainate receptors, contrary to a similar study (Pastoll et al. 2013 Neuron 77:141-154), but consistent with local field potential recordings in mEC (Butler et al. 2018 Eur J Neurosci. 48:2795-2806). In support of the ING model, the specific activation of parvalbumin (PV) expressing interneurons generates fast inhibitory gamma oscillations in all cell types. The frequency of inhibitory oscillations driven by PV interneurons is faster than those driven by thy1 expressing neurons, consistent with a trend of increased gamma frequency under the blockade of excitatory inputs. These results suggest that a fast-firing inhibitory network is sufficient for generating high frequency gamma oscillations. Consequently, a combination of both PING and ING mechanisms likely contribute to generation of theta-nested gamma oscillations in the mEC.

Disclosures: B.D. Williams: None. **F.R. Fernandez:** None. **C.C. Canavier:** None. **J.A. White:** None.

Poster

116. Oscillations and Synchrony: LFP and Unit Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 116.28

Topic: B.07. Network Interactions

Support: Physician Scientist Award
Biological Bases of Drug Seeking Behavior Training Grant (NIDA T32-DA007262)

Title: A mechanistic role of the claustrum-prefrontal cortex circuit in attentional allocation

Authors: *R. J. OLSON[1], A. I. ABBAS[2,3];
[1]Behavioral Neurosci., Oregon Hlth. and Sci. Univesity, Portland, OR; [2]Behavioral Neurosci., Oregon Hlth. and Sci. Univ., Portland, OR; [3]Psychiatry, Portland VA Healthcare Syst., Portland, OR

Abstract: Although we are constantly bombarded by an overwhelming amount of information at any given time, attention allows us to filter and use this information to make decisions. Therefore, we must be able to flexibly engage and direct our attention to optimally interact with

our environment. Despite attentional processes being critical to survival, we still know relatively little on what the underlying neural mechanisms of attention are. While there is extensive literature that the prefrontal cortex (PFC) is implicated in the control of attention, recent anatomical, functional, and optogenetic perturbation experiments suggest that a small subcortical brain region known as the claustrum (CLA) may play a critical role in the neural mechanisms underlying attentional control as well. Here, we elucidate the underlying oscillatory and neural signatures of the CLA-PFC circuit in a novel attentional allocation task in freely behaving mice. Our task requires the mouse to continuously forage for reward in 5 front ports while intermittently attending to a pseudorandomly timed auditory cue signaling a large reward in a port opposite the 5 front ports. We hypothesized that the CLA-PFC circuit plays a critical role in disengaging the mouse from the forage behavior while simultaneously engaging the mouse to attend to the auditory cue. We find that using an intersectional viral approach, we can selectively optogenetically inhibit CLA projection neurons to the PFC causing the mouse to fail to attend to the auditory cue in our attentional allocation task. We also were able to electrophysiologically record simultaneously in the PFC and CLA during optogenetic perturbation allowing us to explore unique task-modulated oscillatory signatures between these regions during different sub-behaviors of our task, quantified by LFP-LFP, spike-LFP synchrony, and causal analyses. Taken together, these findings implicate a causal role in the CLA-PFC circuit in attentional allocation.

Disclosures: **R.J. Olson:** None. **A.I. Abbas:** None.

Poster

116. Oscillations and Synchrony: LFP and Unit Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 116.29

Topic: B.07. Network Interactions

Support: NIGMS Grant R01GM121457

Title: Imaging neuronal activity and system entropy under anesthesia and during emergence in C. elegans

Authors: *A. S. CHANG[1], C. W. CONNOR[2], C. V. GABEL[1];
[1]Physiol. and Biophysics, Boston Univ., Boston, MA; [2]Anesthesiol., Brigham and Women's Hosp., Boston, MA

Abstract: Volatile anesthetics are widely used in modern medicine and are essential to the practice of surgery. While the anesthetized state is characterized by a suite of behavioral and physiological responses, as well as by alterations in EEG patterns, these measures tell us little about the neuron or circuit-level physiological action of anesthetic agents. The advent of comprehensive multi-neuron functional imaging in the nematode worm C. elegans presents an opportunity to define, for the first time, the effects of volatile anesthetics on the dynamics and function of an entire nervous system with cellular resolution. The simple and tractable C. elegans

displays behavioral states paralleling anesthesia in mammals and has proven to be a powerful model system for discovery of molecular factors influencing anesthetic susceptibility. Employing light-sheet fluorescence microscopy, we measured activity of the majority of neurons in the C. elegans head during no, moderate and deep anesthesia as well as during emergence from anesthesia over a period of hours. Power spectral analysis of individual neuron activity reveals a significant elevation in high frequency dynamics in anesthetized animals as well as during the initial stages of emergence. To further our analysis, we have applied novel information theoretic metrics developed based on how entropy, or information content, is shared in the time-evolution of signals between neurons. We find that traditional entropy-derived metrics such as mutual information and transfer entropy do not strongly distinguish between the anesthetized and non-anesthetized states. By contrast, we identify novel entropy metrics that we term “state decoupling”, “internal predictability” and “system consistency”, that strongly differentiate the awake and anesthetized states. During emergence from anesthesia, these metrics resolve slowly over roughly two hours following removal from isoflurane. The slow resolution of these metrics contrasts strongly with the early resolution of high frequency activity immediately post-anesthesia, which suggests the existence of discrete phases of recovery based on the resolution of distinct neurophysiological processes.

Disclosures: **A.S. Chang:** None. **C.W. Connor:** None. **C.V. Gabel:** None.

Poster

116. Oscillations and Synchrony: LFP and Unit Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 116.30

Topic: B.07. Network Interactions

Support: WaNPRC Ignition Pilot Award

Title: Acetylcholine regulates hippocampal cellular resonance in primate

Authors: *A. GAMBRILL[1], C. MARSHALL[2], J. W. RUECKEMANN[3], A. BARRIA[2]; [1]Univ. of Washington, [2]Physiol. & Biophysics, [3]Physiol. and Biophysics, Univ. of Washington, Seattle, WA

Abstract: Cellular resonance is a phenomenon in which hippocampal neurons respond preferentially to specific frequencies of input. Resonance is a product of the membrane capacitance and voltage-gated cation channels present in the soma and dendrites and underlies the microcircuit phenomenon of theta oscillations observed in the local field potential of behaving animals. Because circuit-level manifestation of theta oscillations varies widely between rodents and primates, we tested whether the intrinsic cellular mechanisms which support resonance in rodent are also present in primate hippocampus. We used whole cell somatic recordings in non-human primate (NHP) hippocampal slices to inject a sinusoidal current of constant amplitude and varying frequency (Chirp). We found marked differences in the baseline

cellular resonance at peri-threshold recording potentials between rodent and NHP. Because of this discrepancy in the cellular resonance we investigated the contribution of known inductive elements HCN and M channels as well as the regulation of cellular resonance by acetylcholine (Ach). We found that Ach strongly modulated cellular resonance of NHP neurons We conclude that cellular resonance exhibits significantly different baseline peak frequency distribution in primate as compared to rodent, and that the sensitivity of primate resonance to extrinsic addition of acetylcholine agonists may in part explain the variable and intermittent nature of the theta oscillations seen in primate.

Disclosures: A. Gambrill: None. **C. Marshall:** None. **J.W. Rueckemann:** None. **A. Barria:** None.

Poster

117. Astrocyte-Neuron Interactions in Physiology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 117.01

Topic: B.09. Glial Mechanisms

Title: Multi-faceted spontaneous ATP release events in astrocytes

Authors: *Y. HATASHITA[1], Z. WU[2], Y. LI[2], T. INOUE[1];
[1]Dept. of Life Sci. and Med. Biosci., Waseda Univ., Tokyo, Japan; [2]Sch. of Life Sci., Peking Univ., Beijing, China

Abstract: Astrocytes, the most abundant glial cell type in the central nervous system, regulate synaptic activity by releasing gliotransmitters including glutamate, D-serine, and ATP, contrary to their classical role to support the neuron functions. Although spontaneous ATP release from astrocytes *in vitro* was reported, spontaneous ATP release in the brain tissue remains unclear. We investigated extracellular ATP dynamics using a genetically encoded extracellular ATP sensor, $GRAB_{ATP1.0}$ (G protein-coupled receptor activation-based ATP sensor), and detected tetrodotoxin-insensitive spontaneous ATP release events in neuron-glia co-culture. To further clarify the spontaneous ATP release activity in murine brain tissue, we sparsely expressed $GRAB_{ATP1.0}$ in cortical astrocytes by means of *in utero* electroporation and performed two-photon imaging. In anesthetized 1-2-month-old mice, transient ATP release events were observed within astrocyte territories. The localized ATP release events were also observed in acute slice, and were insensitive to tetrodotoxin. Additionally, fluorocitrate, an astrocyte-specific toxin, significantly suppressed the ATP release events, indicating that astrocytes release ATP independently of the surrounding neuron activity. We then employed a red fluorescent genetically encoded calcium sensor, Lck-REX-GECO1, to simultaneously monitor extracellular ATP and intracellular calcium activity in astrocytes. Dual-color two-photon imaging revealed that more than half of the spontaneous ATP release events did not accompany calcium transients. Besides, no correlation was found between the ATP release and calcium event timing, indicating that the major population of spontaneous ATP release events was calcium-independent. To

further elucidate the mechanisms, we classified the spontaneous ATP release events by their temporal waveforms using hierarchical clustering combined with pharmacological experiments. ATP release events in a minor group, which was characterized by slower rise time, were suppressed by a vesicular release inhibitor, bafilomycin A1, implying that the waveforms well reflected the kinetics of ATP release machinery and suggesting that the non-vesicular release may be the majority of the spontaneous ATP release. In conclusion, our findings suggest that astrocytes spontaneously release ATP in the brain tissue, as well as *in vitro*, via multiple mechanisms, many of which are calcium-independent and non-vesicular.

Disclosures: **Y. Hatashita:** None. **Z. Wu:** None. **Y. Li:** None. **T. Inoue:** None.

Poster

117. Astrocyte-Neuron Interactions in Physiology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 117.02

Topic: B.09. Glial Mechanisms

Support: CIHR Grant 165900

Title: Decreases of extracellular calcium elicit sustained firing in axons of primary afferents through Nav1.6 channels

Authors: ***F. GAUDEL**[1,2], J. GIRAUD[2], M. COUILLARD-LAROCQUE[2], D. VERDIER[1,2], A. KOLTA[1,2,3];
[1]Ctr. Interdisciplinaire de Recherche sur le Cerveau et l'Apprentissage (CIRCA), Montréal, QC, Canada; [2]Dept. of Neurosciences, Univ. de Montréal, Montréal, QC, Canada; [3]Dept. of Stomatology, Fac. of Dentistry, Univ. de Montréal, Montréal, QC, Canada

Abstract: Large- and small-caliber sensory afferents are classically and respectively associated with proprioception and nociception. Interestingly, the onset of neuropathic pain was associated with ectopic firing in large-caliber afferents; this firing always emerges from subthreshold membrane oscillations, which rely on a calcium-sensitive INaP current. We previously showed in a rat model of chronic pain that neurons of the trigeminal mesencephalic nucleus (NVMes), which contains the cell bodies of trigeminal periodontal and jaw-closing muscle spindle afferents, become hyperexcitable and generate ectopic firing. Astrocytes are known to participate in pain etiology, and another of our studies showed their ability to modulate INaP-mediated firing through the release of S100β, a small Ca^{2+}-chelating protein. We hypothesized that astrocytes could regulate ectopic firing in proprioceptive NVMes neurons by modulating the extracellular calcium concentration ($[Ca^{2+}]_e$) through S100β release. Here, we first aimed to locate the preferential subregion for inducing ectopic firing by NVMes neurons. We simulated local $[Ca^{2+}]_e$ decreases by micro-applications of the Ca^{2+} chelators BAPTA and S100β. Both triggered sustained firing of NVMes neurons when applied on the axonal initial segment (AIS), between 20-80 µm from the soma. We then studied the effect of the optogenetic activation of

astrocytes in GFAP-ChR2 mice. Activation of peri-somatic astrocytes induced neuronal depolarization in 19 cells and firing in 5 (total n=27 cells), while peri-axonal astrocytes activation triggered neuronal depolarization in 50 cells and sustained firing in 23 (total n=67 cells). Firing persisted when applying glutamatergic and GABAergic synaptic blockers but disappeared with the application of 4.9anhydro-TTX, a selective Nav1.6 blocker (n=2/2 cells), or of an anti-S100β antibody (n=6/9 cells). Together, our results point to local modulation of neuronal activity by the astrocytic release of S100β, which was induced physiologically by electrical stimulation of NVMes synaptic afferents. Future perspectives include investigating the electrical properties of NVMes neurons and behavioral studies in our newly developed chronic pain model in wild-type and S100β-knockout mice. This work may shed light on mechanisms involved in the onset and maintenance of chronic pain and create therapeutic avenues for treating such afflictions.

Disclosures: F. Gaudel: None. **J. Giraud:** None. **M. Couillard-Larocque:** None. **D. Verdier:** None. **A. Kolta:** None.

Poster

117. Astrocyte-Neuron Interactions in Physiology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 117.03

Topic: B.09. Glial Mechanisms

Support: CIHR
NSERC

Title: Astrocyte functional heterogeneity in the CA1 hippocampus

Authors: *D. CLARKE[1,2], A. BOSSON[1,2], E. AVIGNONE[3], J.-C. LACAILLE[1,2,4], R. ROBITAILLE[1,2,4];
[1]Dept. de Neurosciences, Univ. de Montréal, Montreal, QC, Canada; [2]Groupe de recherche sur la signalisation neurale et la circuitrie, Univ. de Montréal, Montréal, QC, Canada; [3]Interdisciplinary Inst. for Neurosciences, Univ. de Bordeaux, Bordeaux, France; [4]Ctr. Interdisciplinaire de Recherche sur le Cerveau et l'Apprentissage, Montréal, QC, Canada

Abstract: Recent gene expression studies highlight astrocyte heterogeneity between and within brain regions. However, astrocyte functional heterogeneity remains poorly understood. Here, we examine multiple physiological characteristics of astrocytes distinguished by their specific spatial relation to hippocampal CA1 pyramidal cell domains: astrocytes covering the perisomatic area in *stratum pyramidale* (SP), or the apical dendritic area in *stratum radiatum* (SR). Ca^{2+} imaging of SP and SR astrocytes in slices revealed differences in astrocyte spontaneous Ca^{2+} activity. SR astrocytes displayed greater frequency, duration, and synchronicity, but reduced amplitude, of Ca^{2+} events in comparison to SP astrocytes. Whole-cell recordings and confocal imaging showed a typical bushy organisation of SR astrocytes while SP astrocytes were more

polarized. SR astrocytes had a larger syncytium and lower membrane resistance relative to SP astrocytes. Finally, the specific astrocyte regulation of perisomatic and dendritic inhibitory synapses was investigated using optogenetic selective activation of inhibitory interneurons and a Gq-DREADD approach to activate astrocytes. The amplitude of optogenetically-evoked IPSCs in pyramidal neurons were reduced by DREADD-induced astrocyte activation by 42 ± 3% at dendritic inhibitory synapses from somatostatin interneurons and 39 ± 11% at perisomatic inhibitory synapses from parvalbumin interneurons. Importantly, this inhibition was prevented when astrocyte intracellular Ca^{2+} was chelated (BAPTA 20 mM) within, but not outside, the syncytium overlapping the respective inhibitory synapse territory. These results indicate a regulation of specific inhibitory synapses by distinct astrocyte syncytia for SP and SR astrocytes. Overall, our findings highlight a functional heterogeneity of astrocytes in the hippocampus.

Disclosures: D. Clarke: None. **A. Bosson:** None. **E. Avignone:** None. **J. Lacaille:** None. **R. Robitaille:** None.

Poster

117. Astrocyte-Neuron Interactions in Physiology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 117.04

Topic: B.09. Glial Mechanisms

Support: NIH R21 AG074293
NIH R01 NS104530

Title: Dentate Gyrus CCK interneurons modulate astrocyte phagocytosis of excitatory synapses

Authors: *D. S. TART, B. ARISCAN, J. SONG;
Pharmacol., Univ. of North Carolina Chapel Hill, Chapel Hill, NC

Abstract: Cholecystokinin (CCK) is an endogenous neuropeptide released from CCK interneurons in the dentate gyrus (DG). Our recent studies showed that DG astrocytes respond robustly to CCK interneuron activity, and become reactive when CCK is decreased, reminiscent of pathological states, such as in Alzheimer's Disease (AD). Importantly, astrocytes are known to play a critical role in activity-dependent elimination of excitatory synapses. How CCK signaling impacts the ability of astrocytes in eliminating excitatory synapses under physiological and pathological conditions, remains unknown. To address this, we utilized a combination of immunohistochemistry, confocal imaging, and Imaris analysis to elucidate the role of endogenous CCK signaling in modulating astrocyte phagocytosis of excitatory synapses in the DG. We injected Cre-dependent excitatory hM3Dq DREADDs into the DG of CCK-Cre mice to selectively stimulate CCK interneurons. Following chemogenetic stimulation, we analyzed astrocytic phagocytosis of glutamatergic terminals using our customized Imaris pipeline. Our analyses showed that hM3Dq stimulated mice had significantly more excitatory synapse colocalization with astrocytes than control mice, indicative of increased phagocytosis of

excitatory synapses. Next, we overexpressed CCK in the DG and showed a significantly higher percent of excitatory synapses colocalizing with astrocytes than control mice; further supporting that increasing CCK promotes synapse phagocytosis via astrocytes. Interestingly, AD mice exhibited decreased level of CCK but increased CCK interneuron activity during early disease stages, which correlates with impaired spatial memory. In addition, chemogenetic activation of DG CCK interneurons leads to impaired spatial memory. These results suggest that increased CCK interneuron activity may serve as a mechanism to compensate for decreased CCK during early AD, and impaired spatial memory may result from excessive engulfment of the excitatory synapses via a CCK-mediated astrocyte phagocytosis pathway in AD mice. Future experiments will be performed to determine the cognitive and therapeutic implications of regulating DG astrocytes through CCK interneurons in AD mice.

Disclosures: D.S. Tart: None. **B. Ariscan:** None. **J. Song:** None.

Poster

117. Astrocyte-Neuron Interactions in Physiology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 117.05

Topic: B.09. Glial Mechanisms

Support: KBRI Grant 22-BR-01-02

Title: The role of astrocytic synapse phagocytosis in the adult medial prefrontal cortex

Authors: *S. PARK[1,2], J.-Y. KIM[1], H. PARK[1];
[1]Korea Brain Res. Inst. (KBRI), Daegu, Korea, Republic of; [2]Dept. of Brain Sci., DGIST, Daegu, Korea, Republic of

Abstract: The medial prefrontal cortex (mPFC) mediates complex cognitive functions such as decision making, spatial working memory and long-term memory formation by communicating with other brain areas such as the amygdala, thalamus, and hippocampus. Our previous study showed that maintaining the proper synaptic connectivity is essential for normal memory formation in the adult hippocampus, and astrocyte-mediated synapse phagocytosis is involved in this process. Because astrocytic Megf10 and Mertk-dependent synapse phagocytosis has been also observed from the adult cortical areas, it is possible that astrocytic synapse phagocytosis is also involved in maintaining synapse numbers and regulates mPFC-dependent cognitive functions. To test whether mPFC synapse connectivity is dependent on astrocytic synapse phagocytosis, we injected AAV-hGFAP(0.7)-EGFP or AAV-hGFAP(0.7)-EGFP-2a-iCre virus into the mPFC of *Megf10*$^{fl/fl}$*;Mertk*$^{fl/fl}$mice and assessed synaptic properties of the mPFC. When spontaneous excitatory postsynaptic currents (sEPSCs) and inhibitory postsynaptic currents (sIPSCs) from the pyramidal neurons in the mPFC of control or astrocytic *Megf10;Mertk KO* mice were recorded, our results showed no significant changes in frequencies and amplitudes of sEPSCs and sIPSCs in astrocytic *Megf10;Mertk KO* mice compared to those in control mice.

These results suggest that astrocytic Megf10 and Mertk-dependent synapse phagocytosis did not affect functional excitatory or inhibitory synapses in the adult mPFC. Consistent with these results, our immunohistochemical analysis of synapse numbers showed that astrocytic *Megf10;Mertk KO* do not result in excessive synapse numbers. These results suggest that astrocytic phagocytosis-independent mechanisms are involved in synapse homeostasis in the adult mPFC. Finally, astrocytic *Megf10;Mertk KO* mice do not change in mPFC-dependent working memory formation compared to control mice. These results suggest that astrocytic synapse phagocytosis does not regulate mPFC-dependent working memory performance.

Disclosures: S. Park: None. **J. Kim:** None. **H. Park:** None.

Poster

117. Astrocyte-Neuron Interactions in Physiology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 117.06

Topic: B.09. Glial Mechanisms

Support: NSF Research Initiation Award (HRD 1401026)
NSF IOS Neural Systems Award (IOS 1755341)
NSF IOS Neural Systems Award (IOS1755033)

Title: Synaptobrevin (Vamp2) dominant negative prevents glutamate exocytosis by astrocytes

Authors: T. I. AMANFO[1], *V. A. TALABATTULA[1], M. T. MOORE[2], R. DZAKPASU[3], M. K. TEMBURNI[1];
[1]Delaware Ctr. for Neurosci. Res. and Dept. of Biol. Sci., [2]Delaware Inst. of Sci. and Technology, OSCAR Imaging Facility, Delaware State Univ., Dover, DE; [3]Dept. of Physics and Dept. of Pharmacol. and Physiol., Georgetown Univ., Washington, DC

Abstract: The goal of this project is to determine how astrocytes influence the development of synchronous neuronal network activity. We established pure neuron only and mixed (astrocyte and neuron) cultures grown on multielectrode arrays (MEAs) from the embryonic chick optic tectum and recorded network dynamics. Our preliminary results indicate that astrocytes are necessary for synchronous activity of neurons in culture. Mixed neuron and astrocyte cultures show random spiking activity which synchronizes over time whereas astrocyte-free neurons only show random activity and an absence of synchronization. Astrocytes have been shown to modulate network activity by releasing gliotransmitters like glutamate, D-serine and ATP. We hypothesize that glutamate sensing at tripartite synapses via mGluRs elevates local calcium within astrocyte processes. With sufficient activation, the localized calcium elevation crosses a threshold causing a calcium induced calcium release (CICR) within the astrocyte leading to glutamate exocytosis. We targeted the SNARE protein Synaptobrevin (Vamp2) within astrocytes as crucial for communication with neurons via exocytotic release of glutamate. We proposed to test this model by expressing a truncated Vamp2 subunit (Vamp2 DN) which acts as a dominant

negative to block exocytotic release. Astrocytes expressing the Vamp2 DN are expected to release significantly less glutamate upon calcium elevation thereby reducing synchrony of neuronal activity. We have generated primary astrocyte lines expressing the synaptobrevin dominant negative (Vamp2 DN) along with the glutamate sensor iGluSnFR. We demonstrate that Vamp2 DN expressing astrocytes have significantly reduced glutamate exocytosis when CICR is induced with Ionomycin. We will co-culture the Vamp2 DN astrocytes with neurons and record network activity on MEAs (Multi Channel Systems). With these tools a more comprehensive molecular model for astrocyte involvement in the generation of neuronal synchrony can be developed.

Disclosures: T.I. Amanfo: None. **V.A. Talabattula:** None. **M.T. Moore:** None. **R. Dzakpasu:** None. **M.K. Temburni:** None.

Poster

117. Astrocyte-Neuron Interactions in Physiology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 117.07

Topic: B.09. Glial Mechanisms

Support: NIH F32NS120940
ALSA 20-PDF-510
NIH R01NS113565

Title: Norrin modulates neuronal network communication and synaptic biology via a cortical astrocyte subgroup signaling pathway

Authors: *E. G. THOMPSON[1], E. R. KENT[2], B. G. VIJAYAKUMAR[2], J. D. ROTHSTEIN[3]; [1]Johns Hopkins Med. Institutions, Baltimore, MD; [3]Brain Sci. Inst., [2]Johns Hopkins Univ., Baltimore, MD

Abstract: Astrocytes are the most abundant cell type in the central nervous system (CNS) and are essential for brain function. As such, astrocytes play critical roles in ionic and glutamate balance, providing metabolic support to neurons, and regulating neuronal communication. In recent years there has been a newfound appreciation for the heterogeneity of astrocytic functions within sub-regions of the brain and the emergence of astrocyte subtypes. Our group recently identified one such subpopulation of astrocytes in the cerebral cortex that can be distinguished by heightened expression of cystine-knot like growth factor Norrin. While Norrin has previously been studied as a protein critical for vascular development in the retina and a driver of the rare neurodevelopmental genetic disorder Norrie Disease (ND), characterization of Norrin's effects within the cerebral cortex has been limited in breadth. Here we found Norrin to be selectively expressed in astrocytes within layers II, III, and V of the cortex and critical for synaptic maintenance in adulthood. Specifically, Norrin-null (Ndp-/-) animals had a significant decrease in synaptic length and density, that accompanied behavioral deficits. *In vitro* experiments

demonstrated that Norrin significantly increased firing frequency and neuron connectivity in primary cortical neuron cultures with multi-electrode array (MEA) analysis. Upon *in vitro and in vivo* investigation, we found Norrin to have a modulatory effect on the expression of various synaptic components. Finally, utilizing a humanized-mouse model of ND we evaluated Norrin influence in key synaptogenic processes across the lifespan. Initial characterization of these mice has revealed synaptic structure abnormalities at key developmental timepoints and behavioral deficits that recapitulate the human disease. Collectively, these findings suggest that astrocyte-derived Norrin plays a significant modulatory and functional role within the neuronal network of the cerebral cortex.

Disclosures: E.G. Thompson: None. **E.R. Kent:** None. **B.G. Vijayakumar:** None. **J.D. Rothstein:** None.

Poster

117. Astrocyte-Neuron Interactions in Physiology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 117.08

Topic: B.09. Glial Mechanisms

Support: FAPESP GRANT 2018/07027-5

Title: Contribution of Astrocytes from Supraoptic Nucleus to Osmoregulation

Authors: *M. P. DA SILVA[1], K. S. MAGALHÃES[2], D. P. SOUZA[2], D. J. MORAES[3]; [1]Paulista Sch. of Medicine, Federal Univ. of São Paulo,, São Paulo, Brazil; [2]Fac. of Med. of Ribeirão Preto, Univ. of São Paulo, Ribeirão Preto, Brazil; [3]Physiol., Sch. of Med. of Ribeirao Preto, USP., Ribeirao Preto, Brazil

Abstract: The supraoptic nucleus (SON) represents one of several hypothalamic areas involved in the body fluid balance. Since neurons that constitute this nucleus are intrinsically osmosensitive, they have been designated as a perfect model to study osmoreception. In the last years, experimental evidence has suggested that SON astrocytes could trigger the osmoregulatory process and may be involved in the control of magnocellular neuron excitability. However, little is known about how astrocytes initiate these responses and, if so, how they trigger specialized cellular behaviors related to osmoregulation. Here we aimed to investigate the mechanisms involved in the intrinsic osmosensitive of SON astrocytes by combining single and double whole-cell patch-clamp recordings and sulforhodamine 101 staining of astrocytes from juvenile mice. We observed that hypertonic stimulation induced a depolarization of resting membrane potential (-89 ± 0.5 mV vs -87 ± 0.6 mV, n = 14; $p < 0.005$) and an increase in the membrane conductance of astrocytes (0.02 ± 0.21 nS *vs* 0.95 ± 0.29 nS). Membrane depolarization was not blocked by furosemide, amiloride, tetrodotoxin, or ruthenium red. Double patch recordings (neuron and astrocyte) revealed that the depolarization of the resting membrane potential of astrocytes induced by acute hypertonic stimulation precedes the increase in the

activity of magnocellular SON neurons (60 ± 10 sec vs 131± 19 sec; n = 6 pars, $p<0.006$), suggesting that astrocytes could initiate osmoregulatory processes in this nucleus. We conclude that astrocytes from SON respond to hypertonic stimulation and seem to play a role in osmoregulation.

Disclosures: M.P. da Silva: None. **K.S. Magalhães:** None. **D.P. Souza:** None. **D.J. Moraes:** None.

Poster

117. Astrocyte-Neuron Interactions in Physiology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 117.09

Topic: B.09. Glial Mechanisms

Support: NIH R21NS116316
Baruchowitz Family Fellowship for Dysautonomia Research

Title: Investigating the activity-dependent plasticity of the peripheral sympathetic system

Authors: *J. HARRISON, J. WANG, M. HABURCAK, S. J. BIRREN;
Brandeis Univ., Boston, MA

Abstract: Neurons within the sympathetic ganglia directly innervate peripheral organs and contribute to their normal physiological function. Sympathetic neuronal activity is induced by the firing of preganglionic spinal cord neurons and can be modified by local satellite glial cells (SGCs). Diseases, including diabetes, hypertension and several dysautonomias are driven by a chronic increase in neuronal activity, however, the mechanisms that maintain activity within a homeostatic range and prevent pathological patterns of neuronal activity remain elusive. We investigated the activity-dependent regulation of sympathetic neuronal activity, and the role of SGCs, in isolated neonatal sympathetic neurons from the Wistar Kyoto (WKY) rat cultured with or without SGCs. We chronically increased neuronal activity by expressing an excitatory Designer Receptor Exclusively Activated by Designer Drugs (DREADDs) in sympathetic neurons and quantified the change in cholinergic synapses using immunocytochemistry. Chronic activation of neurons cultured alone increased colocalization of pre- and postsynaptic markers. In contrast, this increase was not present when neurons were cocultured with SGCs, suggesting a role for SGCs in homeostatic regulation. These data also suggest that sympathetic neurons grown alone display a feed-forward synaptic strengthening in response to increased neuronal activity. We therefore asked if there was evidence for elevated synaptic properties in neurons cultured from the spontaneously hypertensive rat (SHR), a model in which increased sympathetic drive precedes the onset of hypertension. Our data from whole cell recordings and immunocytochemistry shows that SHR neurons cultured alone have increased synaptic charge and synapse formation compared to WKY neurons. Overall, our data demonstrate an intrinsic activity-dependent potentiation of sympathetic neurons that may be enhanced in hypertension-

prone rats. An important outstanding question is whether the homeostatic role of the SGCs is maintained in prehypertensive rats and how the dynamics of the system change as the animal develops high blood pressure. We are addressing this by quantifying synaptic sites in the sympathetic ganglia during the development of hypertension in the SHR. Future work will focus on understanding glial-dependent mechanisms of peripheral neural plasticity in hopes of identifying new targets for treating diseases characterized by autonomic dysfunction.

Disclosures: **J. Harrison:** None. **J. Wang:** None. **M. Haburcak:** None. **S.J. Birren:** None.

Poster

117. Astrocyte-Neuron Interactions in Physiology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 117.10

Topic: B.09. Glial Mechanisms

Support: 5 T32 GM 7752-42
NIH R01AG065541
Coins for Alzheimer's Research Trust Fund
Sarah Roger's First Year Fellowship, UCSD BMS

Title: Transcriptomic assessment of brain-derived extracellular vesicles (EVs) identifies cell-type specific packaging of intact mRNAs

Authors: *L. RANSOM[1,2], C. S. LIU[1,2], J. CHUN[2];
[1]Biomed. Sci., Univ. of California San Diego, La Jolla, CA; [2]Sanford Burnham Prebys Med. Discovery Inst., La Jolla, CA

Abstract: Cells throughout the body, including the brain, release extracellular vesicles (EVs) called exosomes that contain nucleic acids and proteins and are thought to be a means of intercellular communication. Within the brain, exosomes are known to be released upon neuronal depolarization or in response to inflammatory stimuli and can be transmitted among neurons and glia. We hypothesized that neural cells communicate intercellularly through the exchange of mRNAs transported in EVs. Exosome enriched populations of EVs were prepared from human postmortem brain tissue (from IRB approved sources) and primary murine neural cell cultures using published protocols and validated by Western blot, nanoparticle tracking analysis, and electron microscopy. Parallel preparations were processed for RNA-seq using both short-read and long-read (PacBio) sequencing technologies, followed by appropriate bioinformatics analyses. Thousands of mRNAs including those with novel sequences were identified. EV-packaged mRNAs tended to be specific for brain cell type of origin, along with a shared core set of transcripts relating to translation, oxidative phosphorylation, and mRNA splicing enriched in all EV samples relative to their whole-cell transcriptome of origin. Further informatic analyses combined with select functional studies of EV mRNAs will be presented.

Disclosures: **L. Ransom:** None. **C.S. Liu:** None. **J. Chun:** None.

Poster

117. Astrocyte-Neuron Interactions in Physiology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 117.11

Topic: B.09. Glial Mechanisms

Support: Texas A&M University startup funds

Title: Gsk3β As mediator of astrocyte-regulated synapse formation

Authors: *I. FARHY-TSELNICKER, M. GRAY, G. ALBRECHT, J. ROBERTS;
Texas A&M Univ. - Site 2, College Station, TX

Abstract: Synapse dysfunctions lie at the heart of many brain disorders for which there are limited or no existing treatments, including autism, and Alzheimer's disease. During glutamatergic synapse development, maintaining a balance between active (AMPA receptor containing) and silent (AMPA receptor lacking) synapses is crucially important step, whereupon silent synapses are converted to active, or eliminated. Aberrant silent synapse development has been implicated in neurodevelopmental disorders and drug addiction, while decreased synapse number and activity is prevalent in aging and neurodegeneration. Astrocytes produce factors that modulate both active and silent synapse formation, yet the intracellular neuronal pathways are not well defined. Our previous work identified members of the neuronal LAR family receptor protein tyrosine phosphatases (LAR-RPTPs) as necessary for active and silent synapse formation mediated by astrocyte-secreted proteins glypican 4 (Gpc4) and thrombospondin 1 (TSP1) respectively. To identify the cellular pathways downstream of LAR-RPTPs-Gpc4 and TSP1 interactions we utilized a phosphoproteomic strategy and analyzed changes in protein phosphorylation in neurons treated with Gpc4. This yielded glycogen synthase kinase 3β (GSK3β) as candidate to mediate active synapse pathway. GSK3β canonical mechanism of action, and the one most commonly targeted with drugs, is its inhibition through serine phosphorylation (pS9). Our proteomic and immunofluorescence data show GSK3β activation through increased tyrosine phosphorylation (pY216) in neurons treated with Gpc4, while GSK3β pY216 signal is decreased in brain sections from Gpc4 KO mice. These findings suggest that active synapse formation requires activated GSK3β. Moreover, previous studies show that LAR-RPTPσ (which we show to be required for silent synapse formation) can inhibit GSK3β, suggesting that downstream of Gpc4/ TSP1 interactions with LAR-RPTPs, GSK3β functions as a molecular switch, promoting silent or active synapses. Dissecting how GSK3β activity affects active/ silent synapses, and subsequent circuit function and animal behavior, is a major focus of ongoing work in the lab. This work will lead to a profound understanding of GSK3β activity at the synapse, and identification of cellular pathways leading to specific synapse types, laying the groundwork for future therapeutic studies.

Disclosures: I. Farhy-Tselnicker: None. **M. Gray:** None. **G. Albrecht:** None. **J. Roberts:** None.

Poster

117. Astrocyte-Neuron Interactions in Physiology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 117.12

Topic: B.09. Glial Mechanisms

Support: NSF NeuroNex 1 (1707356) award
NSF NeuroNex 2 (2014862) award

Title: Perisynaptic astroglia enhance synaptic information storage capacity (SISC) in the Dentate Gyrus

Authors: *A. J. NAM[1], M. SAMAVAT[2], M. KUWAJIMA[3], J. M. MENDENHALL[3], V. THIYAGARAJAN[3], D. D. HUBBARD[3], D. C. HANKA[3], P. H. PARKER[3], T. M. BARTOL, Jr.[4], U. MANOR[5], T. J. SEJNOWSKI[6], W. C. ABRAHAM[7], K. M. HARRIS[3];
[1]Inst. For Neurosci., Univ. of Texas At Austin, Austin, TX; [2]CNL-S, The Salk Inst., La Jolla, CA; [3]Ctr. for Learning & Memory, Univ. of Texas at Austin, Austin, TX; [4]CNL-S, Salk Inst., La Jolla, CA; [5]Waitt Advanced Biophotonics Ctr., Salk Inst. for Biol. Studies, La Jolla, CA; [6]Computat. Neurobio. Lab., Salk Inst. for Biol. Sci., La Jolla, CA; [7]Dept. of Psychology, Univ. of Otago, Dunedin, New Zealand

Abstract: Astrocytes are active modifiers of signal transmission at the tripartite synapse, and thus are key actors participating in information processing in the brain. In particular, the thin, irregularly shaped perisynaptic astroglial processes (PAPs) that interdigitate the dense neuropil of dendrites and axons are responsible for exerting significant influence on synapse structure and function. Both *in vivo* and *in vitro* experiments demonstrate that PAPs undergo activity-dependent structural changes that could affect the extent of their synaptic influence. Thus, it is important to explore how processes like long-term potentiation (LTP) and long-term depression (LTD), which are widely accepted cellular mechanisms of learning and memory, alter PAP structure. Delta-burst stimulation in the medial perforant pathway was used to induce LTP *in vivo* in the middle molecular layer (MML) of the awake adult rat hippocampal dentate gyrus. In addition, this stimulation protocol simultaneously produced concurrent long-term depression (cLTD) in the neighboring outer molecular layer (OML). Meanwhile, only baseline stimulation was applied to the medial perforant path of the contralateral control hemisphere. Work in progress based on three-dimensional reconstruction from serial section electron microscopy (3DEM) shows expanded information content at potentiated hippocampal dentate gyrus synapses at 30 minutes and 2 hours following this induction of LTP *in vivo*. Information theory was applied to extract distinguishable functional units (categories) of synapse sizes based on dendritic spine head volume. We then explored the role of PAPs on the SISC of selected synapses. More than 80% of all dentate gyrus synapses exhibited some degree of PAP apposition at the axon-spine interface (ASI). Furthermore, preliminary results suggest that the PAP profile differs between discrete synaptic information storage categories. These findings facilitate understanding about the role of PAPs in influencing information storage capacity at synapses.

Disclosures: **A.J. Nam:** None. **M. Samavat:** None. **M. Kuwajima:** None. **J.M. Mendenhall:** None. **V. Thiyagarajan:** None. **D.D. Hubbard:** None. **D.C. Hanka:** None. **P.H. Parker:** None. **T.M. Bartol:** None. **U. Manor:** None. **T.J. Sejnowski:** None. **W.C. Abraham:** None. **K.M. Harris:** None.

Poster

117. Astrocyte-Neuron Interactions in Physiology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 117.13

Topic: B.09. Glial Mechanisms

Support: RRAG/300

Title: Human induced pluripotent stem cell-derived neuron-astrocyte-microglia tri-culture model shows differential effect of astrocytes and microglia on functional activity of glutamatergic neurons

Authors: *A. PAUL[1], K. BARANES[1], A. ZAKIROV[1], E. METZAKOPIAN[2,3,1], M. KOTTER[1]; [1]Clin. Neurosciences, Univ. of Cambridge, Cambridge, United Kingdom; [2]Natl. Inst. For Med. Res., London, United Kingdom; [3]UK Dementia Res. Inst., Cambridge, United Kingdom

Abstract: Background: Neuron-glia dynamics play a critical role in central nervous system homeostasis through synapse formation, pruning and interactions with neurotransmitters and cytokines. The existing murine models of neuron-astrocyte-microglia triple co-cultures are not ideally suited for recapitulating human physiology in health and disease. Therefore, we have generated a scalable 2D tri-culture system as a model to investigate neurodevelopment and neural pathophysiology. **Objectives:** The aim of this study is to use cellular reprogramming to generate pure homogenous populations of neurons, astrocytes and microglia; and sequentially seed each cell type on multi-electrode arrays as co-cultures to investigate functional neurophysiological activity and neuron-glia interactions. **Methods:** Glutamatergic neurons, astrocytes and microglia were generated from control wildtype iPSC line by optimised inducible overexpression of defined transcription factors (Opti-Ox): NGN2; NFIB and SOX9; SPI1 and CEBPA respectively. Neurons were replated on day 3 with astrocytes (1:0.5 ratio), microglia (1:0.2 ratio) and both (1:0.5:0.2 ratio) in all possible co-culture combinations along with neuron, astrocyte or microglia alone as controls. Electrophysiological recordings from all six *in vitro* culture conditions were obtained using Axion Maestro Pro multi-electrode arrays (N=8 replicates). Weekly recordings were carried out from day 7 onwards. Raw data was processed and analysed using Axion Neural Module platform. **Results:** iPSC derived glutamatergic neurons exhibited significant increase in mean firing rate (MFR) from day 14 to day 21 in pure cultures. Astrocytes and microglia did not show activity (MFR < 0.0005 Hz) when cultured alone. However, when co-cultured with astrocytes, glutamatergic neurons showed 19% increase in firing rates on day 21. In contrast, neurons exhibited a 13% decrease in activity when co-cultured with microglia. MFR increased by 24% from day 14 to day 21 in neuron-astrocyte-

microglia tri-culture which was 10 times lower than that in neuron-astrocyte culture proving negative feedback mechanism of microglia on hyperactive neural networks. **Conclusions:** Astrocytes provide support and increase functional maturity of glutamatergic neural networks. In contrast, microglia dampens heightened neural activity, thereby protecting cortical networks from runaway excitation. Thus, iPSC derived neuron-astrocyte-microglia tri-culture network characterisation shows differential and synergistic effect of astrocytes and microglia in synaptic homeostatic regulation and can be adopted as a novel tool to study human neurophysiology.

Disclosures: **A. Paul:** None. **K. Baranes:** None. **A. Zakirov:** None. **E. Metzakopian:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Bit.Bio Ltd. **M. Kotter:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Bit.Bio Ltd.

Poster

117. Astrocyte-Neuron Interactions in Physiology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 117.14

Topic: B.09. Glial Mechanisms

Support: NIH Grant F31 AG067632-01
T32 GM007445
R01NS046336
High-End Instrumentation grant S10OD021844
Daniel Nathans Innovative Scholar Award

Title: An astrocyte-specific release mechanism generates a subpopulation of extracellular vesicles that regulate postsynaptic function

Authors: *D. DAUDELIN, R. LEVY-MYERS, S. SOCKANATHAN;
Neurosci., Johns Hopkins Univ., Baltimore, MD

Abstract: Neuron-glia communication is critical for proper brain function. Astrocytes in particular are known to regulate aspects of neuronal health, synaptic function, and disease progression, and extracellular vesicles (EVs) comprise one pathway that astrocytes communicate with neurons. EVs are small vesicles released by cells that contain protein and nucleic acid cargo, that can exert large effects on recipient cells. Here we identify a new pathway in astrocytes that releases a subpopulation of EVs important for postsynaptic function. GDE3 (Glycerophosphodiester Phosphodiesterase 3 or GDPD2) is a 6-transmembrane protein expressed on the plasma membrane of astrocytes but not neurons. Whole cell patch-clamp recording experiments on CA1 hippocampal neurons prepared from P12-15 WT and *Gde3*KO mice revealed a significant reduction in the amplitude of miniature excitatory postsynaptic currents (mEPSCs) in *Gde3*KO animals compared with WT ($n \geq 19$ cells, $n \geq 6$ mice per

genotype) but no change in frequency. This *Gde3*KO amplitude deficit was rescued when mGluR1/5 antagonists were applied, suggesting a potential postsynaptic mechanism through which astrocytic GDE3 regulates synaptic function. Experiments and analysis were carried out blind to genotype and treatment, and no sex specific differences were found. Experiments in HEK293T cells and primary cultured astrocytes demonstrate that GDE3 is necessary and sufficient to release a molecularly distinct subclass of EVs from the plasma membrane of astrocytes. We thus hypothesized that GDE3 promotes the release of specialized EVs from astrocytes that are necessary for proper neuronal function. Strikingly, EVs isolated from the medium of cultured WT astrocytes rescued the amplitude deficit in *Gde3*KO cells, while EVs purified from *Gde3*KO astrocytes had no effect. These observations suggest that GDE3 constitutes an astrocyte-specific release mechanism for subsets of EVs required for postsynaptic activity, suggesting that designated release pathways for EV subpopulations underlie modes of astrocyte-neuron communication important for neural circuit function.

Disclosures: D. Daudelin: None. **R. Levy-Myers:** None. **S. Sockanathan:** None.

Poster

117. Astrocyte-Neuron Interactions in Physiology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 117.15

Topic: B.09. Glial Mechanisms

Support: NIH Grant R21NS108508
NIH Grant R01NS121542

Title: Dopaminergic activity mediated by cerebellar astrocytes impacts Purkinje cells and cerebellum-related motor and social behavior

Authors: *C. LI, N. B. SALIBA, H. MARTIN, N. LOSURDO, K. KOLAHDOUZAN, R. SIDDIQUI, W. LI;
Neurobio., Univ. of Alabama at Birmingham, Birmingham, AL

Abstract: Dopamine is a classical neurotransmitter that has been extensively studied in the midbrain. However, the relevance of the cerebellar dopaminergic system is largely undiscovered. Here, we show that Bergmann glial cells, the major cerebellar astrocyte type, express D1 receptors. Dopamine can be synthesized inside the Purkinje cells by cytochrome P450 and released in an activity-dependent manner. We demonstrate that activation of D1 receptors induces membrane depolarization and Ca2+ rise in Bergmann glial cells. These astrocytic activities in turn modify Purkinje cell output by altering both excitatory and inhibitory synaptic input. Lastly, we show that conditional knockout of D1 receptors in Bergmann glial cells results in decreased locomotor activity and impaired social activity. These results demonstrate the molecular, cellular, and circuit mechanisms underlying dopamine actions in the cerebellum, revealing a critical role for the cerebellar dopaminergic system in motor and social behavior.

Disclosures: **C. Li:** None. **N.B. Saliba:** None. **H. Martin:** None. **N. Losurdo:** None. **K. Kolahdouzan:** None. **R. Siddiqui:** None. **W. Li:** None.

Poster

117. Astrocyte-Neuron Interactions in Physiology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 117.16

Topic: B.09. Glial Mechanisms

Support: 1R01NS036692-01A1
1R01CA227149-01A1

Title: Perineuronal nets regulate structural plasticity and homeostatic functions of cortical astrocytes

Authors: ***B. P. TEWARI**[1], A. M. WOO[1], C. PRIM[1], L. CHAUNSALI[1], I. KIMBROUGH[1], K. ENGEL[2], J. BROWNING[2], S. L. CAMPBELL[3], H. SONTHEIMER[1];
[1]Neurosci., Univ. of Virginia, Charlottesville, VA; [2]Sch. of Neurosci., [3]Animal and Poultry Sci. / Sch. of Neurosci., Virginia Tech., Blacksburg, VA

Abstract: Perineuronal nets (PNNs) are highly condensed extracellular matrix structures mainly composed of hyaluronic acid, chondroitin sulfate proteoglycans, tenascins, and link proteins. Developmental formation of PNN ends the critical period of heightened neuronal plasticity in several brain regions. The high density of negatively charged proteoglycans confers PNNs the ability to influence neuronal firing properties as well as diffusion and homeostasis of ions in the extracellular space. Since PNNs form a lattice-like coat on soma, axon initial segment, and dendrites of GABAergic parvalbumin (PV) neurons sparing only lattice holes, we hypothesized that PNN holes are the primary sites for physicochemical interaction of PV neurons with synapses and astrocytic processes. Our immunohistochemical analysis revealed that PNN holes contain all components of a typical synapse including astrocytic processes with differential expression of homeostatic proteins. Our results also suggest that the presence of PNN constrains pericellular astrocytic coverage and enzymatic or genetic deletion of PNN alters the glial coverage of PV neurons. We further hypothesized that to overcome this spatial constraint, PNN holes act as charged conduits to direct synaptic activity-released glutamate and depolarization-released K+ ions towards astrocytic processes and aid their homeostatic functions. Our whole-cell path-clamp and glutamate imaging studies suggest that astrocytic uptake of K+ and glutamate are negatively impacted upon PNN depletion supporting the hypothesis of PNN holes acting as charged conduits to aid astrocytic functions. In conclusion, our results suggest a novel astrocyte-PNN physicochemical interaction that creates a pericellular microenvironment around PV neurons to support astrocytic homeostatic functions.

Disclosures: **B.P. Tewari:** None. **A.M. Woo:** None. **C. Prim:** None. **L. Chaunsali:** None. **I. Kimbrough:** None. **K. Engel:** None. **J. Browning:** None. **S.L. Campbell:** None. **H. Sontheimer:** None.

Poster

117. Astrocyte-Neuron Interactions in Physiology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 117.17

Topic: B.09. Glial Mechanisms

Support: NIH Grant R01NS107315-04

Title: Astrocytic monocarboxylate transporters 1 and 4 (MCT1/4) sustain orexinergic activity and sleep/wake cycle through lactate-shuttling

Authors: *M. CHIACCHIARETTA[1], A. BRAGA[1], L. PELLERIN[2], P. HAYDON[1]; [1]TUFTS Univ. Sch. of Med., Boston, MA; [2]Inserm U1313, Univ. and CHU of Poitiers, Poitiers, France

Abstract: While major progress revealed a fundamental role for astrocytes in sleep/wake cycle control, mechanisms underlying this regulation in different neuronal circuits remain unclear. The astrocyte-neuron lactate shuttle (ANLS) hypothesis postulates that astrocytes are capable of shuttling L-lactate to sustain the energetic demand of active neurons. A rise in lactate during wakefulness has been reported in cortex, however the implication of the ANLS in controlling sleep/wake architecture remains to be fully established. In a previous work, we have shown that astrocytic connexin 43 (Cx43) provided a metabolic network required in the lateral hypothalamus (LH) for lactate trafficking: impairment of this pathway silenced the wake-promoting orexinergic neurons and led to excessive daytime sleepiness. To further determine whether the ANLS was required for orexinergic neuron-mediated metabolic regulation and for sustaining wakefulness, in this study we evaluated the role of astrocytic monocarboxylate transporters 1 and 4 (MCT1/4) as the pathway for lactate release in LH and how each transporter affected orexinergic neurons excitability and sleep/wake behavior. By using novel transgenic mice, we deleted MCT1/4 in an astrocytic-specific manner in the LH. We found that decreased expression of MCT1/4 caused excessive sleepiness during the nocturnal active phase and fragmented wakefulness through sleep/wake cycle, driven by a decreased lactate surges during wakefulness. Moreover, we showed that this specific genetic manipulation decreased the activity of orexin neurons in LH by impairing lactate trafficking. As a matter of fact, *ex vivo* and *in vivo* exogenous lactate delivery was able to rescue orexinergic tonic firing and to restore normal sleep/wake cycle in MCT1/4 KO mice. Our findings provide both *in vivo* and *ex vivo* evidence that astrocytic MCTs, by shuttling lactate to orexin neurons, are critical for maintaining sleep/wake architecture. In this context, our results also support a key role for a tight coupled astrocytic-neuronal metabolism.

Disclosures: **M. Chiacchiaretta:** None. **A. Braga:** None. **L. Pellerin:** None. **P. Haydon:** None.

Poster

117. Astrocyte-Neuron Interactions in Physiology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 117.18

Topic: B.09. Glial Mechanisms

Support: NSF Research Initiation Award (HRD 1401026)
NSF IOS Neural Systems Award (IOS 1755341)
NSF IOS Neural Systems Award (IOS 1755033)

Title: Role of the astrocytic mGluR pathway in the development of neuronal synchrony

Authors: V. A. N. TALABATTULA[1], M. T. MOORE[2], R. DZAKPASU[3], *M. K. TEMBURNI[1];
[1]Delaware Ctr. for Neurosci. Res. and Dept. of Biol. Sci., [2]Delaware Inst. of Sci. and Technology, OSCAR Imaging Facility, Delaware State Univ., Dover, DE; [3]Dept. of Physics and Dept. of Pharmacol. and Physiol., Georgetown Univ., Washington, DC

Abstract: Synchronous oscillations are necessary for establishing functional neuronal networks in normal vertebrate brain development - however, the mechanisms of neuronal synchronization are not fully understood. Existing models of synchronous activity assume that it is intrinsic to neurons. Astrocytes have been shown to modulate oscillatory activity in networks of neurons possibly by releasing gliotransmitters like glutamate and ATP. We have established pure and mixed (astrocyte and neuronal) cultures from the developing chicken brain (optic tectum) and recorded neuronal network activity using three different the multi-electrode array systems, MED64, Axion and Multichannel Systems. Our preliminary results indicate that astrocytes are necessary for synchronous activity of neurons in culture. To further dissect the molecular pathways involved, we targeted the metabotropic glutamate receptor (mGluR) pathway within astrocytes as a mechanism by which astrocytes influence synchronous firing. Astrocytes express mGluRs that consist of the same subunits and stoichiometry as those expressed in neurons. To test this model, we expressed the calcium sensor GCaMP6F to assay Ca^{++}activity and a truncated mGluR subunit (mGluR DN) which acts as a dominant negative by blocking downstream signaling of the mGluR1 pathway using the lentiviral vector pUltrahot in primary chick astrocytes. Preliminary results show that astrocytes expressing the mGluR DN have reduced calcium elevation upon mGluR stimulation.
Lastly, we will take a pharmacological approach and add the mGluR1 antagonist, A841720, to neuron-astrocyte co-cultures and pure neuronal cultures. Synchronous activity will be recorded using the MCS MEA system and network activity parameters such as synchrony index (SI), spike amplitude and spike rates will be determined. We expect that the mGluR1 antagonist treated cultures will have a reduced Synchrony Index.

Disclosures: **V.A.N. Talabattula:** None. **M.T. Moore:** None. **R. Dzakpasu:** None. **M.K. Temburni:** None.

Poster

117. Astrocyte-Neuron Interactions in Physiology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 117.19

Topic: B.09. Glial Mechanisms

Support: RO1NS116059
R56097672

Title: Astrocyte syncytial isopotentiality shapes neuronal excitability and synaptic transmission in hippocampus

Authors: *Y. DU, S. ATEN, B. MA, C. KIYOSHI, L. TRANK, D. MEDIRATTA, E. G. CAMACHO, A. GUIHER, W. SUN, M. ZHOU;
the Ohio State Univ., Ohio State Univ., Columbus, OH

Abstract: Gap junctional coupling is known to confer an isopotentiality to astrocyte networks across the brain. However, the impact of syncytial isopotentiality on neuronal circuit function remains unknown. To answer this question, we explored intracellular Ca^{2+} ($[Ca^{2+}]_i$) as a potential regulator of astrocyte syncytial isopotentiality. In dual patch recorded pairs of freshly dissociated astrocytes, we found that a moderate elevation of Ca^{2+} enhances gap junction coupling, while an excessive elevation of Ca^{2+} inhibits gap junction coupling, indicating that intracellular Ca^{2+} ($[Ca^{2+}]_i$) is able to bidirectionally regulate syncytial coupling strength. We next sought to confirm this observation through the mobilization of $[Ca^{2+}]_i$ in transgenic mice with astrocytic expression of Gq-coupled receptors. In mice with astrocytic expression of Gq-MrgA1, both potentiation and inhibition of gap junctional coupling could be induced by FMRF, an agonist for MrgA1 receptor. Notably, these effects were correlated with the strengthening and weakening of syncytial isopotentiality detected by whole-cell astrocyte recording with K^+-free/Na^+-containing electrode solution ($[Na^+]_p$), a method recently developed in our laboratory (Ma et al., 2016 Glia). The same effects could be fully recapitulated in the second transgenic mouse line with the astrocytic expression of Gq-DREADD. Finally, in astrocytic Gq-DREADD expressing mice, we show that at the concentrations of clozapine/CNO that induce the closure of astrocyte syncytial coupling, there is the following reduction of neuronal excitability and CA3-CA1 synaptic transmission. Thus, astrocyte syncytial isopotentiality is a critical glial mechanism to sustain the basal neuronal circuit function.

Disclosures: **Y. Du:** None. **S. Aten:** None. **B. Ma:** None. **C. Kiyoshi:** None. **L. Trank:** None. **D. Mediratta:** None. **E.G. Camacho:** None. **A. Guiher:** None. **W. Sun:** None. **M. Zhou:** None.

Poster

117. Astrocyte-Neuron Interactions in Physiology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 117.20

Topic: B.09. Glial Mechanisms

Support: Fukuoka University Fund 217302
KAKENHI Grant 20H04506
Science Research Promotion Fund G19001
Fukuoka University Fund G20001
AMED 15ek0109038h0002 and 16ek0109038h0003
KAKENHI Grant 15H02548
KAKENHI Grant 20H03651, 20H03443, and 20H04506

Title: The establishment of a novel autaptic culture system equipped with human-induced pluripotent stem cell-derived astrocytes

Authors: *K. UCHINO[1], Y. TANAKA[4,5,2], S. KAWAGUCHI[1], K. KUBOTA[1], T. WATANABE[1], S. KATSURABAYASHI[1,2], S. HIROSE[2,3], K. IWASAKI[1];
[1]Dept. of Neuropharm., [2]Res. Inst. for the Mol. Pathogeneses of Epilepsy, [3]Gen. Med. Res. Ctr., Fukuoka Univ., Fukuoka, Japan; [4]Dept. of Advanced Pharmacol., Daiichi Univ. of Pharm., Fukuoka, Japan; [5]iONtarget, Co., Inc., Fukuoka, Japan

Abstract: Brain cells are composed of neurons and glial cells. Astrocyte is a glial cell involved in synaptic transmission and the formation and maturation of synapses; thus, they are a constitutive element of the tripartite synapse. The establishment of induced pluripotent stem cells (iPSCs) allows the differentiation of stem cells into various types of cells. Technological advances have provided access to human astrocytes through the induction of iPSCs, and the mRNA profiles, protein expressions, and morphology of iPSC-derived astrocytes (HiAs) have been reported. Furthermore, neurons co-cultured with HiA have been used to study their morphology, synaptic gene expression, protein levels, and spontaneous synaptic responses. However, these studies did not investigate detailed synaptic functions such as synaptic transmission evoked by electrical stimulation and morphological analysis at the single neuron level. In this study, we established a novel autaptic culture with HiAs (HiAs Autaptic Cultures, HiAACs), single neuron cultures grown in isolation on microislands of HiAs that form synapses exclusively with themselves. We evaluated the effect of neural functions co-cultured with HiAs. We found that neurons in HiAACs develop morphologically by co-culture with HiAs and form functional synapses that exhibit excitatory postsynaptic currents. Furthermore, HiAACs mature 2 to 4 weeks after culture and can still be used after 6 weeks in vitro. This methodology could be used to analyze the number of synapses and morphology of single neurons co-cultured with HiAs, and to record evoked synaptic transmission. The methodology presented here should facilitate the study of tripartite synapses, focusing on human astrocytes in the future.

Disclosures: **K. Uchino:** None. **Y. Tanaka:** None. **S. Kawaguchi:** None. **K. Kubota:** None. **T. Watanabe:** None. **S. Katsurabayashi:** None. **S. Hirose:** None. **K. Iwasaki:** None.

Poster

117. Astrocyte-Neuron Interactions in Physiology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 117.21

Topic: B.09. Glial Mechanisms

Title: Application of a novel in silico/ex vivo pipeline to study the effects of vesicular and non-vesicular astrocytic glutamate release on fast, excitatory neurotransmission

Authors: *C. CHEN, I. A. SAVTCHOUK;
Marquette Univ., Milwaukee, WI

Abstract: Title: A novel *in silico*/*ex vivo* pipeline to predict the effects of vesicular and non-vesicular astrocytic glutamate release on fast, excitatory neurotransmission
Authors: ***C.W Chen**[1], I.A. Savtchouk[1]1 Biomedical Sciences, Marquette University, Milwaukee, WI
Glutamate is a key signaling molecule in the brain whose dysregulation is common to pathologies like dementia and drug addiction. Computational (in silico) approaches modeling glutamate diffusion and interactions have the potential to contextualize the experimental observations and have already described key aspects of glutamate behavior. However, their predictive utility has been limited due to lack of precise data on: 1) Extracellular membrane morphology; 2) Transporter and receptor expression profiles; and 3) Glutamate-specific kinetic interactions. Here, we exploited the availability of open-source 3D electron microscopy reconstructions, advances in computer hardware, and growing body of accurate kinetic models for glutamate receptors and transporters to help resolve some of these limitations. Our model consisted of EM reconstruction data of nearly 300 μm^3 of somatocortical space combined with glutamate, receptor, and transporter interactions that were modeled from previously-published kinetic schemes. The workflow consisted of using a Python-based environment to systematically set up simulations, vary parameters, launch simulations in a batch fashion,and analyze simulation readouts on glutamate's location, timecourse and interactions with transporters and receptors. Specifically, we used this model to probe functional effects of glutamate released from astrocytes on synaptic and extrasynaptic glutamate receptor activity using experimental parameters derived from several prior reports of experimentally-observed glutamate gliotransmission. Our data suggest that slow,tonic (non-vesicular) release of glutamate from astrocytes results in elevated steady-state extracellular glutamate concentrations as well as elevated tonic conductance of both synaptic and extrasynaptic NMDARs. Conversely, faster, phasic (vesicular) release of glutamate from astrocytes prior to synaptic glutamate release "primes" receptors, resulting in higher overall conductance during theta-burst synaptic glutamate release from neurons. Future questions include how specific LTP and LTD stimulation patterns and brain region-specific transporter and receptor expression profiles may recruit different receptor subtypes in both computer and live tissue models.
Disclosures: **C.W. Chen,** None; **I. Savtchouk,** None
Keyword(s): PLASTICITY; GLUTAMATE; ASTROCYTES; mouse

Disclosures: **C. Chen:** None. **I.A. Savtchouk:** None.

Poster

117. Astrocyte-Neuron Interactions in Physiology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 117.22

Topic: B.09. Glial Mechanisms

Support: NINDS Grant 5R01NS102306-05
NINDS Diversity Supplement 3R01NS102306-04S1.

Title: Neuron-astrocyte interactions underlying noradrenergic modulation of wake-promoting ventral periaqueductal gray dopamine neurons

Authors: *N. PETERSEN[1,2], S. W. CENTANNI[1,2], G. J. SALIMANDO[1,2], K. E. MCCANN[3], M. A. STAVARACHE[4], D. WEINSHENKER[3], D. G. WINDER[1,2];
[1]Mol. Physiol. and Biophysics, Vanderbilt Univ. Sch. of Med., Nashville, TN; [2]Vanderbilt Ctr. for Addiction Res., Nashville, TN; [3]Human Genet., Emory Univ. Sch. of Med., Atlanta, GA; [4]Neurosurg., Weill Cornell Med., New York, NY

Abstract: Sleep and arousal disorders are exceedingly common; however, the basic underlying physiology governing wakefulness is not fully understood. Previous work has implicated a small population of dopamine (DA) neurons in the ventral periaqueductal gray ($vPAG^{DA}$ neurons) in regulating wakefulness. Activation of these neurons increases wakefulness, while lesioning or inactivating these neurons decreases wakefulness. Recently, we delineated a novel arousal circuit from the locus coeruleus to the $vPAG^{DA}$ neurons. Specific activation of G_q-coupled alpha$_1$-adrenergic receptors (α_1ARs) with phenylephrine increases excitatory drive onto $vPAG^{DA}$ neurons and promotes wakefulness. α_1AR expression is enriched on vPAG astrocytes, and activation of astrocytic G_q signaling is sufficient to promote wakefulness. However, the mechanism underlying this neuron-astrocyte communication is unknown. Astrocytes are known to release extracellular "gliotransmitters" including the purines ATP and adenosine. Here we utilized viral and transgenic mouse approaches with *ex vivo* calcium imaging and behavioral experiments to probe our hypothesis that astrocytic α_1ARs mediate noradrenergic modulation of wake-promoting $vPAG^{DA}$ neurons via purinergic transmission. Activation of α_1AR with phenylephrine increased calcium transients in $vPAG^{DA}$ neurons expressing the calcium indicator GCaMP8s. Phenylephrine also increased calcium in GCaMP8s-expressing astrocytes in the vPAG. Additionally, this increase in astrocyte calcium activity persisted in the presence of tetrodotoxin, suggesting a more direct effect of α_1AR activation on astrocytes. Chemogenetic G_q activation in astrocytes increased calcium transients in $vPAG^{DA}$ neurons, suggesting astrocytic modulation of these cells. Utilizing an shRNA strategy, we found that knockdown α_1AR expression in vPAG astrocytes blunted the ability of phenylephrine to increase $vPAG^{DA}$ neuronal activity without altering spontaneous activity. Animals with decreased vPAG astrocytic α_1AR gene expression also exhibited increased sleep time during the dark phase, further suggesting the

role of vPAG astrocytic α_1ARs in modulating vPAG^{DA} neuron physiology and normal sleep-wake behavior. Furthermore, our pharmacological studies suggest that α_1AR activation of vPAG^{DA} neurons is mediated, at least in part, by the adenosine A_{2A} receptor, and that A_{2A} activation is sufficient to increase vPAG^{DA} neuron activity. Together, these data suggest that noradrenergic modulation of vPAG astrocytes may play an important role in mediating wakefulness via regulation of wake-promoting vPAG^{DA} neuron activity through adenosine gliotransmission.

Disclosures: **N. Petersen:** None. **S.W. Centanni:** None. **G.J. Salimando:** None. **K.E. McCann:** None. **M.A. Stavarache:** None. **D. Weinshenker:** None. **D.G. Winder:** None.

Poster

117. Astrocyte-Neuron Interactions in Physiology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 117.23

Topic: B.09. Glial Mechanisms

Support: Fondo de desarrollo cientifico de jalisco -7964
Infraestructura UDG 2022

Title: Stress-induced c-fos expression in the medial prefrontal cortex differentially affects the main residing cell phenotypes

Authors: *A. AGUILAR DELGADILLO, F. CRUZ-MENDOZA, S. LUQUIN, D. FERNANDEZ-QUEZADA, Y. RUVALCABA-DELGADILLO, F. JÁUREGUI-HUERTA; Neurociencias, Univ. De Guadalajara, Guadalajara, Mexico

Abstract: Stress involves a challenge to homeostasis that activates a set of reactions that allow the organism to respond to the stressful stimuli in the most adapted possible way. Under acute stress, regions such as the prefrontal cortex use to change its physiological parammeters to face the stimuli that implies cellular activation commitment. c-fos is a proto-oncogene whose c-Fos protein has been frequently used to study the effects of exogenous factors on the central nervous system (CNS). Nonetheless, c-fos expression changes has been attributed to neurons, growing evidence sustains that c-fos expression may also include glial cells. Here, we investigated if this proto-oncogene may also be expressed by glial cells under stress conditions. Four male wistar rats were exposed to acute stress and sacrificed two hours after the stimulus started. Double labeling fluorescent immunocytochemistry against c-Fos with GFAP, Iba-1, Olig2, Ng2 and Neun was performed on 35 μm slices belonging to the prefrontal cortex. We demonstrated that besides neurons, astrocytes, oligodendrocytes, microglia and NG2 cells also express this immediate early gene (IEG). Moreover, our experiments also evidenced that stress differentially regulates this expression across the medial prefrontal cortex subregions. This evidence supports the view of c-fos as an activity marker and urges to introduce the glial cell perspective into the brain activity studies.

Disclosures: **A. Aguilar Delgadillo:** None. **F. Cruz-Mendoza:** None. **S. Luquin:** None. **D. Fernandez-Quezada:** None. **Y. Ruvalcaba-Delgadillo:** None. **F. Jáuregui-Huerta:** None.

Poster

117. Astrocyte-Neuron Interactions in Physiology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 117.24

Topic: B.09. Glial Mechanisms

Support: U.S. Army NETRP Grant W81XWH18-00443
National Parkinson's Foundation

Title: Astrocytic regulation of dopamine neurotransmission in the basal ganglia through lactate shuttling

Authors: *D. PHILLIPS[1], A. J. LUNDQUIST[1,3], S. KISHI[2], G. M. PETZINGER[1], M. W. JAKOWEC[1];
[1]Neurol., [2]USC, Los Angeles, CA; [3]BioAge Lab. Inc., Richmond, CA

Abstract: Astrocytes are specialized glial cells in the central nervous system that regulates neurotransmitter homeostasis and provide metabolic support to neurons. During periods of increased neuronal activity and glutamate levels, astrocytes upregulate glycolytic processes to meet energy demands through the astrocyte-neuron lactate shuttle (ANLS). Neurons and astrocytes are metabolically coupled such that, in the presence of cellular oxygen, astrocytes generate high levels of lactate through aerobic glycolysis and shuttle this energetic metabolite to neurons through the monocarboxylate transporter 4 (MCT4). Though astrocytic modulation of neurotransmitters such as glutamate is well established, less is known about the impact of astrocytes on the regulation of dopamine (DA). We previously reported the disruption of lactate transport in the mouse motor cortex through stereotaxic injection of inducible Cre-lox recombination using a lentivirus containing Cre- dependent short-hairpin RNA (shRNA) to knockdown MCT4 (Lundquist et al., 2021). Using this approach to induce MCT4 knockdown in the dorsal striatum, we performed immunohistochemistry, western blots, high-performance liquid chromatography, and mouse behavior test to investigate DA levels and proteins involved in DA production, packaging, and clearance (tyrosine hydroxylase (TH), vesicular monoamine transporter 2, (VMAT2), and dopamine transporter (DAT), respectively). Knockdown of MCT4 increased TH and VMAT2, with no changes to DAT. Mouse rotational behavior was measured with the administration of amphetamines, which significantly increased rotations in MCT4 knockdown compared to control, overall suggesting increased presynaptic dopamine production. We further investigated lactate shuttling disruption with an injured, dopamine depletion model using the dopaminergic neurotoxin, 1-methyl-4- phenyl-1,2,3,6-tetrahydropyridine (MPTP). Following unilateral stereotaxic injection to induce MCT4 knockdown, an acute dose of the MPTP was administered. Interestingly, mouse rotational behavior was inversed with the administration of amphetamines. Utilizing HPLC, we found that there was no significant

difference in DA levels between the two hemispheres. In conclusion, astrocytes can modulate dopamine neurotransmission through lactate metabolism by increasing the levels of presynaptic dopamine, though these effects may vary between normal healthy striatum and a lesioned striatum. These results highlight therapeutic modalities to target astrocytic lactate shuttle for modulating neurotransmission.

Disclosures: D. Phillips: None. **A.J. Lundquist:** None. **S. Kishi:** None. **G.M. Petzinger:** None. **M.W. Jakowec:** None.

Poster

118. Models of Alzheimer's Disease I

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 118.01

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

Support: HU20C0233
NRF-2019M3E5D2A01058328
NRF-2021M3E5D2A01019544

Title: Impairment of Prefrontal Neuronal Synchrony during Memory Retrieval in the 5XFAD Mouse Model of Alzheimer's Disease

Authors: *Y. YEO, J. KWAG;
Dept. of Brain and Cognitive Engin., Korea Univ., Seoul, Korea, Republic of

Abstract: Alzheimer's disease (AD) is a neurodegenerative disease characterized by progressive decline in memory consolidation and retrieval. The prefrontal cortex (PFC) has been suggested to be involved in the consolidation of long-term memory as well as its retrieval. However, how memory consolidation and retrieval are represented in ensembles of PFC neurons and how they are impaired in AD to cause memory impairments is poorly understood. To address this question, we injected AAV-CaMKII-GCaMP6s into the prelimbic (PL) region of PFC and, using a miniaturized microscope, we performed *in vivo* Ca^{2+} imaging in ensembles of GCaMP-expressing excitatory neurons in PFC before (habituation) and after contextual fear conditioning (CFC) in both the control and a 5XFAD mouse model of AD. Memory retrieval was tested on day (D)1, D7, and D14 after CFC to test recent (D1) and remote (D7, D14) memory retrieval. By analyzing pair-wise Pearson's correlation coefficient of normalized Ca^{2+} signal between each of 185 neurons recorded in the control mice (n = 3 mice), we found that the synchronized activity of excitatory neurons significantly increased from D1, D7 to D14. However, from 63 neurons recorded in the 5XFAD mouse, such increase of synchronized activity was impaired and the level of synchronized activity across D1, D7, and D14 were similar. Together, these results indicate that synchronization of ensemble activities in PFC could serve as a neural correlate of remote contextual fear memory retrieval, and impairment of such synchronized ensemble activity could cause deficits in remote memory retrieval in the 5XFAD mouse model of AD.

Disclosures: **Y. Yeo:** None. **J. Kwag:** None.

Poster

118. Models of Alzheimer's Disease I

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 118.02

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

Support: HI19C0646
HU20C0233
2019M3E5D2A01058328
NRF-2021M3E5D2A01019544

Title: Encoding of contextual fear memory in retrosplenial cortical parvalbumin interneurons is impaired in the 5XFAD mouse model of Alzheimer's disease

Authors: *K. PARK, J. KWAG;
Dept. of Brain and Cognitive Engin., Korea Univ., Seoul, Korea, Republic of

Abstract: Alzheimer's disease (AD) is characterized by abnormal accumulations of amyloid beta (Aβ) which cause synaptic dysfunctions in both excitatory and inhibitory neurons, consequently leading to memory impairment. It has been reported that the retrosplenial cortex (RSC) is one of the earliest brain regions affected by Aβ pathology in AD. Especially, RSC is known to play critical roles in memory consolidation by serving as a gateway between hippocampus and prefrontal cortex, the neural circuits for memory consolidation. However, how RSC excitatory and inhibitory neurons are affected by amyloidosis in AD to cause memory deficits is yet unknown. In order to address this question, using miniaturized microscope, we performed *in vivo* Ca^{2+} imaging from GCaMP-expressing excitatory (EX) neurons and parvalbumin-expressing (PV) interneurons before, during, and after contextual fear conditioning (CFC) in the control and 5XFAD/PV-Cre mice model of AD. In the control mice that showed increased freezing responses during contextual fear memory recall, RSC EX neurons and PV interneurons that were responsive to electric foot shocks during CFC (shock-responsive) displayed reduced and enhanced ensemble activities, respectively, compared to those during habituation (shock-responsive EX neurons in control mice: 85 %, 233 out of 275 cells; shock-responsive PV interneurons in control mice: 69%, 46 out of 67 cells). However, in AD mice that showed contextual fear memory deficits, shock responsive EX neurons and PV interneurons displayed no change in ensemble activities before and after CFC (shock-responsive EX neurons in 5XFAD mice: 87%, 294 out of 338 cells; shock-responsive PV interneurons in 5XFAD/PV-Cre mice: 24%, 13 out of 55 cells). These results suggest that ensemble activities of PV might serve important function in regulating CFC-induced EX neuron ensembles. To test this hypothesis, we performed *in vitro* whole-cell patch-clamp recordings *post hoc* CFC. CFC potentiated PV-to-EX synapses in the control mice, while no such change was observed in 5XFAD/PV-Cre mice. Optogenetic activation of RSC PV interneurons during CFC could fully

restore the contextual fear memory deficits in 5XFAD/PV-Cre mice, indicating that synaptic dysfunctions at PV-to-EX synapse may underlie the contextual fear memory deficits in 5XFAD/PV-Cre mice. Together, our results demonstrate that RSC PV interneuron ensembles encode contextual fear memory and dysfunctions of PV interneurons may lead to memory deficits in 5XFAD mouse model of Alzheimer's disease.

Disclosures: K. Park: None. **J. Kwag:** None.

Poster

118. Models of Alzheimer's Disease I

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 118.03

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

Support: HU20C0233
NRF-2019M3E5D2A01058328
NRF-2021M3E5D2A01019544

Title: Layer-specific synaptic dysfunctions of prefrontal somatostatin interneurons in the 5XFAD mouse model of Alzheimer's disease

Authors: *E. LEE, J. KWAG;
Korea Univ., seoul, Korea, Republic of

Abstract: Alzheimer's disease (AD) is a neurodegenerative disease characterized by synaptic dysfunctions in memory circuits caused by abnormal accumulations of amyloid beta (Aβ), which leads to a progressive decline in memory. In the prelimbic area (PL) of the prefrontal cortex, somatostatin-positive (SST) interneurons have been reported to encode long-term memory. However, there is a poor understanding of how SST interneurons are affected by Aβ in AD and how their impairments may be related to memory deficits in AD. To address these questions, we injected AAV-CaMKII-mCherry and AAV-EF1a-DIO-hChR2-EYFP viruses into the PL region of SST-Cre mice or 5XFAD/SST-Cre mice, a model of AD. Using these mice, we performed *in vitro* voltage-clamp recordings from mCherry-expressing excitatory neuron (EX) in acute brain slices to measure optogenetically activated ChR2-expressing SST interneuron-evoked inhibitory postsynaptic current (IPSC) in EXs to characterize changes in paired-pulse ratio (PPR) and short-term plasticity at SST-to-EX synapses in PL layer (L) 2/3 and L5/6 *post hoc* contextual fear conditioning (CFC) in the control mice (SST-Cre) and 5XFAD/SST-Cre mice. In L2/3 of the control mice, paired-pulse depression (PPD) of IPSCs at SST-to-EX synapses in naïve mice without CFC converted to paired-pulse facilitation (PPF) after CFC. Also, short-term depression (STD) of IPSCs at SST-to-EX synapses was significantly decreased in mice that underwent CFC. These results indicate that layer-specific synaptic weakening at PL L2/3 SST-to-EX synapse in PL might play an important role in contextual fear memory consolidation. However, in 5XFAD/SST-Cre mice, such changes in PPF and short-term potentiation (STP) were abolished

and only PPD and STD of IPSCs at SST-to-EX synapses were observed. In L5/6, unlike L2/3, no significant changes in PPD or STD of IPSCs at SST-to-EX synapses were observed in neither control nor 5XFAD/SST-Cre mice after CFC, suggesting that synaptic dysfunctions of SST-to-EX synapse may contribute to long-term memory impairment in AD. Together, these results show that layer-specific synaptic dysfunctions at SST-EX synapses may underlie memory deficits in AD, presenting SST interneurons as potential therapeutic targets for AD in the future.

Disclosures: E. Lee: None. **J. Kwag:** None.

Poster

118. Models of Alzheimer's Disease I

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 118.04

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

Support: NIH grant R56AG072473
The Emory Alzheimer's Disease Research Center Grant 00100569

Title: Vulnerability of cortical PV interneuron neurotransmission after short-term adult-onset hAPP expression

Authors: *A. M. GOETTEMOELLER, M. J. M. ROWAN;
Emory Univ. Sch. of Med., Atlanta, GA

Abstract: Alzheimer's Disease (AD) is a neurodegenerative cascade resulting in neuronal dysfunction and memory loss, yet there remains no effective preventative treatment. AD research has historically focused on treating late-stage plaque-and-tangle pathology, however recent research suggests amelioration of plaques may not prevent cognitive decline. Increasing evidence in AD patients and mouse models has reported cortical hyperexcitability prior to plaque pathology, likely related to synaptic loss at later stages of the disease. Nonetheless, cell and molecular mechanisms underlying hyperexcitability in early-stage AD remain unclear. In healthy brains, hyperexcitability is prevented in part by inhibition from GABAergic interneurons. Recent work from our group and others has shown vulnerability in distinct interneuron subtypes, including fast-spiking parvalbumin interneurons (PV), in mouse models of familial AD. These mice generally exhibit mutations in the amyloid precursor protein (hAPP) related to early-onset AD, which only represents a small proportion of human AD cases. Interestingly, recent studies have found that expression of the late-onset genetic AD risk factor APOE4 leads to increased neuronal expression of 'wild type' (WT) hAPP. The physiological consequences of adult-onset WT hAPP expression changes are unknown. Here, we analyze the potential effects of WT hAPP expression on PV interneurons using an adult-onset, viral expression approach. AAV-mediated hAPP expression in PV cells was confirmed using flow cytometry. Using patch-clamp electrophysiology, we examined intrinsic firing properties of cortical PV interneurons and neighboring pyramidal cells (PC) and assessed PV-to-PC inhibitory neurotransmission using

optogenetics. Furthermore, we stimulated neurons of the ventral posteromedial nucleus (VPM) using optogenetics and observed post-synaptic responses in PC neurons in the barrel cortex following cortical hAPP expression. Notably, we observed increased synaptic depression from PV-to-PC after short-term expression of WT hAPP, without changes to either PV or PC intrinsic properties. Our results indicate even a short-term increase in expression of WT hAPP may result in a specific vulnerability of PV neurotransmission. This examination of PV vulnerability may provide insights into underlying mechanisms of early-phase cortical hyperexcitability observed in mouse models and AD patients, thus providing a potential point for early-disease intervention.

Disclosures: A.M. Goettemoeller: None. **M.J.M. Rowan:** None.

Poster

118. Models of Alzheimer's Disease I

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 118.05

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

Support: DFG
SFB 1089

Title: The role of inputs from hippocampus and entorhinal cortex to the prefrontal cortex in spatial memory impairments in a mouse model of Alzheimer´s disease

Authors: *E. CIFTCI[1], E. AMBRAD GIOVANNETTI[3], M. MITTAG[4], F. FUHRMANN[5], M. FUHRMANN[6], S. POLL[2];
[2]Cell. Neuropathology and Cognition, [1]DZNE, Bonn, Germany; [3]Neuroimmunology and imaging group, German Ctr. For Neurodegenerative Dis., Bonn, Germany; [4]Neuroimmunology and Imaging, DZNE German Ctr. For Neurodegenerative Dis., Bonn, Germany; [5]Deutsches Zentrum Fur Neurodegenerative Erkrankung, Bonn, Germany; [6]Neuroimmunology & Imaging, German Ctr. for Neurodegenerative Dis. (DZNE), Bonn, Bonn, Germany

Abstract: Alzheimer’s disease (AD) is characterized by memory deficits including spatial working memory. The hippocampus (HPC), the entorhinal Cortex (EC) and the prefrontal cortex (PFC), damaged by AD pathology, are relevant brain regions for spatial working memory. Though supporting distinct functions in memory processing, the HPC and the PFC are highly connected and operate in synergy to consolidate and retrieve memories. Specifically, the PFC is involved in the top-down control of memory processing. Furthermore, both excitatory and long-range inhibitory projections between the HPC, EC and the PFC have been poorly characterized in disease-like conditions. In fact, it remains unknown whether structural and functional connectivity deficits between these brain areas are causally linked to spatial working memory deficits under AD-like conditions.Here, we investigated the structural connectivity between these brain regions in APP/PS1 transgenic mice, a widely used animal model for AD-like conditions. For this purpose, we used a cell type-specific Cre-driver mouse line to target somatostatin (SST)-

positive interneurons by AAV-mediated Cre-dependent fluorophore expression to conduct anterograde and retrograde tracings. So far, our data show the accumulation of amyloid β (Aβ) plaques in the PFC and amyloid pathology-associated structural alterations of hippocampal axonal projections in the PFC. In particular, we observed a novel SST-positive axonal projection originating in the ventral HPC and targeting the PFC that displayed axonal loss in APP/PS1 mice. These results indicate that structural connectivity impairments between HPC and PFC in a mouse model of AD-like pathology might underlie spatial working memory deficits.Moreover, it is of our major interest to further investigate the functional connectivity between these brain regions that are affected by amyloid pathology, to shed light on the mechanism that leads to spatial working memory impairment under AD-like conditions.

Disclosures: E. Ciftci: None. **E. Ambrad Giovannetti:** None. **M. Mittag:** None. **F. Fuhrmann:** None. **M. Fuhrmann:** None. **S. Poll:** None.

Poster

118. Models of Alzheimer's Disease I

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 118.06

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

Support: NIH Grant AG062776
NIH Grant AG047313
NIH Grant AG062234
NIH Grant AG064926
Alzheimer's Association Grant IIRG-13-284779
NIH Grant NS097976
NIH Grant AG062629

Title: Altered parvalbumin cell dynamics during gamma oscillatory activity in mouse models of Alzheimer’s disease

Authors: *K. MA[1,2,3], M. MERLINI[1], Y. QIU[1], C. HO[1], K. SHEN[1], K. AKASSOGLOU[1,3,4], J. J. PALOP[1,3];
[1]Gladstone Inst. of Neurolog. Dis., San Francisco, CA; [2]Dept. of Neurobio. of Anatomy, McGovern Med. Sch., Univ. of Texas Hlth. Sci. Ctr. at Houston, Houston, TX; [3]Dept. of Neurol., Univ. of California San Francisco, San Francisco, CA; [4]Ctr. for Neurovascular Brain Immunol., Gladstone Inst. and Univ. of California San Francisco, San Francisco, CA

Abstract: Alzheimer’s disease (AD) causes neuronal network disturbances that are associated with cognitive impairment including aberrant oscillations and network hypersynchrony that results in seizures. Parvalbumin (PV) inhibitory interneurons play a critical role in coordinating neuronal networks that support normal brain function, but the dynamics of PV-cell activity during spontaneous gamma oscillations in wildtype mice and mouse models of AD remain

unknown. We sought to investigate functional deficits in PV interneurons underlying altered gamma oscillations, theta-gamma coupling and network hypersynchrony in J20 and APP/PS1 mouse models of AD. Using simultaneous two-photon calcium imaging of PV interneurons and subdural EEG recordings in head-fixed mice running on a treadmill, we identified sequential activation of PV cells with decreasing calcium GCaMP6f signal over time during locomotor activity-induced gamma oscillation in wildtype mice. The PV/GCaMP6f signal amplitude and the synchronization of PV cells were disrupted in AD mice, resulting in reduced corresponding gamma oscillatory power. Impaired PV-cell calcium dynamics were normalized by enhancing PV cell function with Nav1.1-BAC expression, which also restored theta-gamma coupling, network hypersynchrony, and AD-associated transcriptomic changes. We conclude altered PV dynamics contribute to AD-related pathogenesis.

Disclosures: K. Ma: None. **M. Merlini:** None. **Y. Qiu:** None. **C. Ho:** None. **K. Shen:** None. **K. Akassoglou:** None. **J.J. Palop:** None.

Poster

118. Models of Alzheimer's Disease I

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 118.07

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

Support: NIH Grant NS089456

Title: Link between compartmentalized synaptic loss and defects in hippocampal place cell function in an AD mouse model

Authors: *D. M. VIRGA[1,2], J. K. O'HARE[2], A. LOSONCZY[1,2,3], F. POLLEUX[1,2,3];
[1]Dept. of Neurosci., Columbia Univ., New York, NY; [2]Zuckerman Mind Brain Behavior Inst., New York, NY; [3]Kavli Inst. for Brain Sci., New York, NY

Abstract: Synaptic connectivity is essential for proper circuit function as it underlies complex cognitive processes such as learning, planning, and decision making. In aging brains, failure to maintain connectivity within a circuit is the pathological consequence of many neurodegenerative diseases, such as Alzheimer’s disease (AD). During the early stages of AD progression, both in AD mouse models and in AD patients, soluble Amyloid $\beta_{1\text{-}42}$ oligomers ($A\beta_{42}o$) trigger loss of excitatory synapses in the hippocampus first, prior to plaque accumulation. Surprisingly little is understood about whether and how synaptotoxicity in AD causally affects hippocampal circuit function. Our lab recently demonstrated that $A\beta_{42}o$ triggers synaptic loss through over-activation of the CAMKK2-AMPK kinase dyad. By using a combination of in utero electroporation based genetic manipulation and *in vivo* two-photon calcium (Ca^{2+}) imaging of neuronal activity during spatial navigation, we were able to test whether synaptic loss in pyramidal neurons (PNs) of the hippocampal area CA1 triggers deficits in spatial encoding properties in early and late stages of disease progression. In an AD mouse

model (J20), we found a significant decrease in transient Ca^{2+} frequency, duration, and amplitude in CA1 PNs at early and late stages of the disease, as well as spatial encoding deficits in the late stages. By preventing synaptic loss through sparse, cell-autonomous, double-conditional deletion of AMPKα1/α2 in CA1 PNs, we are testing if both transient and/or spatial encoding deficits are prevented at the early and late stages of the disease. Taken together, our results reveal a potential mechanism by which Aβ oligomers contribute to circuit dysfunction through synaptic loss, and identify a potential molecular target for therapeutic intervention.

Disclosures: D.M. Virga: None. **J.K. O'Hare:** None. **A. Losonczy:** None. **F. Polleux:** None.

Poster

118. Models of Alzheimer's Disease I

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 118.08

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

Support: RF1 AG059405
T32 HD071866

Title: Alzheimer's disease risk factor BIN1 in parvalbumin interneurons

Authors: *N. DAVIS[1], Y. VOSKOBIYNYK[1], R. A. PHILLIPS, III[2], R. VOLLMER[1], N. COCHRAN[3], E. D. ROBERSON[1];
[1]Neurol., [2]Neurobio., Univ. of Alabama at Birmingham, Birmingham, AL; [3]HudsonAlpha Inst. for Biotech., Huntsville, AL

Abstract: Alzheimer's disease (AD) is the most common neurodegenerative disease, affecting more than 5 million Americans. Despite its prevalence, much is still not understood about the disease and only modestly effective treatments currently exist. In the search for a better understanding of the disease, genome-wide association studies have identified *bridging integrator 1 (BIN1)* as a leading genetic risk factor for AD. While the association between *BIN1* and AD has been established, the function of the protein and its contribution to AD remain highly understudied. We previously showed that *BIN1* regulates neuronal excitability (Voskobiynyk & Roth et al., 2020). However, the mechanisms underlying this role are unclear, including which cell types are involved. Parvalbumin (PV) expressing interneurons contribute to the inhibitory interneuron dysfunction seen in AD, play a crucial role in oscillatory network activity, and are involved in cognitive functioning. Therefore, we hypothesized that BIN1 in PV interneurons contributes to its role in regulating neuronal excitability. Here, we used conditional knockout models to reduce *Bin1* selectively in PV interneurons and measured differences in AD-related behaviors and pentylenetetrazol-induced seizure susceptibility. We also performed RNA sequencing to determine differential gene expression and pathway analysis. This study contributes to our understanding of how BIN1 regulates neuronal excitability at a cell type-specific level.

Disclosures: **N. Davis:** None. **Y. Voskobiynyk:** None. **R.A. Phillips:** None. **R. Vollmer:** None. **N. Cochran:** None. **E.D. Roberson:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Owner of IP related to tau. F. Consulting Fees (e.g., advisory boards); Consulting for Lilly, AGTC.

Poster

118. Models of Alzheimer's Disease I

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 118.09

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

Support: F32 AG071073-01A1
5R01NS110383-04

Title: Calcineurin activation and scaffolding in amyloid-beta-induced synaptic dysfunction

Authors: *O. PRIKHODKO, J. L. SANDERSON, R. K. FREUND, E. S. SULLIVAN, M. J. KENNEDY, M. L. DELL'ACQUA;
Univ. of Colorado, Anschutz Med. Campus, Aurora, CO

Abstract: Calcineurin (CaN) is a protein phosphatase that is essential for synaptic long-term depression (LTD) through its regulation of AMPA-type glutamate receptors (AMPAR) and downstream modulation of NMDA-type glutamate receptors (NMDAR). CaN's interaction with its targets is critically mediated by the postsynaptic scaffold protein A-kinase anchoring protein 150 (AKAP150), which localizes a pool of CaN to the postsynaptic membrane. Our lab has generated knockin mice carrying a mutant version of AKAP150 lacking its CaN-binding site, the PxIxIT motif; AKAP150ΔPIX (PIX). LTD does not occur in these mice, underscoring the importance of the synaptic pool of CaN for normal synaptic function and plasticity. Pharmacological inhibition of calcineurin prevents diverse manifestations of Aβ-mediated synaptotoxicity, including long-term potentiation (LTP) blockade, synapse loss, and impaired learning and memory in Alzheimer's disease (AD) mouse models. To test our novel hypothesis that Aβ synaptotoxicity requires spatial positioning of CaN at the synapse via AKAP150 anchoring, we used our innovative AKAP150ΔPIX (PIX) knock-in mouse model. Using primary neuronal cultures, we demonstrate that the PIX mutation protects against acute Aβ-mediated synaptic loss, decreased NMDAR Ca^{2+} permeability, and LTP deficits.Utilizing the 5xFAD AD mouse model, we generated PIX/5xFAD mice to test long-term behavioral and electrophysiological effects of the PIX mutation on the 5xFAD phenotype. Given that the 5xFAD mouse model exhibits sex-based differences in the severity of the phenotype, we used mice of both sexes, with at least 12 animals per sex per genotype for behavioral studies, and 6 slices per sex per genotype for LTP recordings. We found that the PIX mutation does not rescue behavioral or LTP deficits of 5xFAD mice. Thus, synaptically-localized calcineurin is necessary for early Aβ-mediated synaptic deficits, but long-term Aβ exposure engages mechanisms beyond its AKAP-anchored calcineurin pathway.

Disclosures: **O. Prikhodko:** None. **J.L. Sanderson:** None. **R.K. Freund:** None. **E.S. Sullivan:** None. **M.J. Kennedy:** None. **M.L. Dell'Acqua:** None.

Poster

118. Models of Alzheimer's Disease I

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 118.10

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

Support: KBRI Basic Research Program 21-BR-01-10
Korean NRF grant 2017M3C7A1048086

Title: Selective regional loss of cortical synapses lacking presynaptic mitochondria in the 5xFAD mouse model

Authors: N.-Y. SEO[1], G. KIM[1], J. NOH[2], ***K. LEE**[1];
[1]Korea Brain Res. Inst., Korea Brain Res. Insitute, Daegu, Korea, Republic of; [2]Korea Brain Res. Inst., Daegu, Korea, Republic of

Abstract: Synaptic loss in Alzheimer's disease (AD) is strongly correlated with cognitive impairment. Accumulating evidence indicates that amyloid pathology leads to synaptic degeneration and mitochondrial damage in AD. However, it remains unclear whether synapses and presynaptic mitochondria are differentially affected in various cortical regions of the AD brain at the ultrastructural level. Using serial block-face scanning electron microscopy, we assessed synaptic structures in the medial prefrontal cortex (mPFC) and primary visual cortex (V1) of the 5xFAD mouse model of AD. At 6 months of age, 5xFAD mice exhibited significantly elevated levels of amyloid deposition in layer 2/3 of the mPFC but not V1. Accordingly, three-dimensional reconstruction of synaptic connectivity revealed a significant reduction in excitatory synaptic density in layer 2 of the mPFC, but not V1, of male transgenic mice. Notably, the density of synapses lacking presynaptic mitochondria was selectively decreased in the mPFC of 5xFAD mice, with no change in the density of mitochondria-containing synapses. Further classification of spines into shape categories confirmed a preferential loss of thin spines whose presynaptic boutons were largely devoid of mitochondria in the 5xFAD mPFC. Furthermore, the number of mitochondria per bouton in spared mitochondria-containing boutons was reduced in the mPFC, but not V1, of 5xFAD mice. Collectively, these results highlight region-specific vulnerability of cortical synapses to amyloid deposition and suggest that the presence of presynaptic mitochondria may affect synaptic degeneration in AD.

Disclosures: **N. Seo:** None. **G. Kim:** None. **J. Noh:** None. **K. Lee:** None.

Poster

118. Models of Alzheimer's Disease I

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 118.11

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

Support: University of Minnesota Institute for Translational Neuroscience
John Douglas French Alzheimer's Foundation
NIH Grant AG058820

Title: Depletion of voltage-gated potassium channel Kv1.1 contributes to behavioral deficits in transgenic mouse model of Alzheimer's disease

Authors: *K. ADDO-OSAFO[1], J. M. CHOQUETTE[2], S. T. PETERS[3], V. FOMENKO[4], J. C. XU[5], R. J. CRAFT[5], K. GIMLIN[6], K. VOSSEL[1];
[1]UCLA, Los Angeles, CA; [2]Neurol., [3]Neurol. Dept., Univ. of Minnesota, Minneapolis, MN; [4]Kaiser Permanente, San Jose, CA; [5]UCSF, San Francisco, CA; [6]The Jackson Lab., Sacramento, CA

Abstract: Background - Patients with Alzheimer's disease (AD) are at risk for seizures and accelerated cognitive decline. Mechanisms of seizures and related synaptic dysfunction in AD are active areas of investigation. Alterations in ion channels have been identified in transgenic mouse models of AD, but levels of voltage-gated potassium channels (VGKCs) have not been fully explored. In particular, little is known about Kv1.1 channels in AD. Mutations in Kv1.1 or autoantibodies against Kv1.1 cause neuronal overexcitation in several human diseases, including episodic ataxia type 1, epilepsy, myokymia, and limbic encephalitis, indicating that Kv1.1 is critical for regulating neuronal excitability. **Methods -** To explore VGKCs in AD, we used hAPP-J20 mice ages 4-6 months and determined mRNA and protein levels of four highly expressed VGKCs - Kv1.1, Kv1.2, Kv1.4, and Kv4.2 - in dentate gyrus, entorhinal cortex, motor cortex, and somatosensory cortex (SSC). **Results -** Using RT-qPCR, we identified reductions in Kv1.1 mRNA in the SSC of hAPP-J20 mice. Western blotting revealed reductions in the Kv1.1 channel in the SSC of hAPP-J20 mice and human parietal cortex in mild and moderate stages of AD. Immunolabeling revealed that the reductions in Kv1.1 channels in the SSC occurred in pyramidal cells and GABAergic interneurons. Kv1.1 levels in the SSC were lower in hAPP-J20 mice, which overexpress mutant hAPP and have high Aβ(1-42) levels, than in the wild-type hAPP line I5, suggesting some dependence on Aβ(1-42) levels. Levetiracetam treatment (75 mg/kg/day) administered for 28 days did not affect Kv1.1 levels in hAPP-J20 mice. To assess Kv1.1 depletion in an AD model, we crossed Kv1.1 heterozygous mice (Kv1.1 +/-) with hAPP-J9 mice, which have lower expression of mutant hAPP than J20 mice. We performed behavioral tests on mice ages 4-9 months. While Kv1.1 +/- mice and hAPP-J9 mice had normal survival, the double mutant (Kv1.1 +/- hAPP-J9) mice had premature mortality and impairments in elevated plus maze and light-dark box tests (n=16-25 mice/genotype) of anxiety. **Conclusion -** These data indicate that elevated Aβ(1-42) levels may act synergistically with Kv1.1 depletion to exacerbate cognitive deterioration in AD. Ongoing investigation will further characterize the relationships between Kv1.1 loss and AD-related hyperexcitability.

Disclosures: **K. Addo-Osafo:** None. **J.M. Choquette:** None. **S.T. Peters:** None. **V. Fomenko:** None. **J.C. Xu:** None. **R.J. Craft:** None. **K. Gimlin:** None. **K. Vossel:** None.

Poster

118. Models of Alzheimer's Disease I

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 118.12

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

Title: The protective effects of lacosamide on hippocampal synaptic plasticity and learning and memory impairment in animal model of Alzheimer's disease

Authors: *A. KOMAKI, M. HAMEDI, I. SALEHI, A. SARIHI, S. SHAHIDI;
Physiol., Hamadan Univ. of Med. Sci., Hamadan, Iran, Islamic Republic of

Abstract: Alzheimer's disease (AD) is a debilitating disease with complex pathophysiology associated with deficits in synaptic plasticity. Due to the mechanisms involved in AD and the neuroprotective, antioxidant and anti-apoptotic effects of lacosamide (LCM), the aim of this study was to investigate the role of LCM on Aβ-induced impairments in hippocampal synaptic plasticity (long term potentiation; LTP), learning and memory, oxidative stress, and Aβ plaque in AD model rats.In this study, 64 adult male Wistar rats were randomly divided into eight groups (n=8 rats/group); Group1 (Control), Group 2 (LCM), Group 3 (Vehicle), Group 4 (PBS+LCM), Group 5 (Aβ), Group 6 (LCM+Aβ), Group 7 (Aβ+LCM), and Group 8 (LCM+Aβ+LCM). In experimental groups LCM (30 mg/kg in distilled water) was administered via oral gavage, once a day, for 4 weeks before and 4 weeks after the Aβ1-42 (5 μL; ICV) injection. After the treatment period, passive avoidance learning (PAL) and memory were assessed by the shuttle box test, cognitive memory by the novel object recognition (NOR) test, and spatial memory by the Morris water maze (MWM) test. In vivo electrophysiological recordings were performed to quantify the excitatory postsynaptic potential (EPSP) slope and population spike (PS) amplitude in the hippocampal dentate gyrus (DG). LTP was induced by a high-frequency stimulation of the perforant pathway. At the end of the experiments, malondialdehyde (MDA), total antioxidant capacity (TAC), and total oxidant status (TOS) levels of plasma were measured. Thioflavin S staining was performed to show Aβ plaque aggregation in the hippocampus. According to our results, ICV injection of Aβ reduced cognitive memory in the NOR, spatial memory in the MWM, and passive avoidance in the PAL tests. LCM caused a recovery in cognitive memory, spatial memory, and PAL memory. After induction of LTP in Aβ-injected rats, PS amplitude and EPSP slope were significantly reduced compared to the control group. LCM treatment of Aβ-injected rats significantly reduced the effects of Aβ on LTP. Also, Aβ significantly increased MDA and TOS levels, whereas LCM significantly reversed these parameters and increased TAC level. Histological results showed that Aβ plaque formation in the hippocampus of group Aβ was significantly increased compared to the control group. The use of LCM reduced Aβ plaque levels in AD model rats. These findings suggest that LCM treatment provides neuroprotection against

the harmful effects of Aβ on hippocampal synaptic plasticity and learning and memory via preventing the aggregation or induction of Aβ plaque clearance and its antioxidant properties.

Disclosures: **A. Komaki:** None. **M. Hamedi:** None. **I. Salehi:** None. **A. Sarihi:** None. **S. Shahidi:** None.

Poster

119. Alzheimer's Disease Clinical and Preclinical Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 119.01

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

Support: National Cancer Institute
National Institute of Biomedical Imaging and Bioengineering
National Institute on Deafness and Other Communication Disorders
National Institute on Aging of the National Institutes of Health
Kiwanis Neuroscience Research Foundation
Beckman Institute Postdoctoral Fellowship

Title: Microvascular changes in Alzheimer's mouse model visualized using Ultrasound Localization Microscopy

Authors: *N. VAITHIYALINGAM CHANDRA SEKARAN[1], M. R. LOWERISON[2], D. A. LLANO[1], P. SONG[2];
[1]Beckman Institute, Mol. and Integrative Physiol., [2]Beckman Institute, Dept. of Electrical & Computer Engin., Univ. of Illinois at Urbana-Champaign, Urbana, IL

Abstract: Cerebral microvascular changes are not well understood in Alzheimer's Disease (AD). We aimed to investigate the functional cerebrovascular changes impacted in the 5XFAD mouse model of AD using a novel imaging technique known as Ultrasound Localization Microscopy (*ULM*). ULM is an emerging imaging technology for super-resolution in vivo microvascular mapping. This technique helps us achieve deep whole-brain imaging without compromising spatial resolution. We applied super-resolution ULM imaging to 5xFAD mice and quantified vascularity, blood velocity and vessel tortuosity in the hippocampus. We examined 3, 6- and 12-months age group mice along with age-matched controls. Along with functional imaging, histological analysis was done with intravenous injection of FITC dextran to stain the blood vessels. Amyloid beta and GFAP staining were done to confirm the earlier deposition of plaque formation and gliosis in the 5xFAD mouse model. We confirmed previous work that there is early deposition of amyloid beta in 3 months old 5xFAD mouse hippocampus and entorhinal cortex compared to the control group. We also found a decrease in blood velocity, blood volume in hippocampus in the 5xFAD mice at the age of 6 months which further decreased at 12 months of age. Though the amyloid plaque deposition starts early at 3 months, functional imaging of microvasculature in the hippocampus showed significant reduction of vascular function starting

at 6 -12 months old. These ULM and histological studies may provide early detection of microvascular abnormality related to neurodegenerative and cognitive decline in mouse models of AD, facilitating future investigation of microvascular dysfunction in AD.

Disclosures: N. Vaithiyalingam Chandra Sekaran: None. **M.R. Lowerison:** None. **D.A. Llano:** None. **P. Song:** None.

Poster

119. Alzheimer's Disease Clinical and Preclinical Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 119.02

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

Support: NIH Grant P30 AG066509

Title: Relationships between Neuropsychological Language Test Performance and Cortical Thickness in the Language-Relevant Brain Regions in Mild Cognitive Impairment and Alzheimer's Disease Related Dementia

Authors: R. SEO[1], C. M. PARSEY[2,3], D. J. PETERSON[1], T. J. GRABOWSKI[1,3];
[1]Univ. of Washington Dept. of Radiology, Seattle, WA; [2]Univ. of Washington Dept. of Neurol., Seattle, WA; [3]Univ. of Washington Alzheimer's Dis. Res. Ctr., Seattle, WA

Abstract: ABSTRACT In neurodegenerative disorders, such as Alzheimer's disease dementia (AD) or frontotemporal dementia (FTD), patterns of neuropsychological test (NPT) performance can predict structural changes identified on neuroimaging (e.g., memory impairment and hippocampal atrophy; language impairment and temporal lobe degeneration). Advances in neuroimaging have produced regional and network-based metrics to better understand relationships between structural neuroanatomical change and cognitive symptoms. Here, we relate NPT performance and network level organization for language function. Three language-domain tests [measuring phonemic fluency (COWAT), category fluency (Animal naming) and naming (BNT)] were correlated with cortical thickness in language-related and domain-general networks (i.e., in the frontal and temporal lobes, and using Yeo et al. 2011 7-network model). Participants were selected from a memory clinic data repository, which included 3D MPRAGE MRI imaging and NPT. MPRAGE images were processed using FreeSurfer, and cortical thickness was averaged within the regions and networks of interest. Pearson correlations between the anatomical measures and the language test scores were examined in three participant groups: AD (n = 64), mild cognitive impairment (MCI; n = 202), and healthy cognition (HC; n = 72). In the AD group, correlations were significant between phonemic fluency and ventral attention network (r = 0.326, p = 0.021) and somato-motor network (r = 0.286, p = 0.044) cortical thickness, as well as frontal lobe volumes (L: r = 0.363, p = 0.010; R: r = 0.386, p = 0.006). Semantic fluency correlated significantly with frontal-parietal network (r = 0.294, p = 0.040) and default mode network (r = 0.380, p = 0.007). BNT correlated significantly with Yeo's limbic

network (r = 0.355, p = 019) and left temporal volume (r = 0.408, p = 0.007). For the MCI group, BNT scores correlated with cortical volumes in bilateral temporal lobes (L: r = 0.601, p < 0.001; R: r = 0.318, p < 0.001). No significant correlations in the HC group were found. Our findings revealed expected relationships of lower performances on language-specific NPTs with cortical thinning and volume loss in language-associated neural regions, in particular reduced semantic fluency with frontoparietal and temporal regions, and confrontation naming with anterior temporal lobe cortical thinning. However, other relationships between neuroimaging findings and NPT language performance were less clear and warrant further evaluation, including in atypical neurodegenerative presentations where language networks may be disproportionately affected.

Disclosures: R. Seo: None. **C.M. Parsey:** None. **D.J. Peterson:** None. **T.J. Grabowski:** None.

Poster

119. Alzheimer's Disease Clinical and Preclinical Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 119.03

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

Support: NIA: 1K23AG068384-01A1
Alzheimer's Association: 2019-AACSF-643094
Sidney R Baer Jr Foundation: 01028951
NIA: 1R21AG051846-01
NIH: 5R01MH115949-04

Title: Decreased intra-cortical inhibition in early Alzheimer’s disease is related to distributed cortical atrophy

Authors: *S. BUSS[1], D. PRESS[2], V. ZENG[1], D. MANNING[1], A. TOUROUTOGLOU[3], B. C. DICKERSON[5], M. SHAFI[6], A. PASCUAL-LEONE[4], P. J. FRIED[1];
[2]Dept Neurol., [1]Beth Israel Deaconess Med. Ctr., Boston, MA; [3]Harvard Univ., Brookline, MA; [4]Harvard Univ., Boston, MA; [5]Dept Neurol, Massachusetts Gen. Hosp. Dept. of Neurol., Charlestown, MA; [6]UCLA, Los Angeles, CA

Abstract: Background: Alzheimer’s disease (AD) is associated with increased cortical excitability, including an elevated risk of seizures. Transcranial magnetic stimulation with electromyography (TMS-EMG) can be used to index cortico-motor excitability and intra-cortical inhibition non-invasively. Prior work has shown that TMS-EMG excitability measures are increased in AD and are related to disease severity. However, it is not yet known how TMS-EMG measures are related to neurodegeneration within brain regions affected by AD. **Methods:** TMS-EMG was applied to left motor cortex (M1) in 22 participants with biomarker-confirmed mild cognitive impairment due to AD (early AD, aged 70.5±8.4, 11 females). Single pulse TMS was preformed to measure cortical excitability using resting motor threshold (RMT) and average

motor evoked potential amplitude (MEP Amplitude). Paired-pulse TMS was preformed to measure short interval intra-cortical inhibition (SICI, GABA-ergic) and intracortical facilitation (ICF, glutamatergic). Structural MRI scans for each participant were processed using Freesurfer to obtain cortical thickness measurements within the distributed Alzheimer-signature brain regions (AD-signature atrophy). The primary analyses tested the relationship between each TMS measure and Alzheimer-signature atrophy using separate linear models, controlling for age. **Result:** In early AD, SICI was related to AD-signature atrophy (R^2_{adj}=0.40, B=-0.13, *p*=0.018), with less intra-cortical inhibition related to greater atrophy. RMT, MEP Amplitude, and ICF were not related to AD-signature atrophy (*p*-values>0.105). **Conclusion:** Decreased intra-cortical inhibition is related to increased Alzheimer-signature atrophy in participants with early AD. Decreased function of GABA-A circuitry related to cortical atrophy may play a role in the development of cortical hyperexcitability during the early clinical manifestations of AD. Future studies using TMS with electroencephalography (TMS-EEG) to measure excitability outside of motor cortex will be important for understanding the relationship between local cortical excitability and atrophy.

Disclosures: **S. Buss:** F. Consulting Fees (e.g., advisory boards); Kinto Care. **D. Press:** None. **V. Zeng:** None. **D. Manning:** None. **A. Touroutoglou:** None. **B.C. Dickerson:** None. **M. Shafi:** F. Consulting Fees (e.g., advisory boards); Scientific Advisory Board for BioSerenity, Inc. **A. Pascual-Leone:** F. Consulting Fees (e.g., advisory boards); Dr. A. Pascual-Leone serves as a paid consultant on the scientific advisory boards for Neuroelectrics, Magstim Inc., TetraNeuron, Skin2Neuron, MedRhythms, and Hearts Radiant. Other; Dr. A Pascual-Leone is listed as an inventor on several issued and pending patents on the real-time integration of transcranial magnetic stimulation with electroencephalography and MRI.. **P.J. Fried:** None.

Poster

119. Alzheimer's Disease Clinical and Preclinical Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 119.04

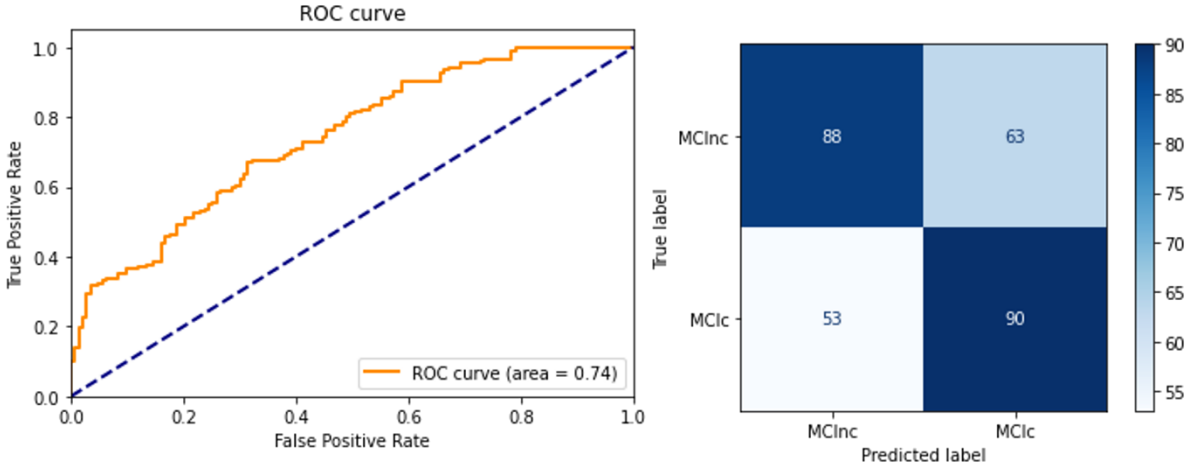
Topic: C.02. Alzheimer’s Disease and Other Dementias

Title: A 3DResNet for early prognosis of Mild Cognitive Impairment converted to Alzheimer's Disease based on structural magnetic resonance imaging data

Authors: *M. HOANG GIA[1], J. KIM[1], U. KIM[2];
[1]Dept. of Biomed. Sci. and Engin., [2]AI Grad. Sch., Gwangju Inst. of Sci. and Technol., Buk-gu, Korea, Republic of

Abstract: Alzheimer's disease (AD) is one of the most common causes of neurodegenerative disease affecting over 50 million people worldwide. Because of the accumulation of Aβ and the deposition of hyper-phosphorylated tau protein, the structure in the brain begins to shrink, called brain atrophy. However, most AD diagnosis occurs in the moderate to late stage, which means that the optimal time for treatment has already passed. Mild cognitive impairment (MCI) is an

intermediate state between cognitively normal people and AD patients. People with MCI tend to convert to AD at a significantly higher rate than normal people. Therefore, the accurate prognosis in the converting process of MCI to AD may allow patients to start preventive intervention to slow or stop the progression of the disease. Nowadays, Convolutional Neural Network (CNN) approaches and their variants, such as ResNet and AlexNet, have been increasingly applied to the AD classification using structural MRI scans in several ways, including using whole brain, image patches. However, there is currently a lack of studies regarding the prognosis of MCI converting to AD. In this study, we implemented a 3D Residual neural network (3DResNet) to structural T-1 weighted MRI scans in the prognosis of MCI converting to AD. The MRI scans used to train the model were retrieved from the database of Alzheimer's Disease Neuroimaging Initiative (ADNI). A total of 772 MCI subjects with 3400 T-1 MRI images were used, out of which 254 patients were labeled MCI converted to AD (MCIc, 1387 images) and 518 as MCI non-converted (MCInc, 2003 images). The results showed that the classification method trained from scratch showed a training accuracy of 98%, test accuracy of 67%, and AUC = 0.74. While training a CNN from scratch has been performed in many experiments, it is usually not optimized. In general, the number of samples for training from scratch is not always sufficient. In our study, the number of images is still small in terms of training from scratch, and thus transfer learning with larger data before training is planned to be applied in the future study.



Disclosures: **M. Hoang gia:** None. **J. Kim:** None. **U. Kim:** None.

Poster

119. Alzheimer's Disease Clinical and Preclinical Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 119.05

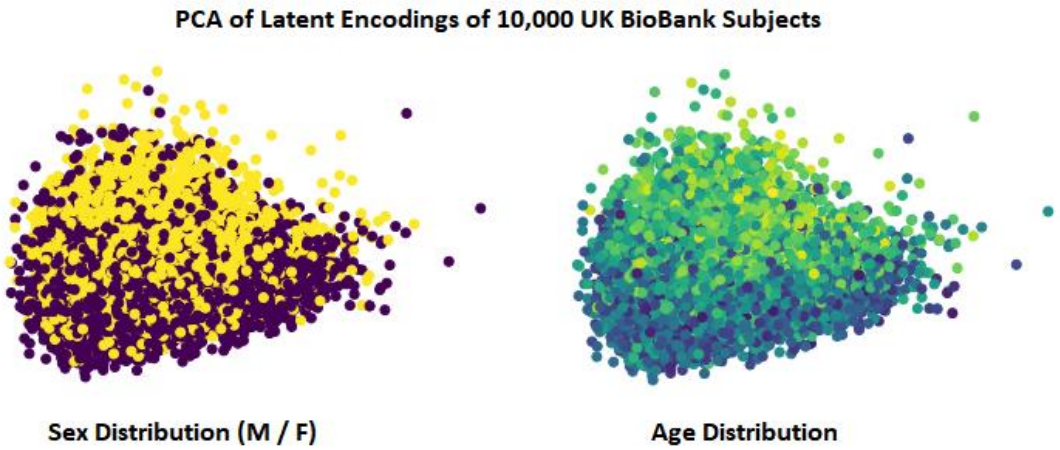
Topic: C.02. Alzheimer’s Disease and Other Dementias

Support: AI4AD Grant U01AG068057

Title: 3D Convolutional Autoencoder for deep latent space embedding based brain age estimation and sex classification on 30,000 UK Biobank MRI scans

Authors: *D. KOMANDUR, T. CHATTOPADHYAY, Y. FENG, N. DHINAGAR, J. NAIK, V. SANTHALINGAM, S. I. THOMOPOULOS, P. M. THOMPSON;
Imaging Genet. Center, Mark and Mary Stevens Neuroimaging and Informatics Inst., USC, Marina del Rey, CA

Abstract: AI methods such as deep learning show great promise for diagnosing brain disease from 3D MRI, but the sheer volume of data makes these models time-consuming to train. To improve key benchmarking tasks such as age and sex prediction, we built a 3D Convolutional Autoencoder to map MRI scans to a low-dimensional latent space while maintaining a good reconstruction score. Our encoder uses 6 Conv blocks each having a 3D Conv layer, Batch norm., 3D Max pooling, and a ReLU activation. The decoder is symmetric in nature, with 3D Conv Transpose and 3D Max unpooling layers instead of their encoder counterparts. Each input to the network is a bias-corrected 3D T1-weighted brain MRI scan of dimension 91x109x91 and encoded to a latent space of dimension 2048x1. The encoder has a compression ratio of 440:1. The model was trained on 20,000 subjects' MRI scans from the UK BioBank dataset (mean: 64.6+/-7.7 (SD) years; 10,305 F / 9,695 M). The model was trained using Mean Squared Error (MSE) loss for 77 epochs and achieved a training MSE of 0.75x10-3 and mean absolute error (MAE) of 0.74x10-3 on the validation data set. We also tracked MAE and peak signal-to-noise ratio (PSNR) as reconstruction metrics during training. The model achieved an MAE of 0.010 and 0.011, PSNR of 31.4 and 31.3 on training and validation, respectively. The trained encoder was then used to generate a latent space encoding of MRI data from 10,000 unseen subjects (mean: 64.6+/-7.7 (SD) yrs., 4,763 male/5,237 female). The low-dimensional output of 2,048 features by the encoder was used to classify genetic sex and predict the age of the subjects. The logistic regression model gave an accuracy of 88.8% and F1 score of 0.884 on training, an accuracy of 87.4%, and F1 score of 0.862 on the test set, for the sex classification task. The linear regression model gave an MSE of 22.9 and MAE of 3.8 on the training set and an MSE of 27.2 and MAE of 4.1 on the test set, on the age prediction task. These initial results show that our ConvAE performs well on key deep learning tasks - despite working with highly compressed data - showing promise for training large-scale diagnostic models.



Disclosures: **D. Komandur:** None. **T. Chattopadhyay:** None. **Y. Feng:** None. **N. Dhinagar:** None. **J. Naik:** None. **V. Santhalingam:** None. **S.I. Thomopoulos:** None. **P.M. Thompson:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Research grant from Biogen, Inc. for research unrelated to this abstract..

Poster

119. Alzheimer's Disease Clinical and Preclinical Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 119.06

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

Support: U01AG068057
ZEN-20-644609

Title: Comparing traditional regression, XGBoost and artificial neural networks for predicting amyloid positivity from brain MRI

Authors: *T. CHATTOPADHYAY, D. KOMANDUR, J. NAIK, S. I. THOMOPOULOS, P. M. THOMPSON;
USC, Los Angeles, CA

Abstract: Abnormal β-amyloid (Aβ) accumulation in the brain is an early indicator of Alzheimer's disease and is assessed using PET or CSF assays, both highly invasive procedures. As a less invasive forerunner to such tests, here we tested machine learning algorithms to predict Aβ positivity (Aβ+) from T1-weighted brain MRI (T1w).We assessed predictive models based on logistic regression, XGBoost and artificial neural networks (ANNs) using easily measured discrete features from T1w. We also ran multiple experiments to compare the predictive abilities of the different features and Aβ+ cutoffs available through the Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset.T1w from 765 ADNI subjects were preprocessed and registered to a common template (mean age 75.13+/-7.6; 397 F/368 M; 238 Dementia, 68 MCI, 459 controls). Two cut-offs, for determining amyloid levels, were used based on PET cortical SUVR uptake (Aβ_1) determined by either mean 18F-florbetapir (Aβ+ defined as >1.11 for cutoff_1 and 0.79> for cutoff_2) or florbetaben (Aβ+ defined as >1.20 for cutoff_1 and >1.33 for cutoff_2), normalized by using a whole cerebellum reference region. The data was split into independent training, validation and testing sets. Three different models (regression, XGBoost, ANN) were used, and test performance was assessed and compared using balanced accuracy. The best results were obtained with the ANN including age, sex, diagnosis, APOE4 values (2 for 2 copies of E4 and 1 for 1 E4), overall volumes of CSF, white and gray matter, and left and right hippocampal and entorhinal cortex volumes as features: a balanced accuracy of 0.771 and F1 score of 0.771.

Classical machine learning algorithms can be used to classify Aβ+ with promising F1 scores; performance may be improved by using larger training samples and additional data modalities.

	XG Boost Cutoff_1		XG Boost Cutoff_2		Linear Regression Cutoff_1		Linear Regression Cutoff_2		Artificial Neural Network Cutoff_1		Artificial Neural Network Cutoff_2	
	Balanced Acc.	F1 Score	Balanced Acc.	F1 Score	Balanced Acc.	F1 Score	Balanced Acc.	F1 Score	Balanced Acc.	F1 Score	Balanced Acc.	F1 Score
Data Except Entorhinal Cortex Volume	0.742	0.678	0.707	0.656	0.77	0.734	0.75	0.709	0.711	0.696	0.771	0.771
Data Except Hippocampus Volume	0.742	0.689	0.708	0.656	0.77	0.734	0.75	0.709	0.711	0.696	0.771	0.771
Data Except Grey Matter, White Matter, CSF Volumes	0.697	0.656	0.721	0.677	0.77	0.734	0.737	0.688	0.755	0.73	0.77	0.764
Data all features	0.756	0.701	0.75	0.709	0.77	0.734	0.75	0.709	0.725	0.716	0.759	0.746

Disclosures: T. Chattopadhyay: None. **D. Komandur:** None. **J. Naik:** None. **S.I. Thomopoulos:** None. **P.M. Thompson:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Research grant from Biogen, Inc. for research unrelated to this abstract.

Poster

119. Alzheimer's Disease Clinical and Preclinical Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 119.07

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

Support: Administrative Supplement to EB029343 to M.D.W
CCSN fellowship by The McDonnell Center for Systems Neuroscience

Title: The level of hub disruption in autosomal dominant Alzheimer’s disease is related to cognitive performance.

Authors: *J. C. TU, J. F. STRAIN, J. C. MORRIS, R. J. BATEMAN, T. L. S. BENZINGER, A. T. EGGEBRECHT, B. M. ANCES, B. A. GORDON, M. D. WHEELOCK, _. DOMINANTLY INHERITED ALZHEIMER NETWORK;
Washington Univ. in St Louis, Washington Univ. in St Louis, St Louis, MO

Abstract: Hubs are high-degree (a.k.a. high total connectivity) brain regions that are crucial for global communication and brain network function (van den Heuvel and Sporns, 2013). Several lines of evidence suggest that hubs have high metabolic demands and are especially susceptible to amyloid beta deposition in Alzheimer’s Disease (AD) (Bullmore and Sporns, 2012). However, detailed characterization of hub disruption and its relation to cognitive changes has not been conducted. Here we constructed a resting-state functional connectivity network using 246 regions of interest (ROI) spanning cortical and subcortical regions (Seitzman et al., 2020) in 122 autosomal dominant AD mutation carriers (MC) and 85 mutation non-carriers (NC) from the Dominantly Inherited Alzheimer Network. The consistent onset of symptoms within autosomal dominant AD families and mutation type allowed for an estimation of years to symptom onset (EYO). We found a global reduction in functional connectivity with increasing EYO, especially within resting-state functional networks in MC but not NC. To further understand the change in total connectivity across different ROIs, we calculated for each individual a modified version of hub disruption index (Achard et al., 2012) based on the proportional change in regional

connectivity in each subject relative to baseline regional connectivity. We found that MC demonstrated a greater proportional decrease in connectivity than NC particularly in hub regions of the posterior section of the default mode (DMN) and cingulo-opercular (CO) networks. We conducted a stepwise linear regression and found that the hub disruption index was positively related with concurrent cognitive abilities of MC measured by a cognitive composite score. This relationship persisted even after regressing out the scan duration and motion level from the hub disruption index, and with EYO, education, and sex as covariates. Taken together, these results suggest that, consistent with an activity-dependent degeneration hypothesis (de Haan et al., 2012), high-degree hub regions are more than proportionally affected in AD, and that this preferential disruption in hubs may be related to cognitive decline. Our study suggests hub disruption may be a potential biomarker for AD disease progression and treatment outcome monitoring.

Disclosures: J.C. Tu: None. **J.F. Strain:** None. **J.C. Morris:** None. **R.J. Bateman:** None. **T.L.S. Benzinger:** None. **A.T. Eggebrecht:** None. **B.M. Ances:** None. **B.A. Gordon:** None. **M.D. Wheelock:** None. **_. Dominantly Inherited Alzheimer Network:** None.

Poster

119. Alzheimer's Disease Clinical and Preclinical Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 119.08

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

Support: K25AG050759
R01AG073362
R01AG072470
R21AG064263
R21AG073973
R61MH119289
R21MH123873

Title: Improved Fluid Cognition and associated changes in functional and microstructure connectivity after a 6-month multi-domain cognitive training in individuals at risk for Alzheimer's disease: a randomized controlled trial

Authors: E. GOZDAS[1], ***B. AVELAR PEREIRA**[2], H. FINGERHUT[2], L. DACORRO[2], B. JO[2], L. WILLIAMS[2], R. O’HARA[2], H. HOSSEINI[3];
[1]Stanford Univ., Palo Alto, CA; [2]Stanford Univ., Stanford, CA; [3]Psychiatry and Behavioral Sci., Stanford Univ., Palo Alto, CA

Abstract: Amnestic mild cognitive impairment (aMCI) is a proximal risk factor for Alzheimer’s disease (AD). There has been increasing attention on multi-domain cognitive training (CT) given evidence that it may slow cognitive decline and potentially delay the clinical onset of AD.

However, most extant work involves interventions of relatively short duration, targeting single cognitive domains, and lacking a proper active control group. We conducted a single-blind randomized controlled trial study to investigate the effect of a 6-month, multi-domain CT on cognitive functioning, brain functional connectivity, and microstructural properties in older adults with aMCI. The study is registered as a clinical trial on ClinicalTrivals.gov (identifier: NCT03883308). Sixty participants were randomly assigned to either the intervention (i.e., multi-domain CT) or an active control (i.e., crossword training (CW) group. Thirty-four participants completed the assessments due to a Covid-19 related halt in the study. The results revealed a significant group by time interaction effect in Fluid Cognition (primary outcome) and a significant post-intervention improvement in the CT group only (Cohen's d = 0.7). Similarly, BRIEF measures of behavioral regulation in everyday life improved solely in the CT group. Functional connectivity analyses showed a significant group by time interaction (Cohen's d > 0.8) in the dorsolateral prefrontal cortex (DLPFC) and inferior parietal cortex (IPC) networks (also primary outcomes). Overall, the CT group displayed post-intervention increases in functional connectivity, whereas the CW group displayed decreases. Moreover, increased functional connectivity strength between the left DLPFC and medial PFC was associated with improved Fluid Cognition scores. At a microstructural level, we observed a decline over the six-month intervention period in fiber density (FD) for both groups, but the CT group declined significantly less steeply than the CW group. Slower decline in FD in several tracts - including the cingulum-hippocampus tract - was associated with better working memory performance within the CT group. Finally, we identified regions in the cognitive control and memory networks for which baseline functional connectivity and microstructural properties were positively associated with change in Fluid Cognition. Overall, our findings suggest that long-term, multi-domain CT improves cognitive functioning and functional connectivity and delays structural brain decline in aMCI.

Disclosures: **E. Gozdas:** None. **B. Avelar Pereira:** None. **H. Fingerhut:** None. **L. Dacorro:** None. **B. Jo:** None. **L. Williams:** None. **R. O'Hara:** None. **H. Hosseini:** None.

Poster

119. Alzheimer's Disease Clinical and Preclinical Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 119.09

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

Support: Australian Research Council Discovery Project DP190102659
Australian Research Council Discovery Early Career Award DP200100143
Australian Research Council Discovery Early Career Award (DE170100628)
Yulgibar/Dementia Australia

Title: Immunotargeted magnetic nanoparticles as MRI/MPI tracers for early diagnosis of Alzheimer's Disease

Authors: *M. ULANOVA[1], H. T. KIM DUONG[2], L. GLOAG[2], A. BONGERS[2], R. TILLEY[3], P. S. SACHDEV[2], N. BRAIDY[2];
[1]UNSW, Univ. of New South Wales Sydney, Kensington, Australia; [2]Univ. of New South Wales, Randwick, Australia; [3]UNSW, Kensington, Australia

Abstract: The diagnostic criteria for Alzheimer's disease (AD) have shifted in recent years to a biological framework which classifies AD by the presence of amyloid beta (Aβ) aggregation, tau aggregation, and neurodegeneration, rather than the manifestation of clinical symptoms. However, currently the only means of detecting Aβ and tau are either with Positron Emission Tomography (PET) imaging or cerebrospinal fluid analysis, which are both invasive, expensive, and in the case of PET expose the patients to radiation. There is an opportunity for Aβ-targeted nanoparticle-based magnetic contrast agents to be used for early diagnosis of AD using magnetic resonance imaging (MRI) or magnetic particle imaging (MPI). MPI is a promising new imaging modality that derives signal from magnetic nanoparticles to produce images with high sensitivity. While this technology is in the preclinical stages, its high spatial resolution and rapid image acquisition renders it a powerful new tool for neuroimaging research. Here, we show the potential for an Aβ-targeted iron oxide nanoparticle formulation for use as a dual mode MRI/MPI tracer for the diagnosis of AD. Targeted iron oxide nanoparticles were first assessed for their *in vitro* biocompatibility and imaging efficacy. APPSwe/PSEN1 and wild type mice were treated with either saline, Aβ-targeted or non-targeted nanoparticles (10 µg Fe/g). 30 minutes following administration, mice were euthanised and their tissues were collected for *ex vivo* imaging and histological evaluation. Another group of mice was observed for 24 h to evaluate any acute toxicological effects. Mice tolerated the high dose over the 24 h period. Extracted mouse brains underwent MRI imaging and signal was observed in the mice which were administered targeted nanoparticles. Furthermore, signal was observed in MPI scans, confirming the presence of iron oxide nanoparticles in the brain. MPI was also used to image peripheral tissues to determine the biodistribution of the nanoparticles following injection. The present work shows promising preliminary results in the development of a targeted non-invasive method of early AD diagnosis using contrast enhanced MRI and presents MPI as a promising imaging modality for AD.

Disclosures: M. Ulanova: None. **H.T. Kim Duong:** None. **L. Gloag:** None. **A. Bongers:** None. **R. Tilley:** None. **P.S. Sachdev:** None. **N. Braidy:** None.

Poster

119. Alzheimer's Disease Clinical and Preclinical Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 119.10

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

Title: High-throughput quantitative whole-brain 3D imaging of congophilic amyloid plaque load in a transgenic mouse model of Alzheimer's disease

Authors: *H. HANSEN, C. ZHANG, C. SALINAS, F. WICHERN, J. PERENS, U. ROOSTALU, J. L. SKYTTE, J. HECKSHER-SØRENSEN;
Gubra, Hoersholm, Denmark

Abstract: Alzheimer's disease is characterized by accumulation of amyloid β (Aβ) plaques in the brain parenchyma and vasculature. While animal models of Alzheimer's disease are important in preclinical drug discovery, changes in histopathological hallmarks are often performed in selected brain areas in preclinical models of amyloidosis. To obtain full spatial information on amyloid pathology in mouse models of Alzheimer's disease, the present study aimed to develop and validate a light sheet fluorescence microscopy (LSFM) pipeline coupled with deep-learning computational analysis for unbiased automated whole-brain 3D mapping and quantification of congophilic amyloid plaques. Brains from 12-month-old double transgenic mice expressing mutant forms of human APP and PSEN1 (ARTE10 mice) and age-matched wild-type C57BL/6J control mice were collected, stained with Congo red, cleared and scanned on a LSFM. A deep-learning image analysis algorithm was developed and validated for automated whole-brain visualization, segmentation, anatomical mapping and quantification of congophilic Aβ plaques in the parenchyma and vasculature using a custom mouse brain atlas. We detected parenchymal and vascular congophilic plaques at micrometre resolution in 93 out of 298 annotated brain regions in the ARTE10 mouse. Regions with most marked congophilic Aβ load included the cortex (somatosensory, motor and prelimbic areas), hippocampus (subiculum, CA1), thalamus and lateral septum. Notable differences were observed in the distribution profile of parenchymal and cerebrovascular Aβ plaques. The pipeline allows for high-throughput quantitative LSFM 3D imaging (≥30 brains per week). In conclusion, we have developed a high-throughput, quantitative LSFM imaging pipeline enabling unbiased and automated analysis of whole-brain amyloid plaque architecture in mouse models of AD. This approach is highly instrumental for profiling brain-wide effects of anti-amyloid therapies in mouse models of Alzheimer's disease and congophilic amyloid angiopathy. In addition, the LSFM-deep learning pipeline allows for combined CNS drug distribution analysis.

Disclosures: H. Hansen: None. **C. Zhang:** None. **C. Salinas:** None. **F. Wichern:** None. **J. Perens:** None. **U. Roostalu:** None. **J.L. Skytte:** None. **J. Hecksher-Sørensen:** None.

Poster

119. Alzheimer's Disease Clinical and Preclinical Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 119.11

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

Support: 772867

Title: Beta-amyloid affects contextual memory and this is reverted by the release of dopamine from Rubi-Dopa

Authors: *C. VELAZQUEZ DELGADO[1], L. CARRILLO REID[2];
[1]Inst. De Neurobiología, UNAM Inst. De Neurobiología, Instituto De Neurobiología, UNAM Instituto De Neur, Mexico; [2]Inst. De Neurobiología, UNAM Inst. De Neurobiologia, Instituto De Neurobiología, UNAM Instituto De Neur, Mexico

Abstract: Recently, the evidence has resalted the role of the soluble forms of beta-amyloid since it causes neuronal loss, alterations in synaptic plasticity, and diminished performance in memory tasks; even in the absence of plaques. On the other hand, dopamine is a neuromodulator, and it participates in processes of learning and memory. Evidence shows alterations in the dopaminergic system during AD development in animal models and patients. We showed that acute administration of oligomers of beta-amyloid (ABo) intra-hippocampus impairs the codification of contextual novelty. We decided to use Rubi-dopa, a caged compound that with optical stimulation releases dopamine, before de administration of the oligomers. Dopamine permits that novelty contextual was codified after the administration of the oligomers. Interestingly, the dopamine release from Rubi-dopa without oligomers prohibits contextual novelty codification. In conclusion, ABo affects the release of dopamine, and its restoration permits average performance. However, an excess of dopamine affects performance.

Disclosures: C. Velazquez Delgado: None. **L. Carrillo Reid:** None.

Poster

119. Alzheimer's Disease Clinical and Preclinical Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 119.12

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

Support: MOST, Taiwan Grant 110-2321-B-A49A-502
MOST, Taiwan Grant 110-2628-B-A49A-509
MOST, Taiwan Grant 110-2634-F-075-001
MOST, Taiwan Grant 110-2634-F-A49-005
Mt. Jade Young Scholarship Award from Ministry of Education, Taiwan
National Yang Ming Chiao Tung University and the Ministry of Education (Aim for the Top University Plan), Taipei, Taiwan

Title: Using gray matter voxel-based structural analysis to investigate structural covariance and stability in patterns of brain regions in Alzheimer's disease

Authors: *T.-Y. CHEN[1], A.-C. YANG[1,2,3];
[1]Inst. of Brain Sci., [2]Digital Med. and Smart Healthcare Res. Ctr., Natl. Yang Ming Chiao Tung Univ., Taipei, Taiwan; [3]Dept. of Med. Res., Taipei Veterans Gen. Hosp., Taipei, Taiwan

Abstract: Previous structural covariance studies in Alzheimer's disease showed altered structural associations in the gray matter structure of intrinsic brain networks. However, no research has explored the similarity in local topological properties in different brain regions. We aimed to

construct morphological patterns based on structural relationships of gray matter voxels and investigate the changes in structural covariance between brain regions in individuals with Alzheimer's disease. T1-weighted MRI data from 342 cognitively normal participants and 276 individuals with Alzheimer's disease were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database. We converted the volume relationships between adjacent gray matter voxels into structural patterns and applied an information-based similarity (IBS) index to calculate the pairwise distances between patterns in 90 brain regions to represent the dissimilarity. Finally, the structural organization was examined by the non-randomness index derived from the IBS method. The results showed that similarities of structural patterns reduced between frontal regions and the insula and increased between the hippocampus and other brain regions in Alzheimer's disease. Additionally, individuals with Alzheimer's disease exhibited significantly lower randomness, mainly in the cingulate gyrus, hippocampus, and temporal regions. In comparison, greater randomness was found in most brain regions of the frontal and occipital lobes. Our findings suggest that similarities of structural patterns varied with trends between different brain regions in Alzheimer's disease. Meanwhile, subcortical regions showed higher stabilities of structural organization than cortical regions. With the structural covariance characteristics, we could further explain the brain structural development and the degenerative process in Alzheimer's disease.

Disclosures: **T. Chen:** None. **A. Yang:** None.

Poster

119. Alzheimer's Disease Clinical and Preclinical Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 119.13

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

Support: Alzheimer’s Drug Discovery Foundation (Grant 20130805)

Title: A functional MRI study of impaired spatial inhibition of return in older adults with mild cognitive impairment or mild Alzheimer’s disease

Authors: *Z. LI[1], K. SHATTUCK[1], C. GALLAGHER, Jr.[1], J. J. HOWARD[1], R. S. TURNER[2], X. JIANG[3];
[2]GUMC Dept Neurol., [3]Dept Neurosci, [1]Georgetown Univ. Med. Ctr., Washington, DC

Abstract: Individuals are slower to respond to stimuli appearing at a previously cued location compared to un-cued locations when the stimulus onset asynchrony between target and cue is approximately 300-500 msec or longer. This phenomenon is known as spatial inhibition of return (IOR). Our previous study showed that IOR is impaired in patients with mild cognitive impairment (MCI) or mild Alzheimer’s disease (AD), and this impairment can be detected using a dual-cue IOR task paradigm (Jiang et al., PLOS ONE, 2021). Combining the dual-cue IOR paradigm and functional MRI, this study sought to identify key brain regions associated with the

spatial IOR effect and investigate probable neural mechanisms underlying IOR impairment in MCI/AD patients. Data from 14 MCI/AD patients (8 MCI and 6 early AD) and 39 demographically comparable controls revealed that IOR effect was associated with increased fMRI signal in a network of brain regions including the right supramarginal gyrus, the right intraparietal sulcus, the right frontal eye field, and the right insula. Moreover, a significant effect of the interaction between trial type and study group (MCI/AD vs controls) was observed within the right supramarginal region. Together, these findings support the involvement of the right inferior parietal lobe and other brain regions in IOR and suggest that IOR impairment in MCI/AD patients may be associated with neuronal dysfunction in the right supramarginal area - a region that has been implicated in early AD progression.

Disclosures: Z. Li: None. **K. Shattuck:** None. **C. Gallagher:** None. **J.J. Howard:** None. **R.S. Turner:** None. **X. Jiang:** None.

Poster

119. Alzheimer's Disease Clinical and Preclinical Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 119.14

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

Title: Cerebral metabolic changes and impaired blood-brain barrier precede amyloid beta deposition in the 5×FAD mouse model

Authors: *M. YAO[1], Z. WEI[2], Z. ZHANG[5], A. LI[6], R. LI[1], A. KAKAZU[1], H. LU[2], J. XU[6], W. DUAN[1,3,4];
[1]Div. of Neurobiology, Dept. of Psychiatry and Behavioral Sci., [2]The Russell H. Morgan Dept. of Radiology and Radiological Sci., [3]Solomon H. Snyder Dept. of Neurosci., [4]Program in Cell. and Mol. Med., Johns Hopkins Univ. Sch. of Med., Baltimore, MD; [5]Dept. of Biomed. Engin., Johns Hopkins Univ., Baltimore, MD; [6]F.M. Kirby Res. Ctr., Kennedy Krieger Res. Inst., Baltimore, MD

Abstract: Alzheimer’s disease (AD) is characterized by cerebral amyloid-β accumulation and progressive decline in cognitive function. Changes in brain energy metabolism arise in the preclinical phase of AD, suggesting an important metabolic component of early AD pathology. In addition, extant studies suggest that impairment of the blood-brain barrier (BBB) is intricately involved in the pathogenesis of AD. Reduced TCA cycle activity has been reported in AD mouse brain. By the time AD is clinically diagnosed, significant neuronal loss has already occurred and becomes irreversible. Therefore, the sensitive biomarkers reflecting early brain functional changes before neuronal loss will be critical for effective intervention. The goal of this study is to develop sensitive and human translatable biomarkers to indicate the early brain functional changes of AD. 3-month-old 5×FAD mice were examined using following magnetic resonance imaging (MRI) measures, including water extraction with phase-contrast arterial spin tagging (WEPCAST) to assess the BBB integrity, T2 relaxation under spin tagging (TRUST) and phase

contrast (PC) to assess cerebral metabolic rate of oxygen ($CMRO_2$), and creatine chemical exchange saturation transfer (CrCEST) to detect cerebral pH changes on a Bruker 11.7T scanner. We found breakdown in the BBB permeability to water, indicated by increased permeability surface area product ($p<0.05$, $n=10$) and water extraction fraction in premanifest 5×FAD mice ($p<0.01$, $n=10$). Moreover, decreased global oxygen extraction fraction ($p<0.05$, $n=10$), unit-mass $CMRO_2$ ($p<0.05$, $n=10$) and total $CMRO_2$ ($p < 0.05$, $n=10$) was manifested in these young 5×FAD mice, together with a relatively intact vascular function ($p=0.27$ for cerebral blood flow) and lack of neurodegeneration ($p=0.47$ for brain volume) at this age. In the CrCEST study, the pH value was significantly lower in the hippocampus of 3-month-old 5×FAD mice than that in the age- and gender-matched controls ($p<0.05$, $n=10$). No cognitive impairment and amyloid beta deposition were detectable in 5xFAD mice at this age. Our findings suggest that altered cerebral metabolism and compromised BBB permeability occur prior to brain hypoperfusion and cognitive decline in AD mice. Further validation of these MRI measures in other AD models and human subjects will benefit early diagnosis and facilitate effective therapeutic development for AD.

Disclosures: **M. Yao:** None. **Z. Wei:** None. **Z. Zhang:** None. **A. Li:** None. **R. Li:** None. **A. Kakazu:** None. **H. Lu:** None. **J. Xu:** None. **W. Duan:** None.

Poster

119. Alzheimer's Disease Clinical and Preclinical Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 119.15

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

Support: NIA U01AG051412-01
NICHD 065160
NICHD R01 AG053555

Title: Longitudinal Amyloid, Tau, and Neurodegeneration in Braak staging in Down syndrome

Authors: *L. TAYLOR[1], M. SATHISHKUMAR[1], L. MCMILLAN[1], E. HEAD[1], E. DORAN[1], M. MAPSTONE[1], I. LOTT[1], W. SILVERMAN[1], M. YASSA[1], D. NGUYEN[1], D. KEATOR[1], J.-B. POLINE[2], D. TUDORASCU[3], J. PRICE[4], M. PULSIFER[4], F. LAI[4], H. ROSAS[4], A. BRICKMAN[5], W. KREISL[5], N. SCHUPF[5], P. LAO[5];
[1]Univ. of California, Irvine, Irvine, CA; [2]Montreal Neurolog. Inst., Monreal, QC, Canada; [3]Univ. of Pittsburgh, Pittsburgh, PA; [4]Massachusetts Gen. Hosp., Harvard Univ., Boston, MA; [5]Columbia, New York, NY

Abstract: Alzheimer’s disease (AD) is the leading cause of death in older adults with Down syndrome (DS) population. However, there are limited longitudinal biomarker data in individuals with DS to better understand how AD pathologies progress during the disease. We investigated how longitudinal tau, amyloid-β (Aβ), and neurodegeneration progress during AD using Braak

staging and an ATN framework in a cohort of adults with DS.
Twenty-one adults with DS (51.45 ± 6.40 years; 16 males) from the Alzheimer's Disease in Down Syndrome (ADDS) Study were split into two groups: Affected (n = 11; dementia or mild cognitive impairment) or Unaffected (n = 10; no signs of dementia). All participants received three T1-weighted MRI, three Aβ florbetapir PET (18F-AV-45), and two tau flortaucipir PET (18F-AV1451) scans. Time intervals between respective scans were roughly 12-18 months. For PET scans, standard uptake value ratio (SUVR) maps were calculated using the cerebellar cortex as a reference region, and mean SUVR of regions of interest (ROI) according to Braak stage I-VI were calculated. For MRI, volumes of regions associated with Braak stage I-VI were calculated. Linear mixed models were used to determine slope of change in all three biomarkers, with adjustment for sex and time between scans in years. An interaction term for time between scans and groups (Affected vs. Unaffected) were computed for all ROIs.
Overall, only the affected group had significant slopes of change across all three biomarkers. For the Aβ biomarker, there was an increasing significant slope of change in Braak stage IV-VI (p values between .015 and .004). The tau biomarker also had an increasing significant slope of change in Braak stage III and IV (p values between .048 and .012). Finally, for MRI neurodegeneration, there was a significant interaction between group status and time between scans in Braak stage IV (p = .031).
While these data inform on the dynamics of biomarker change in AD pathogenesis in DS, they suggest that change in amyloid may continue to be dynamic well into later Braak stages. This is surprising given that amyloid deposits very early in DS. Future work with larger samples is needed to fully understand the dynamic nature of these biomarkers and how they interact in adults with DS.

Disclosures: L. Taylor: None. **M. Sathishkumar:** None. **L. McMillan:** None. **E. Head:** None. **E. Doran:** None. **M. Mapstone:** None. **I. Lott:** None. **W. Silverman:** None. **M. Yassa:** None. **D. Nguyen:** None. **D. Keator:** None. **J. Poline:** None. **D. Tudorascu:** None. **J. Price:** None. **M. Pulsifer:** None. **F. Lai:** None. **H. Rosas:** None. **A. Brickman:** None. **W. Kreisl:** None. **N. Schupf:** None. **P. Lao:** None.

Poster

119. Alzheimer's Disease Clinical and Preclinical Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 119.16

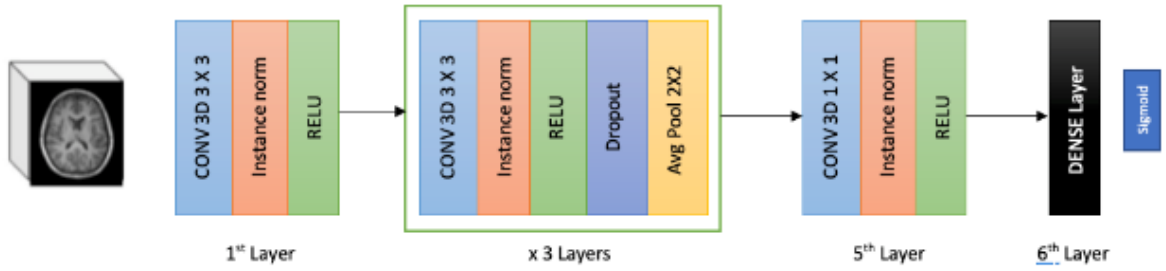
Topic: C.02. Alzheimer's Disease and Other Dementias

Support: AI4AD Grant U01AG068057

Title: Predicting Amyloid Positivity from Brain MRI using a 3D Convolutional Neural Network

Authors: *J. NAIK[1], T. CHATTOPADHYAY[2], D. KOMANDUR[1], S. I. THOMOPOULOS[2], P. M. THOMPSON[3];
[2]IGC, [1]USC, Los Angeles, CA; [3]Neurol., USC, Palos Verdes, CA

Abstract: An early indicator of Alzheimer's disease (AD)is abnormal accumulation of beta amyloid in the brain, which is assessed using PET or CSF samples - highly invasive procedures. As a precursor to such steps, we assessed the potential of predicting β-amyloid positivity (Aβ+) from the less invasive T1-weighted brain MRI scans, using a deep learning algorithm (convolutional neural network, or CNN).We analyzed 3D T1w MRI from 765 subjects (age:75.13+/- 7.6;397F/368M;) with a distribution of (459 CN/67 MCI/236 AD/3 Pending) from the ADNI dataset. The cut-off used, for determining amyloid levels, was based on PET cortical SUVR uptake (Aβ_1) determined by either mean 18F-florbetapir(Aβ+ defined as >1.11for cutoff) or florbetaben(Aβ+ defined as>1.20for cutoff), normalized by using a whole cerebellum reference region. After registering the T1w image to a common template, we split the data into independent training, validation and testing sets in the ratio 70:20:10. For training data augmentation(a typical step in deep learning), elastic deformation was used. The 3D CNN architecture was trained with a learning rate of 1e-4, and test performance was assessed using balanced accuracy. Youden's J index was used to decide the threshold (0.538ALL/ 0.538MCI,Dementia/0.512CN) to classify as 0/1for amyloid positivity during testing and compare it with Truth values**.** We obtained a balanced accuracy score of 0.815 for classifying Aβ+ when considering all subjects. When classifying Aβ+ in individuals with MCI and AD, we obtained a balanced accuracy score of 0.975. In cognitively unimpaired controls (CN), the balanced accuracy was low (0.631), as expected. Based on the Jack et al. model of AD, where brain amyloid accumulates before brain atrophy is evidenced on MRI, Aβ+ was harder to predict in controls than in MCI and AD, where changes in both PET and MRI are evident. Accuracy increased when using MRI-derived tissue maps of CSF as additional inputs, which indirectly indicate subtle brain atrophy. Balanced accuracy results were: CSF:0.815 > GM:0.775 > BiasCorrected:0.76 > WM:0.50.



Disclosures: **J. Naik:** None. **T. Chattopadhyay:** None. **D. Komandur:** None. **S.I. Thomopoulos:** None. **P.M. Thompson:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; PMT received a grant from Biogen, Inc., for research unrelated to this study..

Poster

119. Alzheimer's Disease Clinical and Preclinical Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 119.17

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

Support: Institutional Research Start-up from NEOMED
Institutional Research Start-up from ACH

Title: Changes in optic disc morphology across age and sex in the 3xtg Alzheimer's mouse model

Authors: *M. FUSILLO[1], G. FRAME[2], C. M. DENGLER-CRISH[3], M. A. SMITH[1]; [1]Northeast Ohio Med. Univ., Rootstown, OH; [2]Biomed. Sci., Northeast Ohio Med. Univ., Aurora, OH; [3]Pharmaceut. Sci., Northeast Ohio Med. Univ., Rootstown, OH

Abstract: The retina, as an extension of the central nervous system, has emerged as a prominent neural site impacted early in Alzheimer's disease (AD) pathology. In vivo applications and postmortem histology performed in animal and human subjects have identified several biochemical, neuroanatomical, and neurophysiological retinal occurrences that overlap with the main pathological hallmarks described in the AD brain. However, further study is necessary to better define the temporal relationship between changes occurring in the retina and optic nerve compared to cerebral changes and whether retinal biomarkers can help better diagnose and/or predict AD-related cognitive decline. Our prior work-studying pre-neurodegenerative events in glaucoma implicate alterations in retinal ganglion cell (RGC) axons occurring before the overt soma loss in the retina. Given the similarities between AD and glaucoma pathophysiology, we set out to characterize the morphological integrity of the optic nerve and RGCs axons in the 3xtg Alzheimer's mouse and the potential temporal relationship to cerebral pathological progression. Furthermore, we sought to determine whether changes in optic nerve morphology could be detected from retinal images derived from standard fundoscopy. A Micron IV ophthalmoscope was used to conduct fundoscopic imaging of 3xtg and C57BL/6J (C57) mice across three age groups representing pre- (2-4 months), emerging (8-10 months), and pervasively pathological (12+ months) disease states. Our results describe both a qualitative and quantitative difference in the size of the optic disc between 3xtg and C57 animals that varied based on sex and age. Most notably, twelve-month 3xtg mice had a significantly larger optic disc area compared to C57. In male mice, the 3xtg had increased optic disc area in both the 8-10 and 12+-month-old groups, while no significant difference was apparent in the 2-4-month-old groups. These changes may be able to provide a framework for understanding alterations in RGC axon morphology in the progression of AD.

Disclosures: **M. Fusillo:** None. **G. Frame:** None. **C.M. Dengler-Crish:** None. **M.A. Smith:** None.

Poster

119. Alzheimer's Disease Clinical and Preclinical Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 119.18

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

Support: CIHR 737107711

Title: Association between medial temporal lobe subregion volumes and cognitive assessment scores in healthy older adults

Authors: *N. MAZLOUM-FARZAGHI[1,2], M. D. BARENSE[1,2], J. D. RYAN[1,2], C. E. STARK[3], R. K. OLSEN[1,2];
[1]Univ. of Toronto, Toronto, ON, Canada; [2]Rotman Res. Inst., Toronto, ON, Canada; [3]Univ. of California Irvine, Irvine, CA

Abstract: Volumetric measures of specific subregions of the medial temporal lobe (MTL) have been found to be associated with neurodegeneration related to early stages of Alzheimer's disease (AD). However, it is less clear whether volumetric measures of MTL subregions can identify the earliest signs of atrophy prior to diagnosis of mild cognitive impairment, a condition that often progresses to AD. Current manual segmentation methods that are commonly used to measure the volume of MTL subregions are labour intensive and time consuming. Thus, automated methods have been proposed as a more efficient alternative. In the current study, we used a powerful automated segmentation software tool, Automated Segmentation of Hippocampal Subfields (ASHS), to detect the earliest signs of atrophy in MTL subregions of healthy older adults, as inferred by correlations with scores on the Montreal Cognitive Assessment (MoCA), a dementia screening test. The current study was motivated by previous work from our lab, in which using manual segmentation and a protocol developed in our lab (O-A-P protocol), we found that volumetric measures of the anterolateral entorhinal cortex, an MTL subregion where tau pathology consistently accumulates in early AD, were related to scores on the MoCA (M score = 26.63, SD = 2.86) in healthy older adults (N = 40, age range = 59-81 years, 30 female). In the current study, to assess whether automated methods could produce similar results, we trained ASHS on the O-A-P protocol and applied automated segmentation to the same group of healthy older adults as in our previous work. The automated segmentation resulted in three subfields of the hippocampus (CA_1, $DG/CA_{2/3}$, subiculum) and four MTL cortical regions (anterolateral entorhinal cortex, posteromedial entorhinal cortex, perirhinal cortex, and parahippocampal cortex). Using linear models, we found a significant positive association between MoCA and automated volume in the $DG/CA_{2/3}$ ($t = 2.73$, $p < 0.05$) and automated volume in the perirhinal cortex ($t = 2.47$, $p < 0.05$). In our previous work using manual segmentation, the association between $DG/CA_{2/3}$ and MoCA was marginal, and the association between perirhinal cortex and MoCA was non-significant. Moreover, unlike our previous work, we did not find a significant positive association between automated volume in the anterolateral entorhinal cortex and MoCA. Our study indicated that ASHS was able to align well with manual segmentation methods. However, the discrepancies between the automated and manual methods for the perirhinal cortex and the anterolateral entorhinal cortex could indicate the need for some refinement for the delineation of these regions.

Disclosures: **N. Mazloum-Farzaghi:** None. **M.D. Barense:** None. **J.D. Ryan:** None. **C.E. Stark:** None. **R.K. Olsen:** None.

Poster

119. Alzheimer's Disease Clinical and Preclinical Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 119.19

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

Support: NIH Grant K08AG058749
NIH Grant F32AG050434-01A1
NIH Grant K23 AG038357
NIH Great AG062196
NIH Grant DC017091
NIH Great DC176960
HillBlom Foundation Grant 2019-A-013-SUP

Title: Abnormal Gamma frequency phase-amplitude coupling associated with network hyperexcitability in Alzheimer's Disease

Authors: P. PRABHU[1,3], ***K. RANASINGHE**[4], H. MORISE[2,5], K. KUDO[2,5], L. B. HINKLEY[6], H. LERNER[4], D. MIZUIRI[2], A. LICATA[4], K. A. KOTEGAR[3], M. GORNO-TEMPINI[4], H. KIRSCH[4], J. F. HOUDE[2], K. A. VOSSEL[7,2], S. S. NAGARAJAN[2];
[1]Dept. of Radiology, [2]UCSF, San Francisco, CA; [3]Dept. of Data science and Computer Applications, Manipal Inst. of Technol., Manipal, India; [4]Dept. of Neurol., Univ. of California San Francisco, San Franciso, CA; [5]Med. Imaging Business Center, Ricoh Co. Ltd., Kanazawa, Japan; [6]Univ. of California, San Francisco, San Francisco, CA; [7]Univ. of California Los Angeles, Los Angeles, CA

Abstract: Alzheimer's disease (AD) carries an increased risk of seizures and subclinical epileptiform activity. Network hyperexcitability, which is the underlying phenomenon of epileptic manifestations, is thought to contribute to AD pathophysiological processes. Recently we demonstrated that a greater degree of neural synchronization deficits within delta-theta (2-8 Hz) and alpha (8-12 Hz) range of frequency oscillations are sensitive indicators of network hyperexcitability. Here, we sought to examine the high-frequency gamma-band deficits associated with network hyperexcitability in AD patients. Specifically, we quantified Phase Amplitude Coupling (PAC) between the amplitude of gamma oscillations (30-40 Hz); with the phase of 4-12 Hz oscillations. We used 60s resting-state magnetoencephalography (MEG) recordings from 50 AD patients (age, 60 ± 8 years) (n=20, with subclinical epileptiform activity, AD-EPI+; n=30 without subclinical epileptiform activity, AD-EPI-), and 35 age-matched controls (age, 64 ± 6 years). Resting-state MEG data is reconstructed in source space using LCMV beamforming. The source space data is mapped to the Desikan-Killany atlas to obtain 68 cortical regional level time courses. For each of the 68 regions, PAC is assessed by measuring the mean vector length between the amplitude of gamma oscillations (30-40 Hz) with the phase of 4-12 Hz oscillations (bin size=1, number of surrogates=200). For PAC obtained for each region, a permutation cluster test ($p<0.05$) was performed for statistical comparisons between

AD patients vs. age-matched controls and AD-EPI+ vs. AD-EPI-. Patients with AD showed significantly lower theta (4-8 Hz)-gamma coupling in the left parahippocampal. Importantly, this left parahippocampal theta-gamma coupling was significantly lower in AD-EPI- patients than in AD-EPI+. AD-EPI+ also showed lower-alpha (8-12Hz)-gamma coupling in the right parahippocampal region compared to AD-EPI-. The phase angle from the significant cluster shows that the mean phase angle for AD is different from Control and AD-EPI+ from AD-EPI-. These results not only identify gamma-band coupling deficits specifically localized to medial temporal regions, which are the earliest affected regions in AD pathophysiology, but also delineate the associated vulnerabilities of network hyperexcitability in AD.

Disclosures: P. Prabhu: None. **K. Ranasinghe:** None. **H. Morise:** None. **K. Kudo:** None. **L.B. Hinkley:** None. **H. Lerner:** None. **D. Mizuiri:** None. **A. Licata:** None. **K.A. Kotegar:** None. **M. Gorno-Tempini:** None. **H. Kirsch:** None. **J.F. Houde:** None. **K.A. Vossel:** None. **S.S. Nagarajan:** None.

Poster

119. Alzheimer's Disease Clinical and Preclinical Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 119.20

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

Support: P50 AG05146
P30 AG066507

Title: Posterior cingulate hypoactivation in mild cognitive impairment: an fMRI study of selective attention

Authors: L. CHEN[1], E. CHANG[1], H. MILLER[1], C. SPECK[1], N. RANI[1], C. CORONA-LONG[2], A. MOGHEKAR[1], M. ALBERT[1], *A. BAKKER[1];
[1]Johns Hopkins Univ. Sch. of Med., Baltimore, MD; [2]Johns Hopkins Univ. Sch. of Arts and Sci., Baltimore, MD

Abstract: In addition to the characteristic hippocampal network dysfunction and associated memory impairment, significant structural and functional changes have also been observed in the posterior cingulate cortex (PCC) in patients with Alzheimer’s disease (AD). Neuroimaging studies observed gray matter loss in the PCC in patients with mild cognitive impairment (MCI) and showed that the PCC is the earliest and most prominent area of metabolic decrement in MCI and AD dementia. The PCC is hypothesized to contribute to memory function and self-referential processing, evaluating personal relevance, meaning, and accuracy, also described as metamemory or subjective memory. However, the role of PCC dysfunction in cognitive impairments observed in patients with MCI remains unclear. In this study, we employed a Covert Orienting of Visual Attention Task (Covat) to examine PCC activation with functional magnetic resonance imaging (fMRI) in patients with MCI compared to cognitively normal control

participants (CN). The COVAT task assesses the ability to attend to visual stimuli appearing in the periphery of the visual field after congruent (valid), incongruent (invalid), or non-directional cues. The use of congruent directional cues in this task reduces reaction time and has been shown to generate robust fMRI activation in the PCC. Patients with MCI (mean age: 77.89±8.5y, 10M, 8F) did not significantly differ from CN (mean age: 75.04±5.9y, 13M, 14F) in accuracy ($t = 1.43$, $p = 0.16$) or reaction time ($t = 0.056$, $p = 0.96$) on the valid trials. A contrast of MCI patients and CN during valid congruent trials where a valid directional cue resulted in shorter reaction times (V+) showed a significant cluster of task related activation in the right PCC. In this cluster activation in MCI patients during the performance of V+ trials was significantly reduced compared to CN ($t = 2.82$, $p = 0.007$). MCI patients also showed significantly reduced activation during the invalid trials compared to CN ($t = 2.67$, $p = 0.01$). In fact, across all trial types, including rest trials, patients with MCI showed significantly reduced activation in the right PCC compared to CN ($t = 2.88$, $p = 0.006$). Confirmational analyses using an anatomical region of interest approach showed the same pattern of hypoactivity during the performance of the task in the PCC in patients with MCI compared to CN. Finally, activation in the right PCC was correlated with delayed recall on the Buschke Selective Reminding Task ($r = 0.45$, $p = 0.002$), ptau ($r = -0.37$, $p = 0.012$), and Ab42/40 ($r = 0.45$, $p = 0.004$). These findings show that hypoactivation of the PCC can be observed using fMRI and is associated with AD pathology and memory impairment in patients with MCI.

Disclosures: **L. Chen:** None. **E. Chang:** None. **H. Miller:** None. **C. Speck:** None. **N. Rani:** None. **C. Corona-Long:** None. **A. Moghekar:** None. **M. Albert:** None. **A. Bakker:** None.

Poster

119. Alzheimer's Disease Clinical and Preclinical Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 119.21

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

Title: Changes in resting-state functional connectivity in Alzheimer’s disease and mild cognitive impairment

Authors: *C. J. HUMPHRIES[1], J. BERO[1], Y. LI[1], A. KUMAR[1], S. NAG[1], H. LEE[1], D. LEE[2,1];
[1]Neurogazer USA, Towson, MD; [2]Neurosci., Johns Hopkins Univ., Baltimore, MD

Abstract: Alzheimer’s disease (AD) is a neurodegenerative disorder characterized by progressive cognitive decline that primarily affects older adults. Over the course of the disease, an increasing pattern of brain atrophy results in widespread loss of neuronal function and disruption of connectivity. In recent years, functional magnetic resonance imaging (fMRI) has proven to be a useful tool for measuring changes in brain function in a variety of different human neurological disorders. In the current study, we examined changes in the patterns of resting-state functional connectivity measured using fMRI in subjects diagnosed with AD, mild cognitive

impairment (MCI), and age-matched controls. Structural and functional MRI scans were downloaded from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database. A selection of 188 subjects were used in the analysis, which included 40 AD, 63 MCI, and 85 Controls. MRI processing was conducted using AFNI and included motion correction, registration, normalization, artifact removal using CompCore, and estimation of regions of interest (ROI) time courses using the Schaefer 400 parcellation. Pearson correlation scores were calculated between each ROI and the rest of the brain. A mean correlation value was then estimated for each ROI. These scores were then compared between subject groups using a two-sample t-test. The results showed a reduction in mean correlation in the MCI compared to the Control group bilaterally in the inferior parietal lobule, temporal pole, and prefrontal cortex and an increase in correlation in the visual and somatomotor cortices. In the comparison between AD and Controls, a reduction in correlation in the AD group was observed in the temporal pole and superior temporal lobe and an increase in correlation was observed in somatomotor cortex and the dorsal attention network. The findings suggest that the pattern of functional connectivity for the association cortical areas changes during the course of progression to AD.

Disclosures: **C.J. Humphries:** A. Employment/Salary (full or part-time):; Neurogazer USA Inc. **J. Bero:** A. Employment/Salary (full or part-time):; Neurogazer USA Inc. **Y. Li:** A. Employment/Salary (full or part-time):; Neurogazer USA Inc. **A. Kumar:** A. Employment/Salary (full or part-time):; Neurogazer USA Inc. **S. Nag:** A. Employment/Salary (full or part-time):; Neurogazer USA Inc. **H. Lee:** A. Employment/Salary (full or part-time):; Neurogazer Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neurogazer Inc. **D. Lee:** A. Employment/Salary (full or part-time):; Neurogazer Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neurogazer Inc..

Poster

119. Alzheimer's Disease Clinical and Preclinical Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 119.22

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

Support: NIA Grant F32AG054116
NIA Grant AG034570

Title: Neural correlates of a naturalistic mnemonic discrimination task with implications for Alzheimer's disease

Authors: *L. A. FERGUSON[1], C. M. BANNIS[1], J. B. BUERGLER[1], W. J. JAGUST[2], S. L. LEAL[1];
[1]Rice Univ., Houston, TX; [2]Helen Wills Neurosci Inst., Univ. of California, Berkeley, CA

Abstract: Aging is associated with declines in episodic memory, although emotional memory is relatively spared. The medial temporal lobe (MTL), which contains the hippocampus, amygdala, and surrounding cortices, is especially vulnerable to aging and Alzheimer's disease (AD). The hippocampus is thought to perform two key computations that may be particularly sensitive to early age- and AD-related changes in the MTL: pattern separation, or the ability to distinguish between overlapping events. and pattern completion, or the ability to remember an event when given a partial cue. Mnemonic discrimination tasks have been developed to tax hippocampal pattern separation through the inclusion of lure stimuli, which are similar but not identical images to previously seen images. In the current study, we expanded upon traditional mnemonic discrimination tasks by incorporating more naturalistic study elements: video stimuli to mimic real-world experiences, a range of neutral and emotional stimuli, as well as including both immediate and 24-hour delay memory tests to measure forgetting. We assessed the neural correlates underlying performance on the mnemonic discrimination task in young adults and cognitively normal older adults utilizing high-resolution structural and functional MRI, [^{11}C]Pittsburgh Compound B (PIB) PET to measure global beta-amyloid in the brain, and [^{18}F]AV-1451 PET to measure tau pathology in the MTL. Preliminary results show that higher amyloid burden in cognitively normal older adults was associated with more forgetting of positive relative to neutral lures after a 24-hour delay, as well as less forgetting of negative lures. These effects were selective to measures of forgetting and to emotional stimuli. In contrast, greater MTL tau burden was correlated with worse neutral lure discrimination when tested immediately. However, there was no relationship between tau and forgetting, and the effects were selective to neutral stimuli. These opposing relationships between memory and AD pathology for emotional content and memory delay may be due to differing patterns of cortical spread. Amyloid begins to accumulate in the neocortex, which is involved in memory consolidation after longer delays. Tau accumulates in the MTL early in disease progression, which is essential for memory encoding and retrieval. Thus, there may be differential effects of amyloid and tau pathology on memory processes.

Disclosures: L.A. Ferguson: None. **C.M. Bannis:** None. **J.B. Buergler:** None. **W.J. Jagust:** None. **S.L. Leal:** None.

Poster

119. Alzheimer's Disease Clinical and Preclinical Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 119.23

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

Title: Patients with Alzheimer's Disease Die More Frequently Than Other Patients During the Emergency Department and Subsequent Admission to Hospital

Authors: *T. H. ALKAM;
Save Alzheimer's In Emergency Room Inc., Pomona, CA

Abstract: Background: Patients with dementia have an average 2 to 8 additional comorbidities which may accelerate progression of cognitive and functional impairments in the under-diagnosed and under- treated conditions. Patients with dementia who visit the emergency departments (ED) more frequently are hospitalized more often than patients without dementia and have higher mortality after an ED visit than patients without dementia.
Methods: The Nationwide Emergency Department Sample (NEDS) for the years 2006-2010 was used for the present study. All samples with a diagnosis of Alzheimer's disease (AD) or any of 18 comorbidities in the listed (n=15) ICD-9 diagnoses, and patients aged 55 years and above (35,429,235 samples) were included. The frequencies of 18 comorbidities being listed with the AD diagnoses in the died-in-visit AD sample and their impacts on the likelihood of AD patients died-in-visit were investigated.
Results: In the whole sample, the mean age was 71.33 years, 57.2% were female. The number of patients with AD is 754011 (2.1%). Hypertension is the most frequent diagnosis in total samples (14343260, 40.5%) and in AD samples (379507, 50.3%). The number of total patients died-in-visit is 672722 (1.8%). The number of total AD patients died-in-visit is 26603 (4.0%). Hypertension is the most frequent diagnosis in total samples (40.5%) and in AD samples (50.3%); As for died-in-visit AD samples, dysrhythmias (52.5%) is the most frequent diagnosis followed by hypertension (30.3%), atherosclerosis (23.1%), chronic heart disease (12.7%) hypotension (8.6%), COPD (8.3%), brain hemorrhage (4.2%), and asthma (3.9%). AD patients have increased likelihood of dying with brain hemorrhage (OR=7.06; 95% CI, 6.51 - 7.65, $p<0.001$), hypotension (OR=2.49; 95% CI, 2.36 - 2.63, $p<0.001$), dysrhythmias (OR=2.48; 95% CI, 2.40 - 2.55, $p<0.001$), gastrointestinal ulcer (OR=1.26; 95% CI, 1.02 - 1.55, $p=0.032$), diabetes mellitus (OR=1.21; 95% CI, 1.16 - 1.27, $p<0.001$), and atherosclerosis (OR=1.08; 95% CI, 1.04 - 1.13, $p<0.001$).
Conclusions: cardiovascular comorbidities are overwhelmingly common in AD patients died-in-visit after being admitted to ED. Screening newly admitted AD patients in ED for these comorbidities may help address them early and reduce the likelihood of dying-in-visit.

Disclosures: T.H. Alkam: None.

Poster

119. Alzheimer's Disease Clinical and Preclinical Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 119.24

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

Support: R01AG058533-01A1

Title: Relationship between hippocampal 18F-PI-2620 uptake and hippocampal high resolution subregion volumes in nondemented older adults

Authors: K. V. WHEELER[1], N. LEE[1], B. J. HALL[1], A. M. TWISSELMANN[1], M. A. TUBI[1], J. TERNER[1], N. HAZRA[1], E. MATSIYEVSKIY[1], A. W. TOGA[2], S. E. O'BRYANT[3], M. N.

BRASKIE[1];
[1]Imaging Genet. Ctr., USC, Marina del Rey, CA; [2]USC Stevens Neuroimaging and Informatics Inst., USC, Los Angeles, CA; [3]Hlth. Sci. Ctr., Univ. of North Texas, Fort Worth, TX

Abstract: Accumulation of hyperphosphorylated tau tangles occurs in nondemented older adults and is a key component of Alzheimer's disease (AD). Tau accumulation begins in the entorhinal cortex (Braak stage I) and progresses to the hippocampus (Braak stage II), amygdala, parahippocampal, fusiform, and lingual gyri (Braak stage III), with late staging (III-VI) often being associated with cognitive symptoms. Tau positron emission tomography (PET) neuroimaging quantifies *in vivo* spatial tau distribution. Smaller hippocampal subregional volumes measured by MRI may be early and sensitive markers of preclinical AD. Few studies have examined the relationships between tau staging and early neurodegeneration markers in nondemented older adults, particularly in ethnically diverse samples, reducing the generalizability of results. Using the 18F-PI-2620 (PI2620) PET ligand, we investigated associations between regional tau associated with Braak stages I, II, and III and hippocampal body subregion volumes (CA1, combined CA2, CA3, and dentate gyrus (CA23DG), and subiculum) in a cohort of non-Hispanic White (NHW) and Mexican American (MA) nondemented older adults. In a sample of 50 subjects (mean age 67; 24 males and 26 females; 31 NHW and 19 MA) from the Health & Aging Brain- Health Disparities Study who were cognitively normal at baseline, we acquired T2-weighted hippocampal high resolution (HHR) MRI and PI2620 PET scans 2 years following baseline. We used multiple linear regressions to measure associations between tau uptake and HHR volumes, adjusting for age, sex, years of education, intracranial volume, and number of MRI slices segmented. We corrected for multiple comparisons across regions of interest by using false discovery rate (FDR) adjustments. Our results showed higher Braak II tau PET signal was associated with lower mean bilateral subiculum volume (FDR-adjusted p=0.0498, t= -2.51). Further investigation into subiculum relationships in each hemisphere found a negative association between Braak II tau PET signal and left subiculum volume (uncorrected p=0.012, t= -2.63). We found a trend level negative association between Braak III tau PET signal and mean bilateral CA23DG volume (FDR-adjusted p= 0.092, t= -2.24). Our results align with previous literature that relates tau pathology to neurodegeneration and reports subiculum volume as an early AD biomarker. Findings in Braak stage III may highlight the effects of tau or shared stressors on hippocampal neurodegeneration. Our findings provide insight into Braak stages II and III tau pathology and hippocampal subregion volumes in a nondemented and ethnically diverse sample.

Disclosures: K.V. Wheeler: None. **N. Lee:** None. **B.J. Hall:** None. **A.M. Twisselmann:** None. **M.A. Tubi:** None. **J. Terner:** None. **N. Hazra:** None. **E. Matsiyevskiy:** None. **A.W. Toga:** None. **S.E. O'Bryant:** None. **M.N. Braskie:** None.

Poster

119. Alzheimer's Disease Clinical and Preclinical Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 119.25

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

Title: Diffusion MRI and machine learning distinguish Alzheimer's disease and dementia with Lewy bodies

Authors: *R. CHEN[1], W.-E. WANG[2], A. BARMPOUTIS[3], D. E. VAILLANCOURT[2,1];
[1]Biomed. Engin., [2]Applied Physiol. and Kinesiology, [3]Digital Worlds Inst., Univ. of Florida, Gainesville, FL

Abstract: Freewater imaging is a noninvasive diffusion imaging metric that is associated with neurodegeneration and neuroinflammation. Freewater imaging has been used to successfully differentiate Parkinsonian disorders, and can be leveraged in the domain of dementia (i.e., Alzheimer's disease (AD) and dementia with Lewy body (DLB)). Like Parkinsonian disorders, dementias are difficult to differentiate in the early stages of diseases. AD and DLB are two of the most common variants of dementia, with DLB often misdiagnosed as AD. The main objective of this study was to develop a support vector machine learning model to discriminate between dementia variants and healthy age-matched controls (HC). The three comparisons evaluated in the studies are AD vs DLB, AD vs HC, and DLB vs HC. We used diffusion MRI from 273 retrospective subjects to identify regions of interest on freewater maps. We developed a training and validation cohort for each comparison, using 80% of the data. We test each comparison using the area under the curve (AUC) of the receiver operator characteristic (ROC) curve as a metric of diagnostic selectivity. Freewater is elevated in the brainstem and in corticospinal, thalamic, and cerebellar tracts in DLB compared to AD and HC. Freewater is elevated in the temporal and insular cortex and around the lateral ventricles in AD compared to DLB and HC. In the test cohorts for each comparison, the AUCs were above 0.80. This study indicates that freewater imaging can aid in the differentiation of dementias with similar clinical presentation.

Disclosures: R. Chen: None. **W. Wang:** None. **A. Barmpoutis:** None. **D.E. Vaillancourt:** None.

Poster

119. Alzheimer's Disease Clinical and Preclinical Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 119.26

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

Support: the James S. McDonnel Foundation
NIH grant R01 AG063930

Title: Independent effects of Alzheimer’s disease dementia severity and aging on functional brain network organization at rest

Authors: *Z. ZHANG[1], M. Y. CHAN[1], L. HAN[1], C. A. CARRENO[2], E. WINTER-NELSON[1], G. S. WIG[1,3];

[1]Ctr. for Vital Longevity, Univ. of Texas at Dallas, Dallas, TX; [2]Fralin Biomed. Res. Inst., Virginia Tech. Carilion, Roanoke, VA; [3]Dept. of Psychiatry, Univ. of Texas Southwestern Med. Ctr., Dallas, TX

Abstract: Alzheimer's disease (AD) is the most common cause of dementia. Aging is the biggest risk factor for developing late-onset AD (Hebert et al., 2013). Age and AD are associated with less segregated resting-state functional brain networks (Wig, 2017). A debate exists about whether the process of AD dementia shares commonality with the aging process. We tested this hypothesis by comparing the effects of AD dementia severity and age on resting-state brain system segregation.

Participants included in this study are part of the Alzheimer's Disease Neuroimaging Initiative (ADNI). We used clinical dementia rating (CDR) as a measure to quantify AD dementia severity (Morris, 1993). The subject group of this study contained 190 healthy (CDR = 0) adults, 85 very mild dementia (CDR = 0.5), 20 mild dementia (CDR = 1) and 2 moderate dementia (CDR = 2) patients. The age of the sample ranged from 55 to 96.

To generate functional brain networks for each subject, we first preprocessed and motion-corrected their resting-state fMRI time series. Network nodes were defined using a boundary mapping method (Chan et al., 2014; Wig et al., 2014) and were assigned to pre-defined functional systems (Power et al., 2011). Network edges were Fisher's z-transformed correlations between time series of each pair of nodes. Brain system segregation was calculated to quantify functional brain network organization for each subject (Chan et al., 2014).

We performed multiple linear regression analyses to evaluate how brain system segregation varies in relation to an individual's CDR status and age, with sex, education, APOE4 status, head motion, respiration and heart rate included as covariates. CDR (b=-.043, p=.002) and age (b=-.0016, p=.003) were negatively related to whole-brain system segregation. Further examination revealed that while both CDR (b=-.035, p=.008) and age (b=-.002, p<.001) were negatively related to association system segregation, only CDR (b=-.053, p=.001) was negatively correlated with sensory-motor system segregation (age: b=-.0008, p=.18). The dementia-related differences in sensory-motor system segregation were driven by specific systems including the hand (b=-.069, p=.014) and mouth (b=-.086, p=.012) somato-motor systems. The interaction between CDR and age was not significant for whole-brain (b=.001, p = .55), sensory-motor (b=.003, p =.13) or association system segregation (b=.0007, p=.67). These findings demonstrate that age and AD dementia severity are independently related to altered functional network organization. Aging and dementia may exert impacts on unique and non-overlapping sets of functional brain systems.

Disclosures: Z. Zhang: None. **M.Y. Chan:** None. **L. Han:** None. **C.A. Carreno:** None. **E. Winter-Nelson:** None. **G.S. Wig:** None.

Poster

119. Alzheimer's Disease Clinical and Preclinical Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 119.27

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

Support: U19 AG068054
U01 AG051412

Title: Association Between Regional tau Accumulation and Memory Performance in Adults with Down Syndrome

Authors: *N. QUEDER[1], D. B. KEATOR[2], L. MCMILLAN[1], M. SATHISHKUMAR[1], L. TAYLOR[1], E. DORAN[5], D. NGUYEN[5], C. HOM[2], J. PRICE[6], H. D. ROSAS[6], P. J. LAO[7], A. M. BRICKMAN[7], N. SCHUPF[7], W. SILVERMAN[5], I. T. LOTT[5], E. HEAD[3], M. MAPSTONE[4], M. A. YASSA[1,2,4];
[1]Dept. of Neurobio. and Behavior and Ctr. for the Neurobio. of Learning and Memory, [2]Dept. of Psychiatry and Human Behavior, [3]Dept. of Pathology & Lab. Med., [4]Dept. of Neurol., Univ. of California, Irvine, Irvine, CA; [5]Dept. of Pediatrics, Univ. of California, Irvine Med. Ctr., Orange, CA; [6]Massachusetts Gen. Hosp., Harvard Univ., Boston, MA; [7]Dept. of Neurol., Columbia Univ., New York, NY

Abstract: Down syndrome (DS) is the most common genetic cause of Alzheimer's disease (AD). Similar to late onset AD, the severity of tau pathology is correlated with cognitive deterioration in adults with DS. Here, we assess regional tau accumulation in the hippocampus, entorhinal cortex, and regions associated with Braak stages I-VI in adults with DS and further investigate the association between tau in our regions of interest (ROIs) and memory performance.

We used 18F-AV-1451 (flortaucipir) PET scans to assess the extent of tau accumulation in 40 participants enrolled in the multi-site Alzheimer's Disease in Down syndrome study (ADDS) (age 48.96 +/- 6.07). Memory was measured with the modified Cued Recall Test. We used ANOVA to assess tau standardized uptake value ratio (SUVR) between the hippocampus, entorhinal cortex, and primary motor cortex as a control region, and subsequently assessed the six Braak stages. We further evaluated the relationship between tau SUVRs in our ROIs and memory performance. Sex and scanner site were used as covariates.

Tau SUVRs in the entorhinal cortex and hippocampus were higher compared with the primary motor cortex ($F(2,135)=36.26$, $p<.001$). Additionally, we found significant differences across the six Braak stages ($F(5,276)=7.907$, $p<.001$), with the highest overall SUVR values in regions associated with Braak stages I and II. Higher tau SUVRs in the entorhinal cortex and hippocampus were associated with lower scores on free recall ($r=0.43$, $p<.001$ and $r=0.44$, $p<.001$, respectively) and total recall ($r=0.46$, $p<.001$ and $r=0.42$, $p<.001$, respectively). No association was found between tau in the motor control region and memory performance. Higher tau SUVR in regions Braak stages I-V were associated with lower free recall (stage I: $r=0.43$, $p<.001$; stage II: $r=0.44$, $p<.001$; stage III: $r=0.40$, $p<.001$; stage IV: $r=0.44$, $p<.001$; stage V: $r=0.31$, $p<.01$) and total recall (stage I: $r=0.46$, $p<.001$; stage II: $r=0.42$, $p<.001$; stage III: $r=0.42$, $p<.001$; stage IV: $r=0.50$, $p<.001$; stage V: $r=0.35$, $p<.01$). No association between memory performance and tau SUVR was found in Braak stage VI regions.

Increased levels of tau in the entorhinal cortex and the hippocampus in early Braak stages are associated with worse memory performance in older adults with DS, consistent with observations in late-onset AD. Future analyses will focus on investigating the progression of tau in association with longitudinal memory decline in DS.

Disclosures: **N. Queder:** None. **D.B. Keator:** None. **L. McMillan:** None. **M. Sathishkumar:** None. **L. Taylor:** None. **E. Doran:** None. **D. Nguyen:** None. **C. Hom:** None. **J. Price:** None. **H.D. Rosas:** None. **P.J. Lao:** None. **A.M. Brickman:** None. **N. Schupf:** None. **W. Silverman:** None. **I.T. Lott:** None. **E. Head:** None. **M. Mapstone:** None. **M.A. Yassa:** None.

Poster

119. Alzheimer's Disease Clinical and Preclinical Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 119.28

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

Support: U24AG061340
U54AG065187

Title: Agora: an open platform for exploration of Alzheimer's disease evidence

Authors: ***J. S. BRITTON**[1], J. GLOCKLEY[2], L. BRADIC[1], M. S. FAZZA[1], M. COURVILLE[3], J. HENDRICKSON[1], K. DO[1], N. GROSENBACHER[1], S. SIMON[1], D. S. ALUTHGAMAGE[1], C. E. ALVARADO[3], J. HODGSON[1], A. K. GREENWOOD[1];
[1]Sage Bionetworks, Seattle, WA; [2]Cajal Neurosci., Seattle, WA; [3]GenUI, Seattle, WA

Abstract: Safe and effective therapies for treating Alzheimer's Disease (AD) are urgently needed. Many promising new AD targets have been identified using discovery-based research approaches; however, validation of these targets, development of new experimental reagents, and the advancement of promising new therapeutics require efforts that span many research groups. Agora is an open platform for publicly sharing information about new AD targets with the broader AD research community. Agora aggregates information and experimental resources about nascent AD targets, including a list of over 600 targets nominated by the Accelerating Medicines Partnership in AD (AMP-AD) consortium and by the broader AD research community. Agora also presents interactive visualizations designed to enable non-bioinformaticians to explore data from RNAseq, proteomic, and metabolomic studies. Recent updates to Agora include 1) presentation of target ranking scores based on genomic, genetic, and literature evidence developed by the Target Enablement to Accelerate Therapy Development for AD (TREAT-AD) consortium and 2) a new exploration interface that enables the visual comparison of study data across multiple targets. Agora is a platform to enable the AD research community to unite around promising target hypotheses. Agora is available at https://agora.adknowledgeportal.org.

Disclosures: **J.S. Britton:** None. **J. Glockley:** None. **L. Bradic:** None. **M.S. Fazza:** None. **M. Courville:** None. **J. Hendrickson:** None. **K. Do:** None. **N. Grosenbacher:** None. **S. Simon:** None. **D.S. Aluthgamage:** None. **C.E. Alvarado:** None. **J. Hodgson:** None. **A.K. Greenwood:** None.

Poster

119. Alzheimer's Disease Clinical and Preclinical Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 119.29

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

Support: U54AG054345

Title: The Model AD Explorer: an interactive, open access dashboard sharing phenotypic and gene expression data from Alzheimer's mouse models

Authors: *J. M. HENDRICKSON[1], S. GELFAND[1], R. PANDEY[2], R. YAXLEY, III[1], A. GOMEZ-ARBOLEDAS[3], G. MILINKEVICIUTE[3], J. S. BRITTON[1], N. REZAIE[3], A. UYAR[2], A. L. OBLAK[4], J. MINCER[5], M. A. PETERS[1], A. VANDER LINDEN[1], J. SCHNEIDER[1], M. S. FAZZA[1], A. MORTAZAVI[3], F. M. LAFERLA[3], A. J. TENNER[3], B. T. LAMB[6], K. GREEN[3], G. W. CARTER[3], A. K. GREENWOOD[1];
[1]Sage Bionetworks, Seattle, WA; [2]The Jackson Lab., Bar Harbor, ME; [3]Univ. of California, Irvine, Irvine, CA; [4]Indiana University–Purdue Univ. Indianapolis, Indianapolis, IN; [5]Univ. of Utah, Salt Lake City, UT; [6]Indiana Univ., Bloomington, IN

Abstract: Identifying a representative mouse model for target validation and preclinical testing is a significant impediment to the advancement of basic research discoveries in Alzheimer's disease (AD). Numerous challenges contribute to the inability to identify ideal model systems, including lack of standardized phenotypic measures, lack of mice that fully replicate features of late-onset human disease, and licensing requirements, among others. To counter these issues, the Model Organism Development and Evaluation for Late-onset Alzheimer's Disease (MODEL-AD) consortium has developed new mouse strains that more faithfully model late-onset, sporadic AD, making these available, without restrictions, to the research community. Mice are phenotyped at several ages with a standardized, robust pipeline, and data are openly available at the AD Knowledge Portal. To facilitate the evaluation of phenotypic and gene expression data, we have developed the Model AD explorer (https://modeladexplorer.org/), an interactive dashboard, to enable the exploration of summarized phenotypic data. The Explorer shows pathology and gene expression data from 17 different mouse models. In addition, quantification based on immunostaining is shown for amyloid plaques, astrocytes, dystrophic neurites, and microglia. There are two ways to use the gene expression explorer: 1) using the selected gene explorer as a comparison tool for comparing expression across models, ages, and sex, or 2) viewing all differentially expressed genes simultaneously across the selected mouse model as a function of age and sex. A final explorer illustrates the similarity of expression changes in mouse models and human AD cases. After evaluating phenotypic changes and a subsequent selection of a model of interest, a user can find further information by visiting the Jackson Laboratory website. In the future, the Model AD Explorer will include updates concerning new phenotypic data from additional MODEL-AD mouse strains.

Disclosures: **J.M. Hendrickson:** None. **S. Gelfand:** None. **R. Pandey:** None. **R. Yaxley:** None. **A. Gomez-Arboledas:** None. **G. Milinkeviciute:** None. **J.S. Britton:** None. **N. Rezaie:**

None. **A. Uyar:** None. **A.L. Oblak:** None. **J. Mincer:** None. **M.A. Peters:** None. **A. Vander Linden:** None. **J. Schneider:** None. **M.S. Fazza:** None. **A. Mortazavi:** None. **F.M. LaFerla:** None. **A.J. Tenner:** None. **B.T. Lamb:** None. **K. Green:** None. **G.W. Carter:** None. **A.K. Greenwood:** None.

Poster

119. Alzheimer's Disease Clinical and Preclinical Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 119.30

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

Support: AG014449
AG072599
AG074004
AG017617

Title: Down syndrome mice display a gene expression profile of vulnerability within basal forebrain cholinergic neurons that is markedly attenuated by maternal choline supplementation

Authors: *M. J. ALLDRED[1,2], H. PIDIKITI[1], A. LABUZA[1,2], A. HEGUY[3], P. ROUSSOS[1,6], S. D. GINSBERG[1,2,4,5];
[1]Ctr. for Dementia Res., Nathan Kline Inst., Orangeburg, NY; [2]Dept. of Psychiatry, [3]Genome Technol. Ctr., [4]Dept. of Neurosci. & Physiol., [5]NYU Neurosci. Inst., New York Univ. Grossman Sch. of Med., New York, NY; [6]Genet. & Genomic Sciences, Psychiatry, Inst. for Data Sci. and Genomic Technol., Icahn Sch. of Med. at Mount Sinai, New York, NY

Abstract: Basal forebrain cholinergic neuron (BFCN) degeneration is a hallmark of Down syndrome (DS) and Alzheimer's disease (AD). Current therapeutics have been unsuccessful in slowing disease progression, likely due to complex pathological interactions and dysregulated pathways that are poorly understood. The Ts65Dn trisomic mouse model recapitulates both cognitive and morphological deficits of DS and AD, including BFCN degeneration. We performed high-throughput, single population RNA sequencing (RNA-seq) and bioinformatic inquiry to interrogate transcriptomic changes in BFCNs within the medial septal nucleus at 6 months of age (MO), using laser capture microdissection to individually isolate ~500 choline acetyltransferase-immunopositive neurons in Ts65Dn and normal disomic (2N) mice, in conjunction with maternal choline supplementation (MCS) delivered to dams from conception to weaning. Ts65Dn mice had unique medial septal nucleus BFCN transcriptomic profiles at ~6 MO clearly differentiating them from 2N mice, in which a significant subset were offset by MCS. Leveraging Ingenuity Pathway Analysis (IPA) and KEGG analysis, we linked differentially expressed gene (DEG) changes within BFCNs to several canonical pathways (e.g., glutamatergic, GABAergic, and cholinergic) and aberrant physiological functions which were attenuated by MCS. We also identified neurological disorders via IPA and Gene Ontology analyses that are linked to aberrant behavior in DS mice that show underlying gene expression

changes effected by MCS. Taken together, the beneficial impact of MCS on dysregulated transcriptomic profiles of trisomic BFCNs enables mechanistic insight into molecular underpinnings of the observed behavioral changes seen in this well-established murine model of DS and AD. Via single population RNA-seq and bioinformatic inquiry, we demonstrate MCS, a low cost, easily administered therapeutic, may provide lifelong benefits, possibly through an epigenetic mechanism, to ameliorate cognitive decline associated with human DS and AD.

Disclosures: **M.J. Alldred:** None. **H. Pidikiti:** None. **A. Labuza:** None. **A. Heguy:** None. **P. Roussos:** None. **S.D. Ginsberg:** None.

Poster

119. Alzheimer's Disease Clinical and Preclinical Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 119.31

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

Support: NIH Grant PO1AG014449
NIH Grant RO1AG017617
NIH Grant P30AG072931
Arizona Alzheimer’s Consortium, Barrow Neurological Institute

Title: Posterior cingulate RNA seq reveals an expression profile of resilience in cognitively intact elders

Authors: *E. J. MUFSON[1], C. KELLEY[1], W. LIANG[2], S. E. COUNTS[3], S. GINSBERG[4]; [1]Translational Neurosciences, Barrow Neurolog. Inst., Phoenix, AZ; [2]TGen, Phoenix, AZ; [3]Departs of Translational Neurosci. and Family Med., Michigan State Univ., East Lansing, MI; [4]Neurosci. & Physiol. and, Psychiatry, Ctr. for Dementia Research, Nathan Kline Institute, Orangeburg, NYU, NYU, NY

Abstract: The posterior cingulate cortex (PCC), a hub of the default mode network, underlies autobiographical memory retrieval and shows hypometabolic changes early in Alzheimer disease (AD). To gain an unbiased understanding of molecular mechanisms in the aged PCC that might influence AD pathogenesis, we performed RNA sequencing on tissue obtained from the Rush Religious Orders Study (11 males/15 females; aged 76-96 years) with a premortem clinical diagnosis of no cognitive impairment and postmortem neurofibrillary tangle Braak stages I/II, III or IV. Transcriptomic data collected using next-generation sequencing of RNA generated an average of 60 million paired reads per case. Normalized expression of RNA-seq data was calculated using a global gene annotation and a microRNA profile. Differential expression using Braak staging as the comparison structure isolated genes for dimensional scaling, associative network building, and functional clustering. Curated genes were associated with the Mini Mental State Examination and performance scores (i.e., semantic, working and episodic memory, visuospatial ability and a composite Global Cognitive Score) from each participant. Co-

expression networks with microRNAs and an overlap of transcription factor binding sites determined regulatory mechanisms. Analysis revealed 750 genes and 12 microRNAs significantly differentially expressed between Braak stages I/II and III/IV and an associated 6 groups of transcription factor binding sites. Inputting significantly different gene/network data into a functional annotation clustering model revealed elevated presynaptic, postsynaptic, and ATP-related expression in Braak stages III and IV compared to stages I/II, suggesting these key pathways are integral for cognitive resilience seen in the elderly nondemented cases. Results also suggest cognitive reserve and resilience likely involves synaptic and metabolic pathway expression that increases across Braak stages III and IV as a potential compensatory response to age-related cortical denervation. Although Braak stage was not associated with cognitive function in this cohort, upregulation of synaptic genes positively correlated with visuospatial perceptual orientation tasks. Given the upregulation of these synaptic and neuronal metabolic/homeostatic transcripts in cognitively intact elders displaying elevated AD pathology, we posit that these pathways represent innate compensatory mechanisms associated with cognitive resilience/reserve that may be amenable to therapy for at-risk individuals as part of personalized medicine.

Disclosures: **E.J. Mufson:** None. **C. Kelley:** None. **W. Liang:** None. **S.E. Counts:** None. **S. Ginsberg:** None.

Poster

119. Alzheimer's Disease Clinical and Preclinical Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 119.32

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

Support: AG014449
AG017617
AG072599
AG074004

Title: Expression profiling and bioinformatics of homogeneous populations of frontal cortex pyramidal neurons from Alzheimer’s disease and age-matched controls.

Authors: *A. LABUZA[1,2], M. J. ALLDRED[1,2], H. PIDIKITI[1], A. HEGUY[3], P. D. COLEMAN[6], E. J. MUFSON[7,8], S. D. GINSBERG[1,2,4,5];
[1]Ctr. for Dementia Res., Nathan S Kline Inst., Orangeburg, NY; [2]Psychiatry, [3]Genome Technol. Ctr., [4]Neurosci. & Physiol., [5]NYU Neurosci. Inst., New York Univ. Grossman Sch. of Med., New York, NY; [6]Biodesign Inst., ASU-Banner Neurodegenerative Res. Ctr., Tempe, AZ; [7]Neurobio., [8]Neurol., Barrow Neurolog. Inst., Phoenix, AZ

Abstract: A daunting and unfulfilled challenge is understanding the complex pathobiology underlying Alzheimer’s disease (AD). AD is an irreversible, age-related neurodegenerative brain

disorder affecting an estimated 6.2 million Americans responsible for the gradual and insidious failure of cognitive function. AD is now a recognized spectrum disorder with pathology onset decades prior to clinical symptoms. Currently, confirmed diagnosis requires postmortem neuropathological evaluation. So far, FDA approved treatments have not arrested or prevented the onset of AD. Therefore, there is an urgent need to identify molecular and cellular mechanism(s) underlying AD, which could lead to novel therapeutics. There are several 'omics approaches under development to evaluate changes at transcriptomic, proteomic, and metabolomic levels associated with AD. Accordingly, RNA sequencing (RNA-seq) provides an index of expressed genes as well as noncoding RNAs (ncRNAs) within a given cellular population. However, a limitation is that bulk-tissue resolution masks complex alterations occurring across different cell types. Here, we applied single population RNA-seq using laser capture microdissection (LCM) to isolate Nissl-stained layer III and layer V pyramidal neurons from the superior frontal gyrus (BA22) from postmortem human brain tissue obtained from clinically and pathologically characterized AD (n=3; 2M/1F) and age-matched nondemented control cases (n=3; 2M/1F). A total of 600-900 Nissl-stained pyramidal neurons from each lamina were collected via LCM, RNA was isolated, converted to RNA-seq cDNA libraries, and analyzed on the Illumina NovaSeq platform at an average sequencing depth of 63 million reads per sample. Preliminary bioinformatic pathway analyses including IPA, KEGG, GO, and WGCNA were used to identify changes in differently expressed genes (DEGs) and canonical pathways between the AD and age-matched control cases. A total of 1,147 and 740 DEGs ($p<0.05$) were found between AD and controls in layer III and layer V, respectively. Differences in DEGs between laminae suggest studying single populations can unveil new targets previously masked when assaying admixed neuronal and non-neuronal cell types. By generating and examining molecular fingerprints of vulnerable AD cortical neurons, we expect to discover mechanistic changes via targeted and unbiased pathway analyses to help explain circuit degeneration and inform novel therapeutic strategies.

Disclosures: **A. Labuza:** None. **M.J. Alldred:** None. **H. Pidikiti:** None. **A. Heguy:** None. **P.D. Coleman:** None. **E.J. Mufson:** None. **S.D. Ginsberg:** None.

Poster

120. Alzheimer's Disease: Biomarkers II

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 120.01

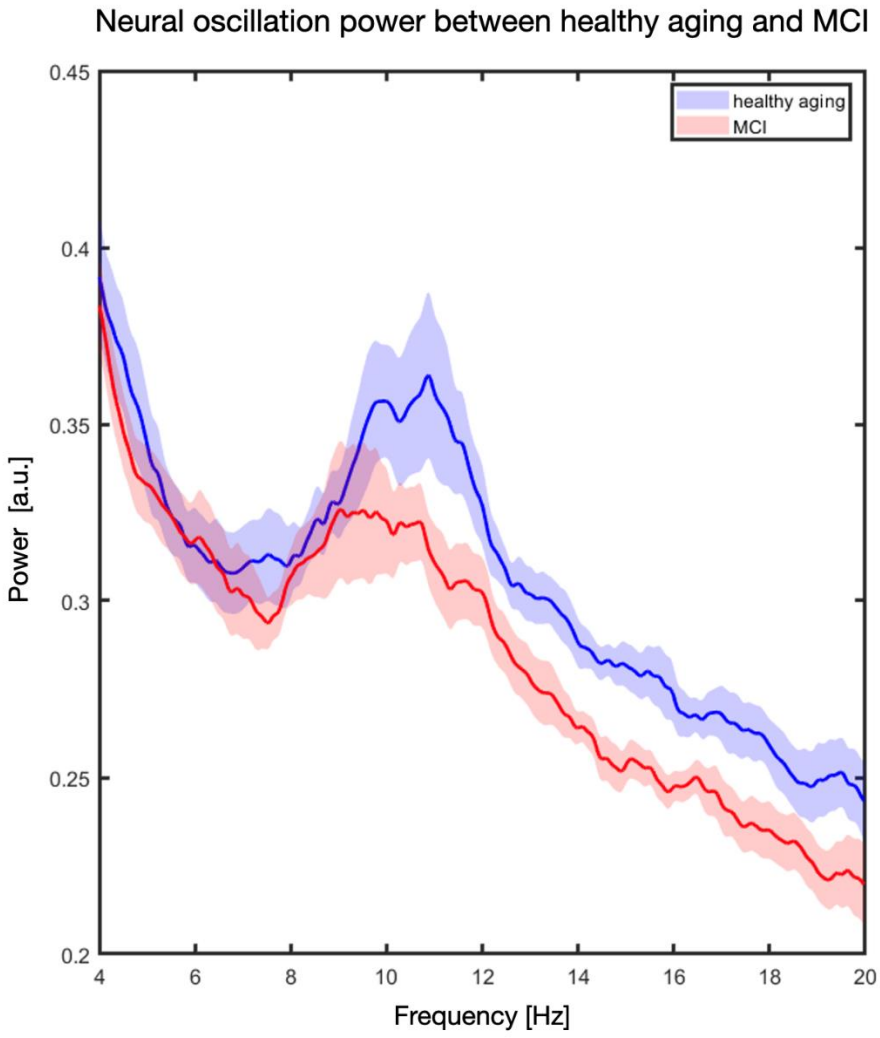
Topic: C.02. Alzheimer's Disease and Other Dementias

Support: The National Research Council of Thailand
The Thailand Science Research and Innovation cisco 63-64 fundamental fund
The Asahi Glass Foundation
The KMUTT Partnering Initiative
The KMUTT's Frontier Research Unit Grant for Neuroscience Center for Research and Innovation

Title: Alpha-bumps as a potential neuromarker for screening mild cognitive impairment

Authors: *S. JARUKASEMKIT[1], W. PHUSUWAN[2], K. BENJASUPAWAN[2], P. SOOKPRAO[3], S. ITTHIPURIPAT[3], C. CHUNHARAS[4];
[1]Fac. of Med. Ramathibodi Hosp., Mahidol Univ., Bangkok, Thailand; [2]Cognitive Clin. & Computat. Neurosci. Lab, Fac. of Med., Chulalongkorn Univ., Bangkok, Thailand; [3]Neurosci. Ctr. for Res. and Innovation, Learning Inst., King Mongkut's Univ. of Technol. Thonburi, Thung Khru, Thailand; [4]Cognitive Clin. & Computat. Neurosci. Lab, Chula Neurosci. Center, Fac. of Med., King Chulalongkorn Mem. Hospital, Thai Red Cross Society, Chulalongkorn Univ., Bangkok, Thailand

Abstract: Neurodegenerative disease like dementia is one of the most health challenges in the 21st century that lead to multiscale problems such as loss of activities of daily living (ADL), caregiver dependency, and economic burden. Early detection and prevention are key strategies in treating patients at the prodromal stage of dementia, also known as mild cognitive impairment (MCI). Growing literature points to the clinical application of electroencephalography (EEG) such as event-related potentials (ERPs) in memory encoding (Micanovic, 2014). While ERP is mainly used for cognitive assessment, it requires many trials of experiment and time-consuming being a gap for clinical application (Beres, 2017). Instead, alpha oscillations (~8-12Hz) in the EEG data can be used to track focused attention and discriminate between healthy versus various neuropsychiatric conditions: Parkinson's disease, stroke, autism spectrum disorder, schizophrenia, etc. (Giovanni, 2017). Alpha oscillation is also known to be stable, and hence, are tentatively more applicable in clinical settings. To test our hypothesis, we compared EEG bandpower during visuospatial attention cueing modified Eriksen Flanker's task between 19 MCI patients and 19 cognitively intact subjects, controlled age and sex match between 55 and 82 years old. Both groups were screened by a standard neuropsychological test, Montreal Cognitive Assessment (MoCA) before recruitment. MCI with age-matched control showed a decrease in power between alpha-to-beta frequency, especially in alpha peak frequency (alpha bumps) as shown in figure below. Therefore, alpha bumps could be a potential screening neuromarker, which in the near future we aim to study neural oscillation in specific domains of cognitive decline. This approach will promisingly help in designing dementia prevention in the current precision medicine era.



Disclosures: **S. Jarukasemkit:** None. **W. Phusuwan:** None. **K. Benjasupawan:** None. **P. Sookprao:** None. **S. Itthipuripat:** None. **C. Chunharas:** None.

Poster

120. Alzheimer's Disease: Biomarkers II

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 120.02

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

Title: Prefrontal cortex neuronal hyperactivity in a mouse model of Alzheimer’s beta-amyloidosis

Authors: *S. HUANG, D. CHENG, B. FOWLER, Jr, D. R. OLLERENSHAW, J. J. NASSI, D. GRAY;
Inscopix Inc., Mountain View, CA

Abstract: Alzheimer's disease (AD) is characterized by a progressive dysfunction of neural circuits, leading to cognitive and affective impairment. However, preclinical drug discovery for AD lacks a reliable biomarker at the neural circuit level to effectively track early stages of disease progression, contributing to a high failure rate in bringing successful new treatments to the clinic. Therefore, a sensitive and reliable neural circuit biomarker is in urgent need to facilitate novel drug discovery for AD. Using Inscopix one-photon microendoscopy, we recorded the calcium dynamics of thousands of neurons in the prefrontal cortex of AD model APP/PS1 Transgenic (Tg) and wild-type (WT) mice while they were freely behaving in a variety of exploratory and cognitive tasks. At eight months of age, despite no documented differences in memory performance at this early stage of disease progression, Tg mice showed aberrant neuronal hyperactivity, consistent with previous findings using two-photon microscopy. In addition, the activity of prefrontal cortical neurons was more synchronized in Tg mice as compared to WT mice, indicating likely impairment in efficient information processing. These abnormal circuit signatures were accompanied by the presence of Aβ plaque formation in Tg mice, further validating their association with AD. Using this method, we can repeatedly image Tg mice and quantify the impact of increasing plaque formation on circuit function, representing a substantial advantage over histologically-based measures. Our findings establish a circuit-level phenotype of beta-amyloidosis with early separation of disease phenotypes and longitudinal tracking ability. These could form the basis for a powerful new neural circuit based assay for screening novel treatments and mechanisms of action aimed at preventing or reversing the neural circuit abnormalities and associated cognitive and affective impairments in AD.

Disclosures: S. Huang: None. **D. Cheng:** None. **B. Fowler:** None. **D.R. Ollerenshaw:** None. **J.J. Nassi:** None. **D. Gray:** None.

Poster

120. Alzheimer's Disease: Biomarkers II

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 120.03

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

Support: BrightFocus Foundation Alzheimer's Disease Research Program Award UMO-2018/30/E/NZ4/00687

Title: From rat to human - Role of relaxin-3 and its receptor, RXFP3, in the hippocampus and memory

Authors: *C. DE AVILA[1], A. GUGULA[2], A. TRENK[2], A. BLASIAK[2], A. L. GUNDLACH[3], J. D. FRYER[1];

[1]Neurosci., Mayo Clin., Scottsdale, AZ; [2]Dept. of Neurophysiol. and Chronobiol., Jagiellonian Univ., Krakow, Poland; [3]Florey Inst. Neurosci. Mental Hlth., Florey Inst., Melbourne, Australia

Abstract: By 2050 more than 115 million people worldwide will be living with Alzheimer's disease (AD). Current treatments marginally attenuate symptoms and have little effect on slowing disease progression. Therefore, more research is required to discover the neural networks that control cognition and related processes, and in turn to develop better treatments to slow progress and reduce the symptoms of dementia leading to AD. Previous preclinical research in rats and mice have established a role for the brain region known as the *nucleus incertus* (NI) in contextual memory by elucidating the strong neural communication between the NI and the septohippocampal system (SHS), which is central to learning and memory. Specifically, the NI contains a major population of relaxin-3 (RLN3)-producing GABAergic neurons which project heavily to limbic circuits that are vulnerable to degeneration in dementia, including the SHS, which expresses abundant RLN3 receptors (RXFP3) in rat brain. Therefore, overactivity or degeneration of these NI inputs may have adverse consequences for memory formation and recall and may contribute to its dysregulation in dementia. In this study we aimed to elucidate the precise localization and role of the RLN3/RXFP3 signaling system in the NI-hippocampus network, in experimental rat models and in postmortem human brain. We used viral-based, neural tract-tracing to label NI-originating fibers in the hippocampus of male Sprague-Dawley rats (n=4). Fluorescent multiplex *in situ* hybridization was used to localize RXFP3 mRNA in relation to the expression of vesicular GABA transporter (vGAT), and vesicular glutamate transporter (vGLUT) or somatostatin (SST) mRNA, in male Sprague-Dawley rat brain (n=3), and in post-mortem human brain tissues from male subjects (n=3) without a history of dementia (Banner Sun Health Research Institute, AZ, USA). Tract-tracing in rats revealed a high-density of NI-originating fibers within the polymorph layer of the dentate gyrus (DG), with the majority being RLN3-immunopositive. In rat brain, a majority of vGAT mRNA-positive neurons in the ventral hippocampus (vHPC) expressed RXFP3 mRNA. In human hippocampus, we observed neuronal co-expression of vGAT, SST, and RXFP3 mRNA. These results indicate that the NI influences information processing in rat vHPC by modulation of the DG, and RXFP3 activation may underlie some of these processes; RLN3/RXFP3 signaling may also influence similar circuits in human brain. Further studies are planned to investigate the expression of RLN3 in the human NI and compare levels of RLN3 and RXFP3 expression in brains from AD and age-matched subjects.

Disclosures: C. de Avila: None. **A. Gugula:** None. **A. Trenk:** None. **A. Blasiak:** None. **A.L. Gundlach:** None. **J.D. Fryer:** None.

Poster

120. Alzheimer's Disease: Biomarkers II

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 120.04

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

Title: The effect of sex on plasma biomarkers in the diagnosis of dementia

Authors: *K. E. FOLEY[1,2], Z. S. WINDER[1,2], E. M. WEEKMAN[1,2], T. L. SUDDUTH[1], D. M. WILCOCK[1,2];
[1]Sanders Brown Ctr. on Aging, [2]Physiol., Univ. of Kentucky, Lexington, KY

Abstract: The effect of sex on human plasma biomarkers in the diagnosis of dementia
Kate E. Foley, Zachary Winder, Erica M. Weekman, Tiffany L. Sudduth, Donna M. Wilcock
While there are many pathological causes of dementia, all coalesce to result in brain atrophy and cognitive impairment. With neuroimaging, including PET, being costly and only accessible in typically urban areas, plasma-based blood biomarkers are emerging as the first line in identifying preclinical dementia patients to target for follow-up testing or, one day, disease modifying therapies. Further, plasma biomarkers have the potential to evaluate multiple etiologies of dementia including Alzheimer's disease (AD) pathology, vascular contributions to dementia, and inflammation. We examined a battery of candidate plasma biomarkers using the Quanterix SiMoA platform in our longitudinal aging cohort at the UK-ADRC. First, we assessed whether plasma biomarkers correlate with each other to form convenient modules for dementia detection. We saw a striking correlation pattern where AD biomarkers (i.e. Aβ40, Aβ42, and Total Tau) correlate well with each other, but inversely correlate with inflammatory biomarkers (i.e. IL6, IL8, and IL10). More importantly, the strength of the correlation between plasma biomarkers differs by sex, suggesting that certain immune and vascular plasma biomarker modules may provide more relevance for one sex over the other. Our next step was to examine plasma biomarker relationships with MRI volumetric measures in the same participants. The effect of sex on biomarker correlation could be further seen in brain structural volume changes. In a subset of these participants that had MRI scans, we evaluated biomarker correlation with brain region volumes (frontal, parietal, temporal, occipital lobes, and left and right hippocampus) via linear modeling. While some biomarkers show significance with brain region volume (frontal lobe:Aβ42, temporal lobe:Aβ42), other biomarkers show an interaction with sex (occipital lobe:MMP9, right hippocampus:MMP9). Together, these preliminary data suggest that plasma biomarkers can be used in modules with correlated expression, and more specifically, that the AD biomarker module inversely correlates with inflammatory biomarkers in the inflammation module, and that this correlation may depend on sex. Further, our data suggests that the association of these biomarkers with brain volumetric changes is also influenced by sex. These findings highlight the importance of sex by biomarker interactions, and have significant implications in the emerging field of plasma biomarkers for dementia diagnoses.

Disclosures: K.E. Foley: None. **Z.S. Winder:** None. **E.M. Weekman:** None. **T.L. Sudduth:** None. **D.M. Wilcock:** None.

Poster

120. Alzheimer's Disease: Biomarkers II

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 120.05

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

Support: Biocodex foundation

Title: Possible role of gut microbiota during the reproductive senescence and the development of Alzheimer's disease

Authors: *I. S. ROMERO-FLORES[1], J. GARCÍA-MENA[1], V. SÁNCHEZ-VALLE[2], C. PÉREZ-CRUZ[2];
[1]Genet. and Mol. Biol., [2]Pharmacol., Ctr. for Investigation and Advanced Studies, Mexico City, Mexico

Abstract: Possible role of gut microbiota during the reproductive senescence and the development of Alzheimer's disease
Ivonne Sagrario Romero-Flores[1], Jaime García-Mena[1]; Vicente Sanchez-Valle[2,] *Claudia Pérez-Cruz[2].[1]Department of Genetic and Molecular Biology, Center of Research and Advance Studies (CINVESTAV). [2]Department of Pharmacology, CINVESTAV - National Polytechnic Institute, Mexico. *cperezc@cinvestav.mx
Alzheimer's disease (AD) the commonest cause of dementia. AD is a growing global health challenge as more than 45 million people are suffering from this condition. Epidemiological data indicate that women are the sector mostly affected, since they represent almost two thirds of patients with this condition. One major sex difference heralded by pre-clinical and human studies as early prognostic for AD is the menopause transition. It is known that women during menopause have a strong depletion of estrogen levels, a hormone related to cognitive function. On the other hand, recent studies show an intestinal dysbiosis in subjects suffering AD. We have recently reported a different gut microbiota (GM) composition in female vs male transgenic (TG) mice, whereas better cognitive performance was associated some bacteria species.In this study, we aimed to assess the possible relationship between GM composition and estradiol (E2) levels in female transgenic mice (APP/PS1) during the reproductive senescence. We used 10 and 15 months-old female APP/PS1 and Wildtype (WT) mice. Water-maze, T-maze and Elevated Plus Maze were used to evaluate behavioral and cognitive alterations. Fecal and serum samples were collected to determine GM composition through DNA sequencing and E2 levels by ELISA kits. We observed alterations in GM, and E2 levels that were more pronounced in TG female mice. These data contribute to the understanding of factors that may increase the risk to develop dementia in women.
Support: Biocodex Foundation- Mexico

Disclosures: I.S. Romero-Flores: None. **J. García-Mena:** None. **V. Sánchez-Valle:** None. **C. Pérez-Cruz:** None.

Poster

120. Alzheimer's Disease: Biomarkers II

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 120.06

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

Support: NIA R01 AG055449
NIA R01 AG068055
NINDS RF1 NS122028
AHA Predoctoral Fellowship 903649

Title: Enlarged perivascular space counts are negatively associated with Uniform Data Set Version 3 executive function composite scores

Authors: *T. J. LIBECAP[1,2], V. ZACHARIOU[1], C. E. BAUER[1], C. A. PAPPAS[1], F. RASLAU[3], B. T. GOLD[1,4];
[1]Neurosci., [2]MD/PhD Program, [3]Radiology, [4]Magnetic Resonance Imaging and Spectroscopy Ctr., Univ. of Kentucky, Lexington, KY

Abstract: Cerebral small vessel disease (cSVD) is an important risk factor leading to the development of vascular contributions to cognitive impairment and dementia (VCID). cSVD is characterized by several in-vivo neuroimaging biomarkers including enlarged perivascular spaces (ePVS). PVS are fluid-filled spaces believed to play a role in the glymphatic system's removal of waste from the brain. Reduced clearance may cause backup and enlargement of the PVS and subsequent accumulation of toxic solutes characteristic of neurodegeneration, including Aβ. Evidence supports the role of ePVS in aging and dementia, but the relationship between ePVS and cognitive function remains unclear**.** We hypothesized that quantitative, baseline ePVS counts in older adults would be associated with baseline executive function, a multifaceted cognitive domain critical to daily life that is impacted by cSVD and VCID. We explored the relationship between ePVS and the Uniform Data Set (v3.0) executive function composite scores (UDS3-EF) in 73 older adults (36F) ranging in age from 56-86. The UDS3-EF is a previously validated composite measure of seven tests which includes category fluency, letter fluency, digit span backwards, and trail making tasks. Participants were scanned on a 3T Siemens Prisma scanner with a 64-channel head coil. All ePVS counts were performed on T1 MPRAGE and T2 FLAIR images by an experienced rater blinded to participant demographics and under the direction of a trained neuroradiologist. In line with previously established guidelines, ePVS were defined as regions of hypointensity less than 3mm in diameter on T1 imaging and were distinguished from lacunar infarcts by the absence of T2 FLAIR hyperintensity. ePVS were individually and manually counted in a single, representative slice in the axial plane of the white matter centrum semiovale, basal ganglia, hippocampus, and midbrain. Regression analyses controlling for age, gender, estimated total intracranial volume, and years of education demonstrated a significant, negative relationship between UDS3-EF scores and ePVS counts in the basal ganglia ($\beta = -0.277$, $P = 0.011$) and in the midbrain ($\beta = -0.216$, $P = 0.042$). These cross-sectional findings suggest that ePVS burden is associated with executive dysfunction. Ultimately, our results support the continued investigation of ePVS as a potential early neuroimaging biomarker of cSVD-related cognitive dysfunction. Future work is required to determine if ePVS burden predicts later UDS3-EF scores.

Disclosures: T.J. Libecap: None. **V. Zachariou:** None. **C.E. Bauer:** None. **C.A. Pappas:** None. **F. Raslau:** None. **B.T. Gold:** None.

Poster

120. Alzheimer's Disease: Biomarkers II

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 120.07

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

Support: NIH Grant R01 AG073282

Title: Single-scan Overlap Index as a means for early tau pet signal detection

Authors: *J. LEE, P. MIN, V. LOWE;
Radiology, Mayo Clin., Rochester, MN

Abstract: Neurofibrillary tangles (NFTs) are a pathologic hallmark of Alzheimer's disease (AD). In vivo positron emission tomography (PET) imaging of tau NFTs has been very useful in understanding the pathology of AD, as well as for the diagnosis and tracking of disease progression. Given the irreversible nature of the neurodegenerative process, identifying early NFTs neuropathology before downstream consequences on neurodegeneration is critical. However, the limited sensitivity of AV-1451 (Flortaucipir) tau PET for early tau deposition has been claimed by a recent autopsy study. In the previous study (Lee et al., 2022), we have proposed a new metric called the "overlap index" (OI) which quantifies the spatial consistency of high-intensity voxels between the serial scans and showed that the OI is useful for detecting subtle tau PET uptake and early disease progression. However, although OI can augment sensitivity to early tau PET uptake, acquiring at least two separate PET scans can be a disadvantage and challenging. In this study, to overcome the limitation and improve the utility of OI, we applied the OI method for the dynamic images of the tau PET (1,114 unique individuals and 1,612 scans). For this purpose, we split the 20 minutes of dynamic scanning of tau PET into two segments (i.e., the first 10 min. and the second 10 min.) and then applied the OI method between the first and second averaged images. Using this technique to calculate OI within single-scan yields similar results as with the longitudinal tau PET, showing a significant correlation with the longitudinal OI ($p<0.005$). Like the longitudinal OI, in testing implications of single-scan OI, OI derived from dynamic images was able to detect significant differences of CU A- to CU A- (cognitively unimpaired with normal amyloid PET level) from the other clinical subgroups including the small degree of clinical changes, CU A+ to CU A+ (cognitively unimpaired with abnormal amyloid PET level; $p<0.001$). The ROI-based measures also showed significant differences from the MCI groups, however, no significant difference was seen in comparison with the earlier disease progression group. In addition, cognitive scores were associated more strongly with the single-scan OI than the meta-ROI SUVR. This result implies that OI derived from a dynamic scan of tau PET may overcome the need for two separate PET scans. Our study shows that the OI method could be helpful in measuring early tau-PET signal. This voxel-wise analysis can overcome the ROI-based measures' limitations of reduced sensitivity to early detection of small areas of tau.

Disclosures: J. Lee: None. **P. Min:** None. **V. Lowe:** None.

Poster

120. Alzheimer's Disease: Biomarkers II

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 120.08

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

Title: Assistive Technology for Early Diagnosis of Dementia Using Electroencephalogram (EEG)

Authors: *T. UENO[1], H. KUGA[2], N. ORIBE[3], K. MOMOSE[4];
[1]Hizen Psychiatric Med. Ctr., Hizen Psychiatric Med. Ctr., Kanzaki, Japan; [2]Natl. Ctr. of Neurol. and Psychiatry, Tokyo, Japan; [3]Psychiatry, Hizen Psychiatric Ctr., Saga, Japan; [4]NTT DATA i, Tokyo, Japan

Abstract: Noninvasive testing methods have been developed for Alzheimer's disease and other dementias, and although technologies such as MRI, CT, and SPECT are becoming more widespread, they are relatively ineffective and the equipment is not yet widely available. In this study, we analyzed data obtained from EEG, an inexpensive noninvasive test, using NAT, a brain potential analysis imaging method, and verified disease specificity using machine learning. We analyzed data from 53 patients (22 males, 31 females) with Alzheimer's disease (AD), 10 patients (4 males, 6 females) with dementia with Lewy bodies (DLB), 7 patients (3 males, 4 females) with frontotemporal dementia (FTLD), 1 patient (1 female) with dementia with granular tardigrade (DB), 1 patient (1 female) with cerebrovascular dementia (VD), 1 patient (1 female) with dementia with vascular dementia (VD), and 1 patient (1 female) with dementia with tardigrade (DB). (1 female), 25 patients with mild cognitive impairment (MCI) (5 males, 4 females), and 2 normal subjects (NC) (2 males) EEG data were obtained and analyzed. All subjects were informed about the study and their written consent was obtained. Informed consent was obtained from the Ethics Committee of the Hizen Psychiatric Center, and the study was conducted accordingly. All patients were recruited at the Hizen Psychiatric Center, and patients were assessed for severity using the Mini-Mental State Examination (MMSE) and Clinical Dementia Rating (CDR), which are neuropsychological tests. Fast Fourier transform was performed on the EEG data and the following two markers were calculated for each of the 10 sub-bands falling in the 4-20 Hz range: sNAT: relative percentage distribution of brain potential power; vNAT: power ratio of sNAT in the neighboring frequency sub-bands. This data was obtained a priori. Cluster analysis was performed on these subbands, and SVM (Support Vector Machine) was used to measure the degree of dementia similarity for each cluster. The diagnostic rate of AD in the SVM-Linear and SVM-CL2 values was 81% and 79%, respectively, above the threshold value of -0.2. The discrimination rate of MCI was highest at the threshold of -0.2. It was found that about 80% of the patients could discriminate dementia.

Disclosures: T. Ueno: B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug

study, report that research relationship even if those funds come to an institution.; NTTi Grant. **H. Kuga:** None. **N. Oribe:** None. **K. Momose:** None.

Poster

120. Alzheimer's Disease: Biomarkers II

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 120.09

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

Support: NIH 5R01AG06098

Title: Transcranial Magnetic Stimulation based Brain Network Integrity Assessment in Alzheimer's Disease

Authors: *R. OZDEMIR[1], P. FRIED[1], S. BUSS[1], S. BARATONO[1], B. PASSERA[1], A. E. BUDSON[2], D. PRESS[1], A. PASCUAL-LEONE[1], M. SHAFI[1];
[1]Harvard Med. Sch., Boston, MA; [2]Boston Univ. Sch. of Med., BOSTON, MA

Abstract: Alzheimer’s disease (AD) has a relatively well-characterized pathology of amyloid-β and tau accumulation. Yet, disease progression from preclinical to clinical stage remains largely unpredictable at the individual level. Growing evidence shows disrupted synaptic signaling in functionally connected brain networks early in the preclinical stage, and suggests impaired network integrity, assessed with functional connectivity measures, as potential markers for disease symptomatology in AD. However, our current understanding of the impact of AD on brain network connectivity is limited to characterization of spontaneous blood oxygenation (i.e., resting-state fMRI), which fails to capture fast evolving neural dynamics, or resting-state electrophysiology (EEG): Both tools have poor signal-to-noise ratio at the individual level and lack direct assessment of causality. Here propose a novel TMS-induced causal connectivity measure reflecting integrity of multi-synaptic signaling within the stimulated brain networks. In a preliminary sample of 4 cognitively normal older adults (Healthy Controls: HCs) and 3 patients with amnestic mild cognitive impairment or mild dementia (early AD), we applied 150 single pulses of TMS to inferior parietal lobule (IPL), a distinct brain region within the default mode network (DMN) showing decreased metabolism in early AD and recorded TMS evoked neural responses with simultaneous electroencephalography (TMS-EEG). We also characterized spontaneous brain activity with resting-state EEG (rsEEG) measurements. We performed source space spectral power analyses and seed-based power envelope correlations (PEC) to estimate cortical distribution of relative alpha power and spontaneous IPL connectivity as rsEEG measurements. Network integrity was defined as the ratio of significantly activated vertices to the total number of vertices within the DMN following TMS of IPL. Although relative alpha power (8-12 Hz) was slightly lower and seed based connectivity was slightly higher within the IPL node in AD participants, no network specific differences was observed across the cortex for both rsEEG measures. On the other hand, DMN integrity was substantially lower in AD participants with an average ratio of 0.53 (0.79 in HC) indicating that almost half of the vertices

within the DMN were not activated by TMS. Overall, these preliminary analyses suggest that perturbation-based (TMS-EEG) measures may reveal neurophysiological signatures of brain network dysfunction that are not observable in spontaneous brain oscillations, and thus may characterize defining features of network failure in preclinical and mild AD.

Disclosures: R. Ozdemir: None. **P. Fried:** None. **S. Buss:** None. **S. Baratono:** None. **B. Passera:** None. **A.E. Budson:** None. **D. Press:** None. **A. Pascual-Leone:** None. **M. Shafi:** None.

Poster

120. Alzheimer's Disease: Biomarkers II

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 120.10

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

Support: USC Center for Sustainable Solutions
USC Strategic Directions for Research Award
3M

Title: Designing a neural probe for acetylcholine recording to understand cholinergic activity in Alzheimer's disease

Authors: *S. BAWARITH, A. MORREL, F. AMIRGHASEMI, M. MOUSAVI;
USC, Los Angeles, CA

Abstract: Alzheimer's disease (AD) is a progressive neurodegenerative disease characterized by abnormalaccumulation of the amyloid-beta peptide and the tau protein. This affects signal transmission ofthe neurotransmitter acetylcholine (ACh) responsible for memory and learning. Much is stillunknown about cholinergic neurons; understanding changes in ACh concentration and itsdegradation allows for the design of relevant therapeutics for AD patients. We address this gap bycreating a yarn-based ion selective electrode that allows for real-time information gathering tomechanistically study ACh. The experimental set up consists of a reference electrode and the ionselective electrode (ISE). The potential expressing the activity of the analyte is measured betweenthem and is governed by the Nernst equation. The ISE is made of yarn, carbon black as theconductive ink, a UV sealant, and an ion selective membrane (ISM). The ISM is hydrophobic andconsists of a polymer, a plasticizer, and an ionic site- the recognition comes from the ionophorewhich selectively binds to the ACh. The electrodes were tested for their ability to detect AChCl atthe mM to nM range by dipping them in a container of AChCl and diluting the solution with DIwater, as well as their ability to detect 50 uL incremental additions of AChCl. The probes werealso tested for their ability to select AChCl in artificial cerebrospinal fluid and over relevantinterfering ions in the brain such as KCl, NaCl, and ChCl by both the separate solution methodwhere interfering ions are diluted with DI water, as well as fixed interference method whereincremental amounts of 10^{-4} M of the interfering ion are added to the

10^{-2} M AChCl solution. Theresults showed that the electrodes (n=4) were selective for AChCl; the limit of detection for theAChCl solution is $10^{-5.2}$ M and the limit of detection for the interfering ions KCl, NaCl, and ChClis 10^{-5} M, $10^{-4.9}$ M, and $10^{-4.4}$ M respectively. The novelty in these ISEs lies in their selectivity,fast response time, and their ability to detect a wide range of ions. Using yarn as a materialinstead of a tube-based electrode allows for increased flexibility and defined spatial resolutionswhich decreases the potential damage to brain tissue upon insertion. The results suggest that thisdeveloped yarn-based electrochemical electrode allows for real-time detection of ACh that canshed light on this neurotransmitter for AD. Future work to improve spatial resolution, selectivity,and detection range can be addressed by nanopatterning conductive fiber and exploringfluorocarbons. These electrodes can be further used to screen cholinesterase inhibitors for AD andtheir efficacy in future studies in vivo.

Disclosures: S. Bawarith: None. **A. Morrel:** None. **F. Amirghasemi:** None. **M. Mousavi:** None.

Poster

120. Alzheimer's Disease: Biomarkers II

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 120.11

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

Title: The use of microbore UHPLC-ECD as a tool for the analysis of monoamine neurotransmitters and metabolites in neurodegenerative disease research

Authors: *H.-J. BROUWER[1], Y. P. Y. VERMEIREN[2,3], M. EYSBERG[4], L. M. VAN HEERWAARDEN[1], P. P. DE DEYN[2,5];
[1]Antec Scientific, Alphen a/d Rijn, Netherlands; [2]Lab. of Neurochemistry and Behavior, Univ. of Antwerp, Antwerp, Belgium; [3]Chair group of Nutritional Biology, Div. of Human Nutr. & Hlth., Wageningen Univ., Wageningen, Netherlands; [4]Antec Scientific LLC, Boston, MA; [5]Dept. of Neurol. and Alzheimer Ctr., Univ. of Groningen, Univ. Med. Ctr. Groningen, Groningen, Netherlands

Abstract: Neurodegenerative conditions such as Parkinson’s and Alzheimer’s disease, or, related proteinopathies (e.g. Lewy body and frontotemporal dementia) are characterized by early-onset alterations of the monoaminergic neurotransmitter system both central (brain) and peripheral (cerebrospinal fluid (CSF); blood). Such alterations contribute to severe behavioral and cognitive disturbances in patients (memory loss, aggression, depression and related neuropsychiatric symptoms). Measuring levels of monoamines, such as (nor)adrenalin, serotonin, dopamine, and, related metabolites (MHPG, 5-HIAA, DOPAC/HVA, respectively), thus provide a window of opportunities for the discovery of disease-specific CSF markers, and, comprise an important tool in overall disease monitoring and development.
Simultaneous quantification of these neurotransmitters in biofluids and brain requires a highly sensitive and selective analysis method. The most commonly applied method for this type of

analysis is High-Performance Liquid Chromatography (HPLC) in combination with sensitive detection techniques such as Mass Spectrometry (MS), Fluorescence (FD), or, Electrochemical detection (ECD). HPLC-ECD is still considered the analytical method of choice because it enables sensitive and direct detection of neurotransmitters without the need for prior derivatization and elaborate sample preparation. Moreover, HPLC-ECD is more cost-effective compared to analysis based on mass spectrometry. With the advent of Ultra High-Performance Chromatography (UHPLC) with sub-2 μm stationary phases, high efficiency separations and faster neurotransmitter analysis has become available.
In this study a fast and reliable microbore RP-UHPLC-ECD method is demonstrated using the ALEXYS neurotransmitter analyzer for the simultaneous analysis of abovementioned 8 monoamines and metabolites in postmortem acquired frozen human brain tissue and CSF. Samples were prepared in phosphate-citrate buffer at 4°C using a simple sample preparation protocol to assure that the analytes of interest are stable for at least 24 hours in the sample matrix without prior antioxidant additions. Good separation of all 8 analytes is achieved within a 15 minute run time on a 15 cm short Waters Acquity C18 BEH UPLC column (1 mm ID, particle size 1.7 μm), using optimized LC conditions and a sample injection volume of only 5 μL. The method sensitivity was good with typical on-column LODs in the range of 0.2 - 0.5 pg (1 - 3 fmol) for all analytes. This validated method has shown to be suitable for routine analyses of low levels of monoamine transmitters in various sample matrices encountered in this research field.

Disclosures: H. Brouwer: None. **Y.P.Y. Vermeiren:** None. **M. Eysberg:** None. **L.M. van Heerwaarden:** None. **P.P. De Deyn:** None.

Poster

120. Alzheimer's Disease: Biomarkers II

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 120.12

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

Support: MSIT Grant IITP-2021-2020-0-01821
KHIDI Grant HI14C3484
KHIDI Grant HX22C0027

Title: Identification of mesenchymal stem cell related predictive and monitoring biomarkers in cerebrospinal fluid samples of patients with alzheimer's disease

Authors: *Y. CHOI[1,2], S. SHIN[3], H. SON[1,2,4,6], N.-H. LEE[1,2,5], S. MYEONG[1,2,5], C. LEE[3,8], H. JANG[1,2,6,7], H. KIM[1,2,4,5,6], D. NA[1,2,7];
[1]Cell and Gene Therapy Inst. (CGTI), Res. Inst. for Future Medicine, Samsung Med. Ctr., 81, Irwon-ro, Gangnam-gu, Seoul 06351, Korea, Republic of; [2]Dept. of Neurol., Samsung Med. Center, Sungkyunkwan Univ. Sch. of Med., 81, Irwon-ro, Gangnam-gu, Seoul 06351, Korea, Republic of; [3]Chemical&Biological Intergrative Res. Ctr., Korea Inst. of Sci. and Technol., Seoul 02792, Korea, Republic of; [4]Sch. of Med., Sungkyunkwan Univ., 81, Irwon-ro, Gangnam-

gu, Seoul 06351, Korea, Republic of; [5]Dept. of Hlth. Sci. and Technology, SAIHST, Sungkyunkwan Univ., Seoul 06355, Korea, Republic of; [6]Neurosci. center, Samsung Med. Ctr., 81, Irwon-ro, Gangnam-gu, Seoul 06351, Korea, Republic of; [7]Alzheimer's Dis. Convergence Res. Ctr., Samsung Med. Ctr., Seoul, Korea, Republic of; [8]Div. of Bio-Medical Sci. & Technol., KIST School, Korea Univ. of Sci. and Technol., Seoul 02792, Korea, Republic of

Abstract: Preclinical studies have shown that the secretion of neurotrophic factors and cytokines by mesenchymalstem cells (MSCs) was effective in reducing tau phosphorylation, amyloid-beta deposition, andinflammation in Alzheimer's disease (AD) mouse models. The major objective of this study was toidentify potential CSF biomarkers that may be used to predict or monitor MSC related responses in ADpatients. Cerebrospinal fluid (CSF) samples were harvested from AD patients who receivedadministrations of human umbilical cord blood-derived MSCs (n=22) or placebo (n=12) (ClinicalTrials.gov, NCT02054208). CSF samples were collected at two different time points: baseline and aday after the third injection. Based on changes in total-tau and phosphorylated-tau levels in the CSF,MSCs received patients were classified into two different groups: good responder (GR), and poorresponder (PR). The CSF protein levels of three typical patients in each group were measured usingliquid chromatography-tandem mass spectrometry (LC-MS/MS). A total of 1,667 proteins wereidentified by LC-MS/MS. A statistically significant difference between the typical GR and PR wasshown from 11 proteins at baseline (FDR $q < 0.05$). Reticulocalbin-3 (RCN3) and follistatin-relatedprotein 3 (FSTL3) were chosen as potential biomarkers to predict MSC response. Compared to baseline,a total of 128 proteins were significantly increased (FDR $q < 0.05$) one day after the third injection onlyin the typical GR except for 45 proteins, which were increased together in the typical PR. Scrapie-responsive protein 1 (SCRG1), neural proliferation and differentiation control protein 1 (NPDC1),apolipoprotein E (ApoE), and cystatin-C (Cys C) were chosen as potential biomarkers to monitor MSCresponse. According to functional analysis, increased proteins in typical GR CSF samples after the thirdinjection were related to synaptogenesis. We conducted an enzyme-linked immunosorbent assay(ELISA) using the same 18 CSF samples to validate the levels of the six target proteins. RCN3 andSCRG1 were not detected by ELISA. FSTL3, showed no significant difference between typical GR andPR. NPDC1, APOE, and CysC levels were decreased after the third injection when compared to baselinein typical GR and PR. Further research is warranted to elucidate why it was not possible to corroboratethe LC-MS/MS results via ELISA. The results of this study suggest that RCN3 and FSTL3 could beused as potential biomarkers to predict MSC response and that SCRG1, NPDC1, APOE, and CysCcould be used as potential biomarkers to monitor MSC response in AD patients.
Keywords: Alzheimer's disease, Mesenchymal stem cell, LC-MS/MS, Biomarker, ELISA

Disclosures: Y. Choi: None. **S. Shin:** None. **H. Son:** None. **N. Lee:** None. **S. Myeong:** None. **C. Lee:** None. **H. Jang:** None. **H. Kim:** None. **D. Na:** None.

Poster

120. Alzheimer's Disease: Biomarkers II

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 120.13

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

Support: NIA Grant 1R03AG063248

Title: Impact of KIBRA levels on synaptic plasticity, PKMζ stability, and cognition in tauopathy

Authors: *K. PAREJA-NAVARRO[1], G. KAUWE[2], J. CHEN[3], W. W. SEELEY[4], J. KRAMER[5], T. C. SACKTOR[6], L. GAN[7], K. B. CASALETTO[5], T. E. TRACY[3];
[1]Tracy lab, [2]Buck Inst. for Age Res., Novato, CA; [3]Buck Inst., Novato, CA; [4]Neurol., Univ. of California San Francisco, San Mateo, CA; [5]UCSF, San Francisco, CA; [6]Dept Physiol. & Pharmacol., SUNY Downstate Med. Ctr., Brooklyn, NY; [7]Brain and Mind Res. Inst., Weill Cornell Med., New York, NY

Abstract: KIBRA (KIdney/BRAin) is a postsynaptic protein that regulates synaptic plasticity and memory. Reduced KIBRA levels in the brain are associated with dementia and the accumulation of pathogenic acetylated tau in Alzheimer's disease. Determining how KIBRA levels are linked to synapse dysfunction and memory loss in Alzheimer's disease requires further investigation. KIBRA is a large scaffold protein which contains multiple binding domains for various proteins that influence synaptic function. We found that the C-terminal domain of KIBRA (CT-KIBRA) was sufficient to restore synaptic plasticity and memory in transgenic mice with human tau that mimics hyperacetylated tau found in Alzheimer's disease (tauKQ^{high}). CT-KIBRA binds to PKMζ, an isoform of atypical protein kinase C, and slows its degradation. In cultured neurons expressing pathogenic tau, we found that co-expression of CT-KIBRA increased levels of PKMζ in postsynaptic spines compared to control neurons. Furthermore, we found that the interaction between CT-KIBRA and PKMζ is required for CT-KIBRA to repair long-term potentiation (LTP) in neurons expressing pathogenic tau. To evaluate KIBRA signaling in neurodegenerative disease, we measured KIBRA and PKMζ levels in human tauopathy brains. There was a significant correlation between lower levels of KIBRA and PKMζ and higher levels of acetylated tau across Alzheimer's disease and Pick's disease cases. Lower KIBRA levels in brain were also associated with cognitive impairment. To further investigate the relationship between KIBRA levels and cognition, we also measured KIBRA in cerebrospinal fluid (CSF) of humans. We found that KIBRA is elevated in CSF of patients with Alzheimer's disease-related cognitive impairments compared to controls. Moreover, high KIBRA levels in CSF were strongly associated with increased levels of total tau and phosphorylated tau in CSF, which are biomarkers for Alzheimer's disease. The reduced levels of KIBRA in brains and the elevated levels of KIBRA in CSF of Alzheimer's disease subjects suggest that KIBRA may serve as a synaptic biomarker for the disease. These findings demonstrate a potential mechanism to repair synapse dysfunction caused by pathogenic tau and they support a strong relationship between KIBRA levels, tau, and cognition.

Disclosures: K. Pareja-Navarro: None. **G. Kauwe:** None. **J. Chen:** None. **W.W. Seeley:** None. **J. Kramer:** None. **T.C. Sacktor:** None. **L. Gan:** None. **K.B. Casaletto:** None. **T.E. Tracy:** None.

Poster

120. Alzheimer's Disease: Biomarkers II

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 120.14

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

Support: NIH Grant R01AG053588 to HD
NIH Grant R01AG059753 to HD
NIH Grant R01AG075108 to HD
NIH Grant P30 AG035982 to RS
Brightfocus Foundation Research Grant A20202259S to HD
KUMC Research Grant to LG
KU Career Development Grant to LG

Title: Nonobese male patients with Alzheimer's disease are vulnerable to decrease in plasma leptin

Authors: *T. WANG[1], J. TIAN[4], K. JIA[2], L. GUO[5], R. H. SWERDLOW[6], H. DU[3];
[1]Pharmacol. and Toxicology, The Univ. of Kansas, Lawrence, KS; [2]Pharmacol. and Toxicology, The Univ. of Kansas, Lawerence, KS; [3]Dept. of Pharmacol. and Toxicology, and Higuchi Biosci. Ctr., The Univ. of Kansas, Lawrence, KS; [4]Pharmacol. & Toxicology, [5]Pharmacology&Toxicology, Univ. of Kansas, Lawrence, KS; [6]Dept Neurol, Univ. Kansas Sch. Med., Kansas City, KS

Abstract: Alzheimer's disease (AD) is a devastating neurodegenerative disorder is characterized by insidious onset of memory loss and cognitive decline. Metabolic dysfunctions have long been linked to the cognitive deficits that are a hallmark of AD. Among these metabolites, leptin is an anti-obesity hormone that is responsible for maintaining energy homeostasis as well as modulating memory function. Although leptin deregulation has been implicated in mouse models of AD-like brain pathology, previous clinical studies have shown inconsistent results with regards to an association of leptin with AD development. Here, we examined plasma leptin levels in nonobese patients with AD. In contrast to unchanged circulating leptin levels in females, male patients exhibited decreased plasma leptin levels in comparison their age- and sex-matched cognitively unimpaired counterparts. Moreover, plasma leptin levels showed no correlation with cognitive performance, currently known AD blood biomarkers, or conventional AD symptom-modifying treatments in patients of either sex. Of note, females, but not males, demonstrated an association of plasma leptin with body mass index and high density lipoprotein-cholesterol (HDL-C) as well as with total cholesterol/HDL-C and triglyceride/HDL-C ratios. The simplest interpretation of our findings is that leptin deficiency is associated with nonobese male patients with AD, supporting systemic dysmetabolism in the development of AD in certain populations. Although plasma leptin may be limited in the reflection of disease severity or progression, future mechanistic studies on the regulation of leptin in nonobese patients with AD will deepen our understanding of the sex-related disparity of AD etiopathogenesis.

Disclosures: **T. Wang:** None. **J. Tian:** None. **K. Jia:** None. **L. Guo:** None. **R.H. Swerdlow:** None. **H. Du:** None.

Poster

120. Alzheimer's Disease: Biomarkers II

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 120.15

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

Support: NIH Grant 1R01AG053961

Title: Non-invasive blood-based biomarkers may indicate impaired generalization performance in older African Americans

Authors: Z. OSIECKA[1], K. MARTILLO[1], G. TAN[1], N. ASHTON[2], B. A. FAUSTO[1], H. ZETTERBERG[2], K. BLENNOW[2], *M. A. GLUCK[1];
[1]Ctr. for Mol. and Behavioral Neurosci., Rutgers Univ. Newark, Newark, NJ; [2]Univ. of Gothenburg, Gothenburg, Sweden

Abstract: The $A\beta_{42/40}$ ratio, measured in cerebrospinal fluid or plasma, is an extensively studied biomarker of Alzheimer's disease (AD), with lower levels associated with brain amyloidosis. Accumulating evidence further suggests that higher levels of neurofilament-light chain (NfL), a marker of neuroaxonal injury, may also be an indicator of AD-related neurodegeneration. However, NfL is not disease-specific, with elevated levels also found in amyotrophic lateral sclerosis, multiple sclerosis, traumatic brain injury, and cerebrovascular diseases. Therefore, the association between NfL and AD risk remains unclear. Evaluating these markers is critical, especially in older African Americans who are at double the risk for AD. Deficits in generalization-the ability to learn rules and apply these rules to new situations and contexts-is an early cognitive marker of AD risk in otherwise cognitively normal older individuals. The current study evaluated whether NfL and $A\beta_{42/40}$ ratio correlates with generalization performance in older African Americans. Sixty-three cognitively healthy African Americans aged 60 and older (M_{age} = 73.40 years, SD = 6.12; M_{edu} = 14.32 years, SD = 2.24; n = 49 women) provided blood samples and responded to measures of cognitive function. From the blood samples, plasma was extracted to assess for NfL and $A\beta_{42/40}$ levels. Participants' cognitive performance was evaluated using a measure of generalization. Results show that plasma NfL, but not $A\beta_{42/40}$, was significantly associated with generalization performance (B = -0.287, p = .041). Participants with higher levels of neuroaxonal damage (plasma NfL) had poorer accuracy in applying past learning to new contexts. Increased plasma NfL concentration, indicating greater neuroaxonal damage, better predicted performance on a cognitive marker of AD risk in a cohort of older African Americans. These findings suggest that NfL levels may be more sensitive than plasma $A\beta_{42/40}$ ratio to the type of pathophysiology associated with early cognitive changes in this population.

Disclosures: Z. Osiecka: None. **K. Martillo:** None. **G. Tan:** None. **N. Ashton:** None. **B.A. Fausto:** None. **H. Zetterberg:** None. **K. Blennow:** None. **M.A. Gluck:** None.

Poster

120. Alzheimer's Disease: Biomarkers II

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 120.16

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

Support: Institutional Support from Northeast Ohio Medical University
Institutional Support from Akron Children's Hospital (Akron, OH)

Title: Melanopsin ganglion cell morphology in the 3xTg mouse model of Alzheimer’s disease (AD)

Authors: *S. S. DEWAN, C. M. DENGLER-CRISH, J. M. FERRELL, M. A. SMITH; Pharmaceut. Sci., Northeast Ohio Med. Univ., Rootstown, OH

Abstract: Circadian rhythm abnormalities are reported in AD patients very early in the course of the disease. These include abnormal timing and duration of the sleep cycle, reduction of melatonin levels during the night, and alternating expression of clock genes. Although these deficits could be caused by dysregulation within several brain sites, the retina has been postulated as one of the earliest neural structures affected in AD. Melanopsin-expressing retinal ganglion cells (mRGCs) are responsible for maintaining circadian rhythms, thus making the retina an attractive target for investigating pathological mechanisms. Loss of mRGCs has been reported in other neurodegenerations such as Parkinson’s disease and glaucoma. While there is amyloid-β accumulation, mRGC loss, and gliosis in the retinas of mouse models of AD, little is known about the progression of pathology in mRGC axons. Using a combination of immunohistochemistry and high-resolution fluorescent microscopy, we examined mRGC morphology in 4-7 month-old 3xTg mice, a commonly used murine model of AD. We found significant decreases in dendritic field complexity, dendritic area, and soma size in the retina. Importantly, these changes occurred independent of a reduction in total RGC and mRGC soma density in the corresponding retinas, a finding that mimics the progression of other age-related neurodegenerations. In conclusion, the 3xTg mouse exhibits early changes in mRGC morphology in the absence of cell body loss. The accessibility, isolation, and simplicity of the anterior visual system may provide a useful framework for studying the mechanisms of axonopathy in AD.

Disclosures: S.S. Dewan: None. **C.M. Dengler-Crish:** None. **J.M. Ferrell:** None. **M.A. Smith:** None.

Poster

120. Alzheimer's Disease: Biomarkers II

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 120.17

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

Support: Ontario Brain Institute
CIHR Grant MOP-FDN-148418
Parkinson Canada Graduate Student Award

Title: Free viewing of video clips exposes saccade- and pupil-related changes across multiple neurodegenerative diseases

Authors: *H. C. RIEK[1], D. C. BRIEN[1], B. C. COE[1], B. J. WHITE[1], A. ABRAHAO[2], S. R. ARNOTT[3], D. BEATON[4], M. A. BINNS[3], S. BLACK[2], E. FINGER[5], C. E. FISCHER[4], A. R. FRANK[6], D. A. GRIMES[7], S. KUMAR[8], A. E. LANG[9], W. LOU[10], C. MARRAS[9], M. MASELLIS[2], S. H. PASTERNAK[5], B. G. POLLOCK[8], T. K. RAJJI[10], T. D. L. STEEVES[4], K. M. SUNDERLAND[3], B. TAN[3], D. F. TANG-WAI[10], M. C. TARTAGLIA[10], J. TURNBULL[11], L. ZINMAN[2], O. INVESTIGATORS[12], D. P. MUNOZ[1];
[1]Ctr. for Neurosci. Studies, Queen's Univ., Kingston, ON, Canada; [2]Sunnybrook Hlth. Sci. Ctr., Toronto, ON, Canada; [3]Rotman Res. Inst., Baycrest Hosp., Toronto, ON, Canada; [4]St Michael's Hosp., Toronto, ON, Canada; [5]Univ. of Western Ontario, London, ON, Canada; [6]Bruyere Res. Inst., Ottawa, ON, Canada; [7]Ottawa Hosp., Ottawa, ON, Canada; [8]Ctr. for Addiction and Mental Hlth., Toronto, ON, Canada; [9]Toronto Western Hosp., Toronto, ON, Canada; [10]Univ. of Toronto, Toronto, ON, Canada; [11]Dept. of Med., McMaster Univ., Hamilton, ON, Canada; [12]Ontario Brain Inst., Toronto, ON, Canada

Abstract: Discovering behavioural biomarkers in neurodegenerative disease may prove crucial to the development of novel therapeutics and early disease detection. Saccades and pupil responses have been proposed as potential biomarkers because circuitry modulating these behaviours is also implicated in multiple neurodegenerative diseases. Although instruction-based tasks such as the antisaccade task have previously been examined as biomarker sources, patients with limited cognitive or physical abilities may be unable to complete them successfully; additionally, few studies have evaluated multiple neurodegenerative pathologies concurrently. Using a novel task involving 10 minutes' free viewing of short, frequently changing video clips, we evaluated saccade and pupil behaviour in a large cohort of neurodegenerative disease patients from the Ontario Neurodegenerative Disease Research Initiative: 42 Alzheimer's disease (AD, age 54-88, 25 male), 69 mild cognitive impairment (MCI, age 55-86, 38 male), 21 amyotrophic lateral sclerosis (ALS, age 40-75, 14 male), 18 behavioural variant frontotemporal dementia (age 54-80, 13 male), 10 progressive supranuclear palsy (age 63-78, 6 male), and 129 Parkinson's disease (age 55-85, 100 male), plus 100 healthy age-matched controls (age 54-86, 33 male). Various saccade parameters were measured, including centre bias (tendency to fixate the centre of the screen), saccade and microsaccade frequency and amplitude. Parameters measured in relation to clip changes were also extracted: saccade and microsaccade rates both immediately following clip change and later during each clip, and pupil constriction and dilation responses. Preliminary data indicates various low-level behavioural alterations in multiple disease cohorts: increased centre bias, lower overall saccade rate and reduced saccade amplitude. For clip-aligned analyses, patients generally demonstrated lower saccade rate but higher microsaccade rate following clip change relative to control participants. Additionally, a subset of disease groups (AD, MCI, ALS) displayed blunted pupil responses to clip changes relative to controls. This task

may therefore be a comparatively inexpensive and easily implemented method to produce behavioural biomarkers for neurodegenerative disease, even at advanced disease stages. Future work should explore the possible effects of factors such as medication and disease stage on free viewing-derived parameters, as well as parameters that differentiate neurodegenerative diseases from one another.

Disclosures: H.C. Riek: None. **D.C. Brien:** None. **B.C. Coe:** None. **B.J. White:** None. **A. Abrahao:** None. **S.R. Arnott:** F. Consulting Fees (e.g., advisory boards); Indoc Research Canada. **D. Beaton:** None. **M.A. Binns:** None. **S. Black:** None. **E. Finger:** None. **C.E. Fischer:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Vielight Inc, Hoffman La Roche. **A.R. Frank:** None. **D.A. Grimes:** None. **S. Kumar:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Soterix Medical. **A.E. Lang:** None. **W. Lou:** None. **C. Marras:** None. **M. Masellis:** None. **S.H. Pasternak:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Zywie Bio LLC. **B.G. Pollock:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); US Provisional Patent, Canada Provisional Patent. Other; American Geriatrics Society. **T.K. Rajji:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Newronika, Scientific Brain Training Pro. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); US Provisional Patent. F. Consulting Fees (e.g., advisory boards); Biogen Canada Inc. **T.D.L. Steeves:** None. **K.M. Sunderland:** None. **B. Tan:** None. **D.F. Tang-Wai:** None. **M.C. Tartaglia:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Biogen, Janssen, Anavex, Green Valley, Roche. **J. Turnbull:** None. **L. Zinman:** None. **O. Investigators:** None. **D.P. Munoz:** None.

Poster

120. Alzheimer's Disease: Biomarkers II

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 120.18

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

Title: Neuronal tissue responses in the presence of amyloid beta and tau

Authors: *V. NORMAN[1], A. GRAY[2], R. PROSSER[1];
[1]Biochem. and Cell. and Mol. Biol., [2]Chem., Univ. of Tennessee, Knoxville, Knoxville, TN

Abstract: Alzheimer's disease (AD) is a progressive and irreversible brain disorder. It is pathologically defined as the accumulation of amyloid- (A) peptides and strings of hyperphosphorylated tau proteins. The formation and spreading of amyloid plaques and neurofibrillary tangles are thought to cause the neuronal loss associated with AD but how neuronal tissues respond to the initial presence of these peptides remains unknown. In this study, we are investigating cytotoxicity within the brain and identifying proteins being released from brain tissue slices exposed to A and/or tau. We are also comparing the effects of A and tau across the suprachiasmatic nucleus (SCN), anterior hypothalamus (AH) and entorhinal cortex (EC). Coronal brain tissue slices containing the SCN/AH or EC were prepared from adult male C57/Bl mice and maintained in interface brain slice chambers. The tissues were incubated for 12 hours with no treatment or medium containing 10M A, tau, or both. Media from the slice chambers was collected and replenished every 2 h for later LC-IMS-MS analysis of peptides released from the tissues. The same media samples were also analyzed for lactate dehydrogenase (LDH) content as a measure of cell death. After 12 hours, the slices were incubated with propidium iodide, then fixed, sectioned, and imaged for histological quantification of cell death. Preliminary data shows that there is no significant difference in the amount of cell death seen in the SCN/AH or EC when incubated with A and/or tau in comparison to the control. LDH quantification shows increased cell death over the 12 hours in the SCN/AH compared to the controls. LC-IMS-MS data show differences in peptides released from the tissues under the different conditions. We are currently repeating these experiments with higher concentrations of A and tau. In the future, we hope to incorporate the use of microfluidics in order to obtain real-time information on the tissues in the presence of A and tau. By integrating the data sets, we hope to identify possible biomarkers or therapeutic targets for AD.

Disclosures: V. Norman: None. **A. Gray:** None. **R. Prosser:** None.

Poster

121. Parkinson Disease: Biomarkers

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 121.01

Topic: C.03. Parkinson's Disease

Support: ISF-grant 1657-16
Ministry of health grant 3000-14527

Title: Heart-rate variability as a new marker to identify predisposition to freezing events in persons with Parkinson's Disease

Authors: *B. HEIMLER[1], O. KOREN[2], R. INZELBERG[3,4], U. ROSENBLUM[2], R. BARTSCH[5], M. PLOTNIK[1,3];
[1]Ctr. of advanced technologies in rehabilitation, [2]Sheba Med. Ctr., Ramat Gan, Israel; [3]Tel Aviv Univ., Tel Aviv, Israel; [4]Weizmann Inst. for Sci. and Technologies, Rehovot, Israel; [5]Bar-Ilan Univ., Ramat Gan, Israel

Abstract: Freezing of gait (FOG) is a debilitating symptom of advanced Parkinson's disease (PD). It is a brief, episodic absence or significant reduction in forward progression of the feet despite an intention to walk. The etiology of FOG is still unknown, but accumulating evidence unraveled physiological signatures of the autonomous nervous system (ANS), both before and during FOG episodes. Here we aimed at further investigating the involvement of the ANS in the emergence of FOG by characterizing the balance between parasympathetic and sympathetic contributions. We thus analyzed heart-rate variability (HRV), i.e., the fluctuations in time intervals between adjacent heart-beats, mainly generated by heart-brain interactions and considered a marker of sympathovagal balance and an indirect measure of ANS tone. Higher HRV (or greater variability between heart-beats) indicates balanced sympathetic/parasympathetic activity and reflects great adaptability to the environment. To achieve our aim, we measured heart-rate at rest (while standing) for one minute from 21 persons with PD with FOG (PD+FOG; as defined by the N-FOG questionnaire) and without cardiac arrhythmia, while OFF levodopa medications, as well as from 22 elderly controls (EC). Then, PD+FOG participants performed walking trials containing FOG-triggering events (e.g., turns). During these trials, n=13 did experience FOG (PD+FOG$^+$), while n=8 did not experience it (PD+FOG$^-$). Most participants (n=16: 9 PD+FOG$^+$ and 7 PD+FOG$^-$) repeated the experiment 2-3 weeks later, while being ON their L-DOPA medications. While ON, none of the patients experienced freezing. Results show that during OFF, HRV parameters at rest were significantly lower in PD+FOG$^+$ patients (i.e., more pathological), reflecting a more damaged ANS regulatory capacity. PD+FOG$^-$ patients and EC showed comparable HRV measures. During the ON condition, HRV did not differ between groups. HRV parameters in the PD group did not correlate with age, PD duration, levodopa consumption, UPDRS scores, nor N-FOGQ scores.Taken together, these findings suggest for the first time a link between HRV pathological alterations and FOG phenomena. In addition, these results may strengthen recent novel evidence documenting a correlation in PD patients between alterations in HRV and dopamine depletion in the striatum. Supplementary within-subjects comparisons are needed to confirm that variations in the 'physiological state' of patients modify FOG propensity. If so, ANS state monitoring might be an effective innovative approach to 'forecast' upcoming FOG occurrences.

Disclosures: B. Heimler: None. **O. Koren:** None. **R. Inzelberg:** None. **U. Rosenblum:** None. **R. Bartsch:** None. **M. Plotnik:** None.

Poster

121. Parkinson Disease: Biomarkers

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 121.02

Topic: C.03. Parkinson's Disease

Support: NIH Grant R01 NS058487

Title: Functional activity of the motor cortex is impaired in idiopathic rapid eye movement behavior disorder and Parkinson's disease

Authors: *E. R. TOBIN[1], D. J. ARPIN[1], M. B. SCHAUDER[1], M. L. HIGGINBOTHAM[1], R. B. BERRY[2], M. S. JAFFEE[3], D. E. VAILLANCOURT[1,3,4];
[1]Applied Physiol. and Kinesiology, [2]Medicine, Div. of Pulmonary Critical Care and Sleep, [3]Neurology, Fixel Ctr. for Neurolog. Disease, Program in Movement Disorders and Neurorestoration, [4]Biomechanical Engin., Univ. of Florida, Gainesville, FL

Abstract: Introduction: Idiopathic rapid eye movement (REM) behavior disorder (iRBD) is a disruptive sleep-related disorder that has a high risk of developing Parkinson's disease (PD).[1] About 80-90% of individuals with iRBD will develop a neurodegenerative alpha-synuclein disorder in the following decades.[2-5] It is unclear how early and in which structures we observe functional changes in the brain in patients with iRBD that do not have a diagnosis of another neurodegenerative disorder. **Objective:** In this study, we use task-based functional magnetic resonance imaging (fMRI) to observe blood oxygen level dependent (BOLD) signal changes in individuals with PD, iRBD, and healthy controls (HC). **Methods:** Participants include a total of 33 subjects, with 11 in each group (PD, iRBD, and HC). All participants were scanned in a 3T Philips MRI scanner, while they performed a unimanual grip force task. We performed a three-factor (3X3) repeated measures ANCOVA for the primary motor cortex (M1) covarying for age and sex. Scan (3 scans) was a within-subjects factor, and diagnosis (PD, iRBD, HC) was a between-subject factor. Post-hoc comparisons were carried out by using a 2X3 repeated measures ANCOVA, covarying for age and sex. **Results:** There was a main effect of diagnosis in the M1 [$F(2,28)=6.172$, $p=0.006$]. In post hoc analysis for M1, we found that patients with PD have reduced BOLD signal compared with HCs [$F(1,18)=7.500$, $p=0.013$]. We also observed that patients with iRBD have reduced BOLD signal compared with HCs [$F(1,18)=9.090$, $p=0.007$]. No difference was observed in BOLD signal between iRBD and PD [$F(1,18)=0.300$, $p=0.426$]. **Conclusion:** We replicate prior work that during a force control task the M1 has a reduced BOLD signal in early-stage PD. The novel finding here is that iRBD patients have a reduced BOLD signal in the M1 compared with HCs. This finding suggests that functional changes are occurring in the primary motor cortex early on before clinical motor symptoms are present. This finding may have implications regarding a top-down or bottom-up hypothesis for how PD originates in the nervous system.

Disclosures: E.R. Tobin: None. **D.J. Arpin:** None. **M.B. Schauder:** None. **M.L. Higginbotham:** None. **R.B. Berry:** None. **M.S. Jaffee:** None. **D.E. Vaillancourt:** None.

Poster

121. Parkinson Disease: Biomarkers

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 121.03

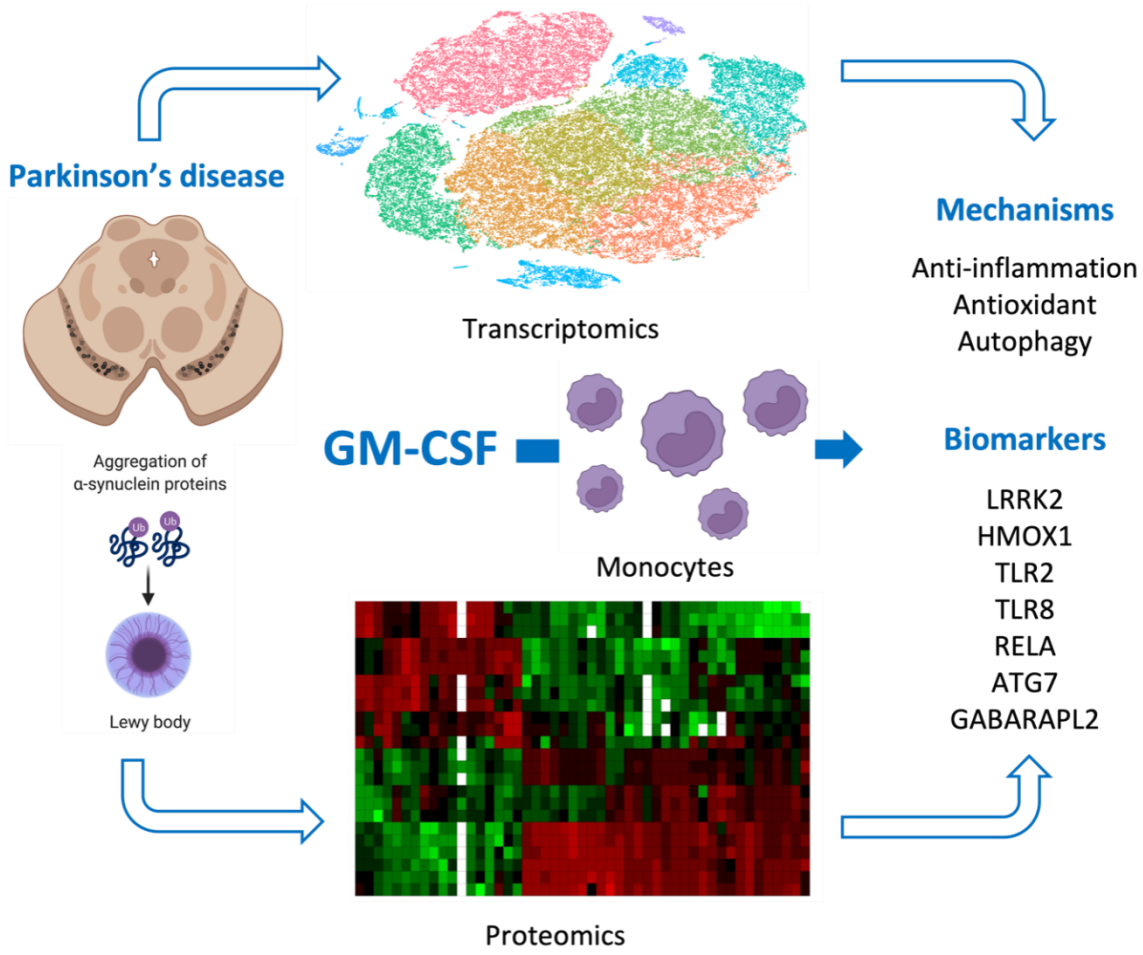
Topic: C.03. Parkinson's Disease

Support: University of Nebraska Foundations
Partner Therapeutics

Title: Monocyte biomarkers define sargramostim treatment outcomes for Parkinson's disease

Authors: *M. ABDELMOATY[1], J. MACCHI[1], P. YEAPURI[1], F. SHAHJIN[1], V. KUMAR[2], K. OLSON[1], L. MOSLEY[1], H. GENDELMAN[1];
[1]Univ. of Nebraska Med. Center, Dept. of Pharmacol. and Exptl. Neurosci., Omaha, NE; [2]Univ. of Nebraska Med. Center, Mass Spectrometry and Proteomics Core, Omaha, NE

Abstract: Monocyte biomarkers define sargramostim treatment outcomes for Parkinson's disease Mai M. Abdelmoaty[1], Jatin Machhi[1], Pravin Yeapuri[1], Farah Shahjin[1], Vikas Kumar[2], KatherineE. Olson[1], R. Lee Mosley[1], and Howard E. Gendelman[11]Department of Pharmacology and Experimental Neuroscience, College of Medicine, Universityof Nebraska Medical Center, NE 68198, USA[2]Mass Spectrometry and Proteomics Core, University of Nebraska Medical Center, Omaha, NE68198, USA**Abstract**Dysregulation of innate and adaptive immunity heralds both the development andprogression of Parkinson's disease (PD). Deficits in innate immunity in PD are defined byimpairments in monocyte activation, function, and pro-inflammatory secretory factors. Eachinfluences disease pathobiology. To define monocyte biomarkers associated with immunetransformative therapy for PD, changes in gene and protein expression were evaluated before andduring treatment with recombinant human granulocyte-macrophage colony-stimulating factor(GM-CSF, sargramostim, Leukine®). Monocytes were recovered after leukapheresis and isolationby centrifugal elutriation, before and 2 and 6 months after initiation of treatment. Transcriptomeand proteome biomarkers were scored against clinical motor functions. Pathway enrichments fromsingle cell-RNA sequencing and proteomic analyses from sargramostim-treated PD patientsdemonstrate a neuroprotective signature, including, but not limited to, antioxidant, anti-inflammatory, and autophagy genes and proteins (LRRK2, HMOX1, TLR2, TLR8, RELA, ATG7,and GABARAPL2). This monocyte profile provides a novel strategy to track clinical immune-based interventions.



Disclosures: **M. Abdelmoaty:** None. **J. Macchi:** None. **P. Yeapuri:** None. **F. Shahjin:** None. **V. Kumar:** None. **K. Olson:** None. **L. Mosley:** None. **H. Gendelman:** None.

Poster

121. Parkinson Disease: Biomarkers

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 121.04

Topic: C.03. Parkinson's Disease

Title: Poly(adp)-ribose (par)-alpha-synuclein signature in csf: a potentially distinguishing biomarker for a specific subtype of parkinson's disease?

Authors: K. HALL, V. SIMBI, L. KOBAYASHI, B. O. VAN EMBURGH, J. HEAVIN, ***S. BRAHMACHARI**, I. LOFTIN;
Valted Seq, Inc, Gaithersburg, MD

Abstract: PARP-1 activation-dependent accumulation of poly(ADP-ribose) (PAR) contributes to cell death in relevant neurological disorders. It has been shown earlier that PARP-1/PAR kills dopaminergic neurons via parthanatos, a cell death pathway. Recent studies demonstrate a central role of PAR in driving pathologic α-synuclein neurodegeneration in Parkinson's disease (PD). PAR also accelerates fibrillization of α-synuclein and potentiates its neuronal toxicity. Elevated level of PAR in postmortem PD brain and patient CSF implicates its potential as a biomarker for PD. In this current exploratory study, we investigated, association of PAR and α-synuclein in the CSF from PD patients and further evaluated their potential as biomarkers for PD. In a pilot study cohort of PD patients and age-matched neurologically healthy controls, we measured the CSF levels of total α-synuclein by an electrochemiluminescence immunoassay developed in-house on MSD platform, and PAR by a sandwiched immunoassay. Only a subset of PD patients (27% of total PD CSF samples) showed detectable PAR in CSF. In contrast, although PAR was detectable in 20% of the controls, their levels were markedly low compared to PD with detectable PAR. Interestingly, except one, the rest of the PD patients with detectable PAR have robustly elevated level of α-synuclein in the CSF. Although, the subgroup of PD patients with detectable PAR and high α-synuclein did not show any correlation with the disease severity, this remains inconclusive because of the low sample size and lack of complete data availability on the disease stage of the patients. However, strikingly, this small subgroup of PD patients with PAR-α-synuclein signature in the CSF, are the only group of patients in this study cohort who have mild dementia. Taken together, our preliminary observations of strong association between CSF PAR and α-synuclein in PD and its correlation with dementia, suggest that PAR-α-synuclein signature in the CSF could potentially be a distinguishing biomarker for Parkinson's disease patients with dementia.

Disclosures: K. Hall: None. **V. Simbi:** None. **L. Kobayashi:** None. **B.O. Van Emburgh:** None. **J. Heavin:** None. **S. Brahmachari:** None. **I. Loftin:** None.

Poster

121. Parkinson Disease: Biomarkers

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 121.05

Topic: C.03. Parkinson's Disease

Support: NIH Grant R01 NS085070
NIH Grant U54 NS110435

Title: Identifying mitophagy regulators in Lewy body disease: a genome-wide association study in autopsy brain

Authors: *X. HOU[1], M. G. HECKMAN[2], F. C. FIESEL[1,3], S. KOGA[1], P. K. BONESKI[1], A. I. BEASLEY[1], P. W. JOHNSON[2], L. J. WHITE[2], Z. S. QUICKSALL[2], D. W. DICKSON[1,3], O. A. ROSS[1,3], W. SPRINGER[1,3];

[1]Neurosci., [2]Biomed. Statistics and Informatics, Mayo Clin., Jacksonville, FL; [3]Neurosci. PhD Program, Mayo Clin. Grad. Sch. of Biomed. Sci., Jacksonville, FL

Abstract: Loss of function mutations in *PINK1* and *PRKN* are the most common causes of early-onset Parkinson disease (PD). The genes encode the ubiquitin (Ub) kinase PINK1 and the E3 Ub ligase PRKN, two enzymes that regulate the autophagic degradation of dysfunctional mitochondria, termed mitophagy. During this cytoprotective process, PINK1 and PRKN identify and jointly decorate damaged mitochondria with phosphorylated Ub (pS65-Ub) that serves as the mitophagy tag. Accumulating evidence strongly suggest a pathogenic role for impaired mitophagy in PD and related neurodegenerative conditions. This is in line with our previous finding of increased levels of the mitophagy marker pS65-Ub in the hippocampus of postmortem brains with Lewy body disease (LBD). We here undertook an unbiased genome-wide association study (GWAS) using hippocampal pS65-Ub level as quantitative trait to identify novel regulators of the PINK1-PRKN-directed mitophagy in autopsy brain. In a two-stage GWAS, we obtained autopsy confirmed LBD samples from Caucasian participants of European ancestry. Using an established, mostly automated workflow, hippocampal sections were immunostained for pS65-Ub, scanned, and quantified with unbiased algorithms. In the discovery stage (n=754), we performed an analysis of 8,696,291 variants and identified one genome-wide significant association ($p<5x10^{-8}$) and six suggestive associations ($p<5x10^{-6}$). In the replication stage (n=258), we performed genotyping of significant and suggestive hits from the discovery stage. Lastly, we did a meta-analysis of both stages for a joint analysis. Our findings identified that *APOE* variation rs429358 (β: 0.5, 95% CI: 0.39 to 0.62, $p=1.18 \times 10^{-17}$) is strongly associated with pS65-Ub levels in LBD cases. One additional association was confirmed in the joint analysis (β: -0.33, 95% CI: -0.45 to -0.22, $p=1.42 \times 10^{-8}$). Our findings nominate novel mitophagy regulators in LBD brain and highlight a strong association of *APOE* variants with mitophagy alteration. With *APOE4* as the strongest known risk factor for Alzheimer's disease and dementia with Lewy body, our findings suggest a common mechanistic link underscoring the importance of mitochondrial quality control. Our ongoing efforts will provide functional validation of the two identified variants in patient-derived iPSCs and mouse models. This study is supported by NIH [R01 NS085070 and U54 NS110435].

Disclosures: **X. Hou:** None. **M.G. Heckman:** None. **F.C. Fiesel:** Other; Filed a patent related to PRKN activators. **S. Koga:** None. **P.K. Boneski:** None. **A.I. Beasley:** None. **P.W. Johnson:** None. **L.J. White:** None. **Z.S. Quicksall:** None. **D.W. Dickson:** None. **O.A. Ross:** None. **W. Springer:** Other; Filed a patent related to PRKN activators.

Poster

121. Parkinson Disease: Biomarkers

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 121.06

Topic: C.03. Parkinson's Disease

Support: Sentinelle Nord
CIHR
Quebec Parkinson Network

Title: Retinal biomarkers for the diagnosis of prodromal Parkinson's disease

Authors: *V. SOTO LINAN[1], C. GORA[1], M. R. PERALTA, III[2], N. DUPRÉ[3], M. HÉBERT[1], M. LEVESQUE[1];
[1]CERVO Brain Res. Ctr. - Laval Univ., Quebec City, QC, Canada; [2]CRIUSMQ - Laval Univ., Quebec City, QC, Canada; [3]CHU of Quebec - Laval Univ., Quebec City, QC, Canada

Abstract: Parkinson's (PD) diagnosis primarily occurs after severe neurodegeneration, despite early non-motor symptomatology being present decades prior. With the need for efficient biomarkers, we aimed to validate non-invasive techniques — electroretinogram (ERG) and oral microbiota — to detect emerging peripheral effects reflecting early central dysfunction. We used homozygous M83 transgenic mice overexpressing human A53T variant of α-synuclein (n=8) as a PD model. Mice of both sexes underwent behavioral tests and ERG measurements (Scotopic, Photopic, and PhNR). At eight months, mice were sacrificed, and neural and retinal tissue histological analyses were performed to assess synucleinopathies and neurodegeneration. Simultaneously, early-onset PD patients (n=13, mean age 63.9 ±2.2; mean disease duration 3.6 ±0.3) and healthy age-matched controls (n=11, mean age 62.7 ±2.6) were recruited including both genders. They underwent ERG testing, oral bacteria Salivette swabs, and an unstimulated saliva collection for complementary proteomic/metabolomic analysis. ERG analysis in mice revealed a significant b-wave amplitude reduction in the photopic ERG (two-way ANOVA with Sidak's multiple comparisons, $p<0.05$). Compared to control mice, an average of 25.9% ±0.4 of b-wave amplitude reduction ($p= 0.0031$) was measured at two months, 33.2% ±1.8 at four months ($p= 0.0031$), and 33.6% ±0.9 at six months ($p= 0.0335$) of age. Echoing animal models, PD patients also presented a diminished b-wave amplitude, constituting an average 25.4% ±0.2 and 12.1% ±0.7 reduction in the scotopic and photopic tests, respectively. Photopic oscillatory potential (OPs) extraction showed patients had an average 28.8% ±0.03 reduction in OP1 amplitude, by 18.9% ±0.2 in OP2, 18.1% ±1 in OP3, and 18.3% ±0.2 in OP4. PD patients also exhibited an average 19.8% ±0.1 PhNR wave amplitude reduction.Our results in sex-inclusive mice and human cohorts suggest that in PD, bipolar cell output driving the b-wave peak is diminished regardless of photo processing pathways via the cone (photopic) or mixed rod-cone (scotopic) input. This weaker output to light stimulus in the outer retina culminates in the inner retina—where retinal ganglion cells signal back through the optic nerve (stimulated in the PhNR). Considering changes in OPs driven by dopamine-containing amacrine cells, synapse impairments within the retina appear to distinguish Parkinson's early pathology in the periphery. Altogether, the ERG has the potential to indirectly track central neurological changes, helping us detect Parkinson's early and providing a wider window for treatment and intervention in the future.

Disclosures: V. Soto Linan: None. **C. Gora:** None. **M.R. Peralta:** None. **N. Dupré:** None. **M. Hébert:** None. **M. Levesque:** None.

Poster

121. Parkinson Disease: Biomarkers

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 121.07

Topic: C.03. Parkinson's Disease

Title: Motor symptoms severity, levodopa dosage and semantic verbal fluency predict levodopa induced dyskinesia in Parkinson's disease patients

Authors: D. A. B. LEAL[1], C. M. V. DIAS[2], R. P. RAMOS[1], P. PETERSSON[3], ***I. BRYS**[4,5]; [1]Postgraduate Program in Hlth. and Biol. Sci., [2]Postgraduate Program in Psychology, Federal Univ. of Vale do São Francisco, Petrolina, Brazil; [3]Exp.Med. Sci., Lund Univ., Lund, Sweden; [4]Federal Univ. of Vale Do Sao Francisco, Petrolina, Brazil; [5]Umeå Univ., Umeå, Sweden

Abstract: Dyskinesias are abnormal involuntary movements that represent the extreme limitation of the long term gold standard treatment of Parkinson's disease (PD), throughout the dopamine precursor levodopa. Dyskinesias are not preventable, and currently when a patient is diagnosed with PD and starts the dopaminergic therapy, it is not possible to know if she/he will develop dyskinesia in the future. Applying machine learning techniques on the data extracted from the Parkinson's Progression Marker Initiative (PPMI, Michael J. Fox Foundation), this study was aimed to identify PD patients who are at high risk of developing dyskinesia based on behavioral, clinical and neurological features. Our results show that the Random Forest classifier had the most consistent performance among the tested classifiers, reaching the area under the receiver operating characteristic (ROC) curve of up to 91.8% with only seven features. Information regarding the patient's symptoms severity, semantic verbal fluency, and levodopa dosage were the most important for this prediction, and were used to further create a Decision Tree, whose rules may be used to guide the pharmacological management of PD symptoms. In summary, our results contribute to the identification of PD patients who are prone to develop dyskinesia, and may be considered in future clinical trials aiming at developing new therapeutic approaches for PD.

Disclosures: D.A.B. Leal: None. **C.M.V. Dias:** None. **R.P. Ramos:** None. **P. Petersson:** None. **I. Brys:** None.

Poster

121. Parkinson Disease: Biomarkers

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 121.08

Topic: C.03. Parkinson's Disease

Support: The Royal Physiographic Society of Lund
Promobilia

Karolinska Institutet Research Funds
The Swedish Brain Foundation
Southern and Eastern Norway Regional Health Authority
Michael J Fox Foundation
Åke Wibergs foundation

Title: Investigating the potential association of PLPP4 to Parkinson's disease

Authors: *K. BROLIN[1], C. RAN[2], P. SVENNINGSSON[3], M. TAN[4], L. PIHLSTRÖM[4], A. CARMIN BELIN[2], M. SWANBERG[1];
[1]Exptl. Med. Sci., Lund Univ., Lund, Sweden; [2]Dept. of Neurosci., [3]Dept. of Neurol. and Clin. Neurosci., Karolinska Institutet, Stockholm, Sweden; [4]Dept. of Neurol., Oslo Univ. Hosp., Oslo, Norway

Abstract: The disease etiology for the majority of individuals living with Parkinson's disease (PD) is complex and influenced by common genetic variants. Large genome-wide association studies (GWAS) in individuals of European ancestry have identified 90 independent PD risk-associated variants. These collectively account for 16-36% of the heritable PD risk, indicating that more variants remain to be identified. Despite the general close genetic similarities among European populations, genetic differences between countries exist and the genomes of Swedes have been reported to contain a substantial amount of genetic variation that is not represented in other European populations. We have previously conducted the largest GWAS of PD with individuals solely from Sweden in which we nominate an unconfirmed and potentially population-specific genome-wide significant association to PD in the PLPP4 locus. However, subsequent studies are needed to validate whether PLPP4 is associated with PD. We therefore aimed to investigate the potential association between variants in PLPP4 and PD risk.
Candidate variants in PLPP4 were initially determined in a Swedish case-control cohort of PD comprised of 929 individuals with a confirmed PD diagnosis and 935 population-based controls, matched by age, sex, and residential area. The previously imputed top variants (n=2) were genotyped. The frequency and potential association were also investigated by genotyping of the nominate variants along with a disease-associated haplotype in additional 515 Swedish PD patients and 389 controls. Variant- and haplotype frequencies were studied in an additional reference population of 1,000 Swedish individuals (the Swegen dataset). Regression analyses were also done for individuals of European origin in the cohort available from the Accelerating Medicine Partnership - Parkinson's Disease (AMP-PD) and in samples of Norwegian ancestry. In total, 4,628 PD patients and 6,165 controls were analyzed.
Previous results revealed a genome-wide significant imputed variant in PLPP4 as being associated with PD with an odds ratio of 0.64 and a minor allele frequency of 27% among the patients and 36% among the controls. This finding could be confirmed in the genotyped data by a statistically significant associated haplotype in the region. The MAF for the candidate variant was 32% in the reference cohort Swegen. The initial analyses of additional Swedish, Norwegian and European PD cohorts have not replicated the association to PD. This work contributes to the knowledge about the role of PLPP4 in PD, providing insights on genetic risk factors in PD.

Disclosures: **K. Brolin:** None. **C. Ran:** None. **P. Svenningsson:** None. **M. Tan:** A. Employment/Salary (full or part-time):; Oslo University Hospital, Southern and Eastern Norway Regional Health Authority. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug

study, report that research relationship even if those funds come to an institution.; Michael J Fox Foundation. **L. Pihlström:** None. **A. Carmin Belin:** None. **M. Swanberg:** None.

Poster

121. Parkinson Disease: Biomarkers

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 121.09

Topic: C.03. Parkinson's Disease

Support: BBSRC BB/R01583X/1
NIH R01-DA048096
NIH R01-MH121099
NIH R01-NS092701
NIH KL2TR001421
NIH R01-MH124115

Title: Sub-second time perception reflects individual differences in motor and non-motor symptoms in Parkinson's disease

Authors: *E. DIMARCO[1], R. SADIBOLOVA[5], A. JIANG[2], R. JONES[3], B. LIEBENOW[7], I. U. HAQ[8], M. S. SIDDIQUI[9], D. B. TERHUNE[6], K. T. KISHIDA[4];
[1]Wake Forest Univ. Sch. of Med., Winston-Salem, NC; [2]Physiol. Pharmacol., [3]Physiol. & Pharmacol., [4]Physiol. and Pharmacol., Wake Forest Univ. Sch. of Med., Winston Salem, NC; [5]Psychology, [6]Goldsmiths, Univ. of London, London, United Kingdom; [7]Wake Forest Sch. of Med., Winston-Salem, NC; [8]Neurol., Miami Miller Sch. of Med., Miami, FL; [9]Neurol., Atrium Wake Forest Baptist Hlth., Winston-Salem, NC

Abstract: Changes in striatal dopamine efficacy is at the core of Parkinson's disease (PD) motor symptoms but has also been associated with many comorbid non-motor symptoms. Dopaminergic signaling in the striatum has also been shown to play a critical role in the perception of time. We hypothesized that patients with PD perceive time differently and in accordance with their specific clinical presentation. We recruited patients with PD (N=19) and compared individual differences in patients' clinical presentation with their ability to discriminate sub-second time intervals (500ms-1100ms) while on or off their prescribed dopaminergic medications. We report that individual differences in comorbid non-motor symptoms and PD disease duration and pharmacotherapeutic strategy accounted for individual differences in time perception performance: impulse control disorder is associated with temporal overestimation ($n = 11$, $p < 0.01$); depression is associated with decreased accuracy ($n = 4$, $p < 0.05$); and PD disease duration (distribution = 1 - 8 years, $p < 0.01$) and levodopa monotherapy ($n = 11$, $p < 0.01$; versus poly-dopaminergic pharmacotherapy) are both associated with reduced temporal precision. Our results suggest that individual differences in the combination of motor and non-motor symptoms in PD are associated with changes in specific mechanisms underlying sub-second time perception. Observed differences in time perception behavior are consistent

with hypothesized mechanisms thought to underlie the respective motor and non-motor symptoms in PD. In future work, time perception tasks like the one used here may provide translational and reverse translational utility in investigations aimed at disentangling complex interactions between neural and cognitive systems underlying PD symptom etiology.

Disclosures: E. DiMarco: None. **R. Sadibolova:** None. **A. Jiang:** None. **R. Jones:** None. **B. Liebenow:** None. **I.U. Haq:** None. **M.S. Siddiqui:** None. **D.B. Terhune:** None. **K.T. Kishida:** None.

Poster

121. Parkinson Disease: Biomarkers

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 121.10

Topic: C.03. Parkinson's Disease

Support: Department of Defense Grant #W8XWH-04-1-0666
Department of Defense Grant W8XWH-19-1-0443

Title: Physical activity intensity is associated with cognition, connectivity, and blood solutes in Parkinson's Disease

Authors: *R. FOREMAN[1], E. K. DONAHUE[1], S. VENKADESH[2], V. BUI[1], D. WING[3], A. PETKUS[1], B. LUND[1], I. LITVAN[3], E. BAYRAM[3], J. VAN HORN[2], M. JAKOWEC[1], D. SCHIEHSER[3], G. PETZINGER[1];
[1]USC, Los Angeles, CA; [2]Univ. of Virginia, Charlottesville, VA; [3]UCSD, San Diego, CA

Abstract: Background: Cognitive impairment is common in Parkinson's disease (PD) and often leads to dementia. Aging studies suggest that intensity of physical activity (PA) is important for maintaining cognitive performance. Few studies have examined PA parameters and cognitive function in PD. Mechanisms that drive the PA benefits in cognition remain poorly elucidated. We examined the relationship between PA intensity and parameters of structured exercise (SE) in cognitive performance in PD and potential underlying mechanisms. **Methods:** 96 PD individuals underwent a neuropsychiatric battery. Time spent in moderate intensity PA (MIPA) was determined using a wearable device. Duration, frequency, and variety of SE were collected using a seven-day exercise log. 3T resting-state fMRI was assessed in a subset of individuals. Blood was assessed using a cytochrome bead array. **Results:** MIPA, but not light PA or SE duration, frequency, or variety, was associated with better global cognition, visual-spatial function, memory, and executive function. Individuals who met the WHO recommendation of ≥150 minutes/week of MVPA (high-MVPA) demonstrated high global cognition, visual-spatial, and executive function. Resting-state functional connectivity associated with meeting the WHO recommendation included brainstem, hippocampus, and regions in the middle frontal, cingulate, and posterior parietal cortices, which showed higher connectivity degrees in those who met the recommendation. Achieving 150 minutes of MIPA positively moderated the associations

between identified functional connectivity and global cognition, language, and visual-spatial function. MIPA was also associated with higher plasma levels of IL-10 and MIP1b and lower plasma levels of leptin.
Conclusion: PA intensity is important for cognitive function in PD. Encouraging MIPA, particularly the WHO recommendation of ≥150 minutes of MIPA/week, may represent an important new prescription for PD cognition**.**

Disclosures: R. Foreman: None. **E.K. Donahue:** None. **S. Venkadesh:** None. **V. Bui:** None. **D. Wing:** None. **A. Petkus:** None. **B. Lund:** None. **I. Litvan:** None. **E. Bayram:** None. **J. Van Horn:** None. **M. Jakowec:** None. **D. Schiehser:** None. **G. Petzinger:** None.

Poster

121. Parkinson Disease: Biomarkers

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 121.11

Topic: C.03. Parkinson's Disease

Support: DoD grant W8XWH-04-1-0665
DoD grant W8XWH-19-1-0443

Title: White matter perivascular spaces in parkinson's disease are associated with decreased cognition, interrupted sleep and less physical activity, and blood levels of mmp9

Authors: *E. K. DONAHUE[1], R. P. FOREMAN[1], J. J. DURAN[1], V. BUI[1], S. VENKADESH[4], D. WING[5], A. PETKUS[1], B. LUND[1], I. LITVAN[6], E. BAYRAM[5], D. SCHIEHSER[5], J. CHOUPAN[2], M. W. JAKOWEC[3], G. PETZINGER[7];
[2]Psychology, [3]Neurol., [1]USC, Los Angeles, CA; [4]Univ. of Virginia, Charlottesville, VA; [5]UCSD, La Jolla, CA; [6]UC San Diego, La Jolla, CA; [7]Parkinson's Inst., Sunnyvale, CA

Abstract: Background: Perivascular spaces (PVS) are the fluid-filled spaces surrounding blood vessels in the brain. PVS comprises on aspect of the glymphatic system, an important glia-lymphatic system responsible for distribution of essential molecules, clearances of waste produce including alpha synuclein, and is a site of immune surveillance in the brain. Recent evidence indicates greater PVS in PD compared to healthy controls, but PVS role in non-motor (cognition and sleep) behaviors and how physical activity and PVS are related remains poorly elucidated. Further, PVS relationship with circulating blood proteins have not been assessed in PD.
Methods: 3T T1w MRI images were used to determine PVS volume fraction (VF) in centrum semiovale (CSO), basal ganglia, as well as medial orbitofrontal (MOF), rostral middle frontal (RMF) and superior frontal (SF) white matter regions and compared to non-motor aspects of PD. Cognition was assessed using a neuropsychological battery. Sleep and physical activity parameters were assessed using a wearable accelerometer (ActiGraph). Blood analytes were assessed using cytochrome bead array. **Results**: There was a significant relationship between RMF PVS VF and global cognition (MoCA, global cognition z-score) as well as RMF PVS VF

and visuospatial function. There was also a significant association between CSO, RMF and SF PVS VF and higher average duration of disrupted sleep. Lower RMF PVS was also associated with increased minutes of moderate to vigorous physical activity (MVPA). Higher CSO, MOF, RMF, and SF PVS were associated with decreased blood levels of matrix metalloproteinase 9. **Conclusion**: Increased white matter PVS may be associated with decreased cognition, disrupted sleep, less physical activity, and decreased peripheral MMP9 in PD.

Disclosures: E.K. Donahue: None. **R.P. Foreman:** None. **J.J. Duran:** None. **V. Bui:** None. **S. Venkadesh:** None. **D. Wing:** None. **A. Petkus:** None. **B. Lund:** None. **I. Litvan:** None. **E. Bayram:** None. **D. Schiehser:** None. **J. Choupan:** None. **M.W. Jakowec:** None. **G. Petzinger:** None.

Poster

121. Parkinson Disease: Biomarkers

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 121.12

Topic: C.03. Parkinson's Disease

Title: Regional transcriptional analysis of the neuroinflammatory environment in Parkinson's Disease

Authors: *A. CURLE[1], A. KOULI[2], A. QUAEGEBEUR[2], D. RAINBOW[2], C. H. WILLIAMS-GRAY[2], R. A. BARKER[2], J. JONES[2];
[2]Clin. Neurosciences, [1]Univ. of Cambridge, Cambridge, United Kingdom

Abstract: Parkinson's disease (PD) is a progressive neurodegenerative disorder in which the role of the immune system and neuroinflammation is still not well defined. Utilising Nanostring nCounter technology, we profiled 78 post-mortem human brain samples across 4 regions (prefrontal cortex (PFC), amygdala, putamen, and substantia nigra (SN)) of 10 PD donors and 10 age- and sex-matched controls. We tested neuroinflammation and glial profiling panels, totalling approximately 1,500 genes, which revealed regional differential gene expression between PD and control samples. There was evidence of neuroinflammation across all regions, confirmed also by gene set enrichment analysis in which the 'Inflammatory Response' pathway was enriched in the PD group across all regions. However, the strongest inflammatory phenotype was seen across the amygdala and putamen - most upregulated genes included those of the complement pathways, IFN response genes and antigen presentation markers - whereas glial activation and dysfunction was more limited to the amygdala - evidenced by upregulation of *GFAP* and toll-like receptor genes and downregulation or *MERTK*. The PFC displayed a more wide-spread set of genes involved in pathways such as the DNA damage response and oxidative stress, while the SN showed strong upregulation of angiogenesis-related genes and downregulation of genes involved in vascular remodelling and nerve regeneration, both regions showing a lesser inflammatory phenotype. These preliminary analyses are now informing a further in depth spatial transcriptomic project utilising the same tissues to better examine

peripheral infiltrate and characterisation of activated microglia and astrocytic subtypes, with particular reference to Lewy body localisation.

Disclosures: **A. Curle:** None. **A. Kouli:** None. **A. Quaegebeur:** None. **D. Rainbow:** None. **C.H. Williams-Gray:** None. **R.A. Barker:** None. **J. Jones:** None.

Poster

121. Parkinson Disease: Biomarkers

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 121.13

Topic: C.03. Parkinson's Disease

Support: Marie Skłodowska-Curie grant agreement No: 860954

Title: Characterizing human dopamine transporter missense mutants from psychiatric patients: insights into DAT-mediated dopamine efflux.

Authors: *A. CAMPANA[1], C. K. HERENBRINK[1], J. F. STØIER[1], T. WERGE[2], F. HERBORG[3], U. GETHER[3];
[2]Dept. of Clin. Med., [3]Dept. of Neurosci., [1]Univ. of Copenhagen, Copenhagen, Denmark

Abstract: Characterizing human dopamine transporter missense mutants from psychiatric patients: insights into DAT-mediated dopamine efflux.
Anna Campana[1], Carmen Klein Herenbrink[1], Jonatan F. Støier[1], T. Werge[1, 2], Freja Herborg[1], and Ulrik Gether[1]
[1]Molecular Neuropharmacology and Genetics Laboratory, Department of Neuroscience, Faculty of Health and Medical Sciences, University of Copenhagen, DK-2200 Copenhagen, Denmark.
[2]The Lundbeck Foundation Initiative for Integrative Psychiatric Research (iPSYCH), Copenhagen, Denmark
The dopamine transporter (DAT) shapes extracellular dopamine (DA) levels through high-affinity Na^+-dependent reuptake of DA. Several reports suggest that missense mutations in the DAT gene (SLC6A3) are associated with neuropsychiatric diseases including ADHD, autism and bipolar disorder. DAT mutations have also been implicated in both infantile and early-onset parkinsonism. Here, we systematically characterize DAT rare missense mutations in vitro to identify and classify mutational phenotypes. From an exome-sequenced Danish cohort of 19,005 individuals (iPSYCH2012), we chose 53 DAT mutants predominantly identified in patients with ADHD, ASD, schizophrenia or bipolar disorder. The mutants were expressed in HEK293 cells and evaluated using classical [^{3}H]-dopamine uptake assays and a new "sniffer cell" assay exploiting T-Rex 293 cells expressing genetically encoded DA sensors. A large fraction of mutants was functionally impaired with lowered Vmax and/or increased Km values. For 14 mutations we were unable to detect any activity. Additionally, we identified two variants with enhanced uptake capacity. To further dissect the molecular phenotype, the mutants are being tested for altered surface expression/inhibitor binding using a novel, fluorescently tagged cocaine

analogue, DG3-80. Moreover, by use of the sniffer cells, all mutants were screened for constitutive DA efflux, a phenotype earlier reported for disease-associated DAT mutants. Remarkably, constitutive efflux was only observed for the autism associated T356M variant that previously was shown to possess this phenotype. Summarized, our results provide an important framework for deciphering mechanisms underlying how perturbed DAT function may contribute to neuropsychiatric disease.

Disclosures: A. Campana: None. **C.K. Herenbrink:** None. **J.F. Støier:** None. **T. Werge:** None. **F. Herborg:** None. **U. Gether:** None.

Poster

121. Parkinson Disease: Biomarkers

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 121.14

Topic: C.03. Parkinson's Disease

Support: The Alzheimer's Association, The Michael J. Fox Foundation, Weston Brain Institute, and Alzheimer's Research UK Biomarkers Across Neurodegenerative Diseases (BAND 3) 17990.
CurePSP 665-2019-07.
The Michael J. Fox Foundation 18303.
Cure Sanfilippo Foundation 20215318.
The Binder Foundation.
Karen Toffler Charitable Trust.
U.S. Department of Health and Human Services ((DHHS) and National Institute of Neurological Disorders and Stroke (NINDS)/National Center for Advancing Translational Sciences (NCATS) grant U54NS092089.

Title: Exploration of diagnostic and progression biomarkers for parkinsonian syndromes in CNS-originating extracellular vesicles.

Authors: *H. TAHA[1,2], L. FENWICK[1], S. DUTTA[1], K. HOWE[1], N. ELABED[1], I. ROSARIO[7], D. WONG[3,4], A. FOLLE[7], D. MARKOVIC[5], J.-A. PALMA[8], U. J. KANG[8], R. ALCALAY[9], M. SKLEROV[10], H. C. KAUFMANN[8], B. L. FOGEL[6,3], J. M. BRONSTEIN[1], B. RITZ[7], A. AVIDAN[1], G. BITAN[1];
[1]Neurol., Univ. of California Los Angeles, Los angeles, CA; [2]Integrative Biol. & Physiol., [3]UCLA Clin. Neurogenomics Res. Center, David Geffen Sch. of Med., [4]Neurol., [5]Dept. of Medicine, Div. of Gen. Intrnl. Med. and Hlth. Services Res., [6]Departments of Neurol. and Human Genetics, David Geffen Sch. of Med., Univ. of California Los Angeles, Los Angeles, CA; [7]Dept. of Epidemiology, Fielding Sch. of Publ. Hlth., Univ. of California, Los Angeles, CA; [8]Dept. of Neurology, Dysautonomia Center, The Marlene and Paolo Fresco Inst., New York Univ. Sch. of Med., New York, NY; [9]Dept. of Neurology, Taub Inst. for Res. on Alzheimer's

Dis. and the Aging Brain, Columbia Univ., New York, NY; [10]Dept. of Neurol., Univ. of North Carolina Sch. of Med., Chapel Hill, NC

Abstract: A minimally invasive blood test for objective and reliable biomarkers to aid the diagnosis of parkinsonian diseases and measure their progression is currently not available. Extracellular vesicles (EVs) are released from all the cells and contain cell-specific cargo that may communicate the status of the original cell. Importantly, EVs released from the CNS can diffuse rapidly through the blood-brain-barrier. Such CNS-derived EVs may be isolated by immunoprecipitation from the total pool of blood EVs and serve as a source of biomarkers. Previously, we showed that measuring α-synuclein in neuronal (nEVs) and oligodendroglial EVs (oEVs) distinguished multiple system atrophy from Parkinson's disease or healthy controls with high sensitivity and specificity (Dutta et al. 2021). Here, we build on these initial promising results by adding biomarkers, such as tau, expanding the strategy to additional parkinsonian diseases, and testing whether the biomarkers measured in CNS-originating EVs can report on disease progression and phenoconversion in patients with idiopathic REM-sleep behavior disorder (iRBD). Following isolation and quality-control characterization of the EVs, we use high-sensitivity electrochemiluminescence ELISA or single-molecule array (Simoa) to measure the biomarker concentrations. Initial results show that in contrast to α-synuclein concentration, which is significantly higher in both nEVs and oEVs from MSA than in PD and control, total tau concentration in nEVs and oEVs is significantly lower in MSA than in PD and control samples, suggesting that combining the biomarkers could increase the diagnostic power. Moreover, initial results suggest a longitudinal increase in nEV and oEV α-synuclein concentrations in iRBD samples. Additional data will be reported after data unblinding at the conference.

Disclosures: H. Taha: None. **L. Fenwick:** None. **S. Dutta:** None. **K. Howe:** None. **N. Elabed:** None. **I. Rosario:** None. **D. Wong:** None. **A. Folle:** None. **D. Markovic:** None. **J. Palma:** None. **U.J. Kang:** None. **R. Alcalay:** None. **M. Sklerov:** None. **H.C. Kaufmann:** None. **B.L. Fogel:** None. **J.M. Bronstein:** None. **B. Ritz:** None. **A. Avidan:** None. **G. Bitan:** None.

Poster

121. Parkinson Disease: Biomarkers

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 121.15

Topic: C.03. Parkinson's Disease

Support: NRF-2019R1A5A2026045
NRF-2020R1A2C1010399

Title: Analysis of autophagy-associated proteins in Parkinson's disease patient PBMCs

Authors: M. LEE[1], J. KIM[1], J. KANG[1], J. YOON[2], *J. CHANG[1,3];
[1]Dept. of Biomed. Sci., [2]Dept. of Neurol., [3]Dept. of Brain Sci., Ajou Univ. Sch. of Med., Suwon, Korea, Republic of

Abstract: The current diagnosis method for Parkinson's disease (PD) is mostly based on clinical criteria such as motor symptoms including shaking, rigidity, and postural disturbances. Given that the motor symptoms appear after the loss of 60 to 80% dopaminergic neurons in the brain, it is important to diagnose the disease before the motor symptoms begin. Thus, it is necessary to develop pre-diagnostic biomarkers based on the understanding of molecular characteristics of PD pathology, such as dysregulated autophagy-lysosomal pathway (ALP). In this study, we analyzed levels of ALP-associated proteins and autophagy activities using peripheral blood mononuclear cells (PBMCs) from PD patients and compared them with that of the healthy control group. We found that levels of ALP-associated proteins were significantly changed in PD patient PBMCs. We further analyzed the results using multivariate logistic regression and found that levels of ALP-associated proteins in PBMCs showed high performance to distinguish PD patients from healthy control subjects. In conclusion, our results suggest that levels of ALP-associated proteins of PBMCs could be developed as diagnostic biomarkers for PD.

Disclosures: M. Lee: None. **J. Kim:** None. **J. Kang:** None. **J. Yoon:** None. **J. Chang:** None.

Poster

121. Parkinson Disease: Biomarkers

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 121.16

Topic: C.03. Parkinson's Disease

Support: Fondation Courtois
Natural Sciences and Engineering Research Council of Canada (NSERC), RGPIN- 2020–05242
Fonds de Recherche du Québec –Santé

Title: Fmri evidence of spinal cord functional connectivity alteration associated with Parkinson's disease progression

Authors: *C. LANDELLE[1], L. SOLSTRAND DAHLBERG[1], O. LUNGU[1], T. VLIEGHE[1], B. MISIC[1], B. DE LEENER[2], J. DOYON[1];
[1]McConnell Brain Imagin Centre, The Neuro, McGill Univ., Montreal, QC, Canada; [2]Dept. of Computer Engin. and Software Engin., Polytechnique Montreal, Montreal, QC, Canada

Abstract: Introduction: Even though Parkinson's disease (PD) has been viewed traditionally as a brain disease, increasing evidence from post-mortem humans and animal experimental models indicates that spinal cord may also be affected by PD (Del Tredici et Braak 2012, 2016). In recent years, reliable functional imaging protocols have been developed and used to assess the functional changes and organization of the cervical spinal cord during task and at rest in healthy individuals (Landelle et al. 2021). Here, we employed such a technique in order to characterize the resting state spinal cord functional connectivity in PD patients and healthy controls.
Methods: 70 PD patients (64.4 ± 9.1 yrs) and 24 healthy controls (63.6 ±10 yrs) were included

in the study and provided written consent. They first underwent clinical interviews including the UPDRS (Unified Parkinson's Disease Rating Scale,2003). Patients were divided into three groups based on the severity of UPDRS scores part III (motor examination): PD_{low} group, PD_{med} group and PD_{adv} group. Cervical spinal cord anatomical and functional images at rest were acquired with a 3T Siemens Prisma MRI scanner and preprocessed using a pipeline that employed the Spinal Cord Toolbox and FSL (Vahdat et al. 2015). Spinal functional connectivity (FC) changes were assessed using a combination of independent component analysis (ICA) and a seed-based approach. **Results:** The ICA analysis revealed that intrinsic spinal cord FC organization was highly structured and followed the known neurophysiological pathways. The seed-to-seed analysis revealed a reduced segregation of spinal neural networks that was closely associated with PD progression (Groups $\chi^2_{(3)} = 11.3$, $p < 0.001$). In addition, the average spinal FC decreased between segments and was associated with the severity of PD patients' upper limb motor symptoms ($t_{(69)} = -2.70$, $p = 0.0085$), but not with that of the lower-limb as assessed by the UPDRS scores ($t_{(69)} = -0.58$, $p = 0.56$). Notably, the FC-UPDRS association was also found between adjacent segments known to subserve upper limb functions: C4-C5 ($t_{(69)}$=-3.2, p-corrected=0.011) and C5-C6 ($t_{(69)}$=-2.5, p-corrected=0.036). **Conclusion:** These results demonstrate, for the first time, disease-related FC differences in the cervical spinal cord associated with the severity of PD patients' motor symptoms. This study suggests that spinal fMRI may be a sensitive tool to detect the impact of neurodegeneration at the spinal cord level in PD patients, in line with recent post-mortem studies. In addition, it may offer new perspectives for monitoring the impact of treatment approaches, such as the use of electrical spinal cord stimulation in PD.

Disclosures: C. Landelle: None. **L. Solstrand Dahlberg:** None. **O. Lungu:** None. **T. Vlieghe:** None. **B. Misic:** None. **B. De Leener:** None. **J. Doyon:** None.

Poster

121. Parkinson Disease: Biomarkers

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 121.17

Topic: C.03. Parkinson's Disease

Support: the Ministry of Health, Labor and Welfare Grant 20FC1049

Title: Neuroimaging characteristics of impulse control disorders and dopamine dysregulation syndrome in Parkinson's Disease

Authors: *I. KIMURA[1,2], Y. KAJIYAMA[1], G. S. REVANKAR[1], K. OGAWA[1], K. AMANO[3], H. MOCHIZUKI[1];
[1]Dept. of Neurology, Osaka Univ. Grad. Sch. of Med., Suita, Japan; [2]Grad. Sch. of Frontier Biosciences, Osaka Univ., Suita, Japan; [3]Grad. Sch. of Information Sci. and Technology, The Univ. of Tokyo, Tokyo, Japan

Abstract: Parkinson's Disease (PD) is a neurodegenerative disease, characterized by the degeneration of dopamine-producing cells in the substantia nigra. Around 30% of patients with PD complain of impulsive compulsive behaviors in the treatment course of dopamine replacement therapy (Zhang et al., 2014). These behaviors include impulse control disorders (ICD) and dopamine dysregulation syndrome (DDS). Both symptoms worsen patients' quality of life and objective biomarkers are required to detect these behaviors for early intervention. It is also important to detect ICD and DDS separately from patients with PD since interventions are different in these two symptoms. Previous neuroimaging studies found that the functional connectivities (FC) of cortico-basal ganglia networks were altered in PD patients with impulsive compulsive behaviors (Weintraub et al., 2017). However, FC distinguishing ICD or DDS are unknown. Therefore, we compared the FC between PD patients with ICD and DDS. 37 PD patients with impulsive compulsive behaviors were investigated from our existing cohort study. We defined patients as having ICD or DDS following the Japanese version of Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease. Resting-state functional MRI data were analyzed to reveal the FC specific to ICD and DDS. To investigate the contributions of the FC to ICD or DDS in the networks that were previously shown to be related to impulsive compulsive behaviors, we performed seed-based analyses of 6 seeds; caudate, putamen, and nucleus accumbens (NAcc) in the right and left hemispheres. Compared to patients with DDS, those with ICD showed increased FC between the right putamen and the left superior temporal gyrus and between the left caudate and the bilateral middle occipital gyrus. In contrast, patients with ICD had decreased FC between the left NAcc and the right posterior cingulate cortex (PCC) than those with DDS. These significant differences in FC did not depend on other clinical characteristics, such as disease durations, the severity of motor symptoms, nor the presence of cognitive and psychiatric symptoms. These results suggest that altered cortico-basal ganglia networks were different in the patients with ICD and DDS. Notably, since NAcc and PCC are important in reward-based learning (Heber et al., 2010), the occurrence of ICD and DDS might be mediated by the different regions of alterations in reward networks. Taken together, these significantly different networks might be useful biomarkers in detecting ICD or DDS in patients with PD. Future prospective studies are required to validate whether these FC can predict the early stage of such symptoms.

Disclosures: I. Kimura: None. **Y. Kajiyama:** None. **G.S. Revankar:** None. **K. Ogawa:** None. **K. Amano:** None. **H. Mochizuki:** None.

Poster

121. Parkinson Disease: Biomarkers

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 121.18

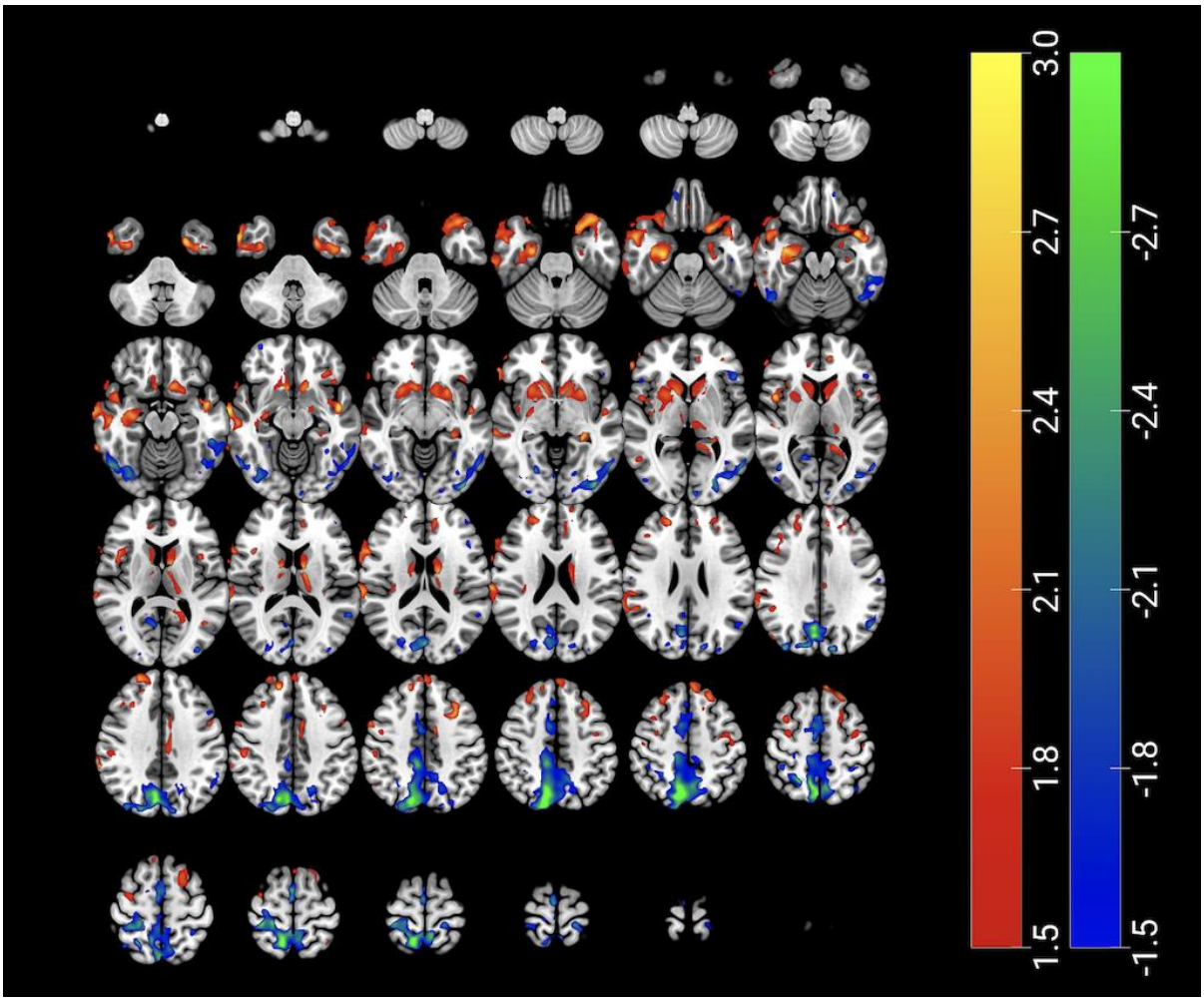
Topic: C.03. Parkinson's Disease

Support: P01 NS015655
RO1 NS070856
P50 NS091856

Title: Alzheimer like covariance pattern of amyloid deposition in a patients with parkinson disease with declining cognition.

Authors: *P. KANEL, T. BROWN, J. BARR, S. ROYTMAN, K. FREY, N. BOHNEN; Univ. of Michigan, Ann Arbor, MI

Abstract: Amyloid-β (Aβ) deposition, a key feature of Alzheimer's disease (AD), is linked to compromised cognitive function. The presence of amyloid plaque in the cerebral region, notably in the early stages of the cognitive decline in Parkinson's disease (PD), is poorly defined. For this study, we investigate the covarying pattern of amyloid deposition that influence cognitive decline as measured by the change in the Montreal Cognitive Assessment (MoCA) scores in 39 subjects with PD (27/11 M/F; 66.15±5.9 yrs; MoCA 26.72±2.60; Hoehn & Yahr stage; 2.38±0.4 yrs; UPDRS-III 30.15±10.68). [11C] Pittsburgh compound B β-amyloid PET imaging was performed in all subjects for 70 minutes with a bolus dose of 18 mCi [11C] PiB. [11C] PiB distribution volume ratios (DVR) were estimated with the Logan plot graphical analysis method using cerebellar cortical as reference tissue. We analyzed clinical assessments, including demographic characteristics, motor severity, and cognitive tests. The subjects were brought back after three years, and clinical assessments were repeated. We conducted cortical, subcortical, and white matter segmentation on T1 MRI using the Freesurfer image analysis suite. SPM was used to normalize the MR registered PET cerebral region to MNI space. Multivariate spatial covariance analysis based on the scaled subprofile model (SSM) using the covariance analysis software module (http://www.nitrc.org/projects/gcva_pca/) on the parametric β-amyloid PET image in MNI and the change in MoCA score to compute the covariance pattern of amyloid distribution in the baseline PET image. Increased amyloid uptake in the frontal, temporal, hippocampus, parahippocampal, fusiform and anteroventral striatal was associated with poorer performance on global cognition, as assessed by the decreased MoCA scores on their follow-up visit. These findings suggest that early amyloid deposits in areas like those affected in AD might contribute to future cognitive decline in PD.



Disclosures: **P. Kanel:** None. **T. Brown:** None. **J. Barr:** None. **S. Roytman:** None. **K. Frey:** None. **N. Bohnen:** None.

Poster

121. Parkinson Disease: Biomarkers

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 121.19

Topic: C.03. Parkinson's Disease

Title: Hyperparameter Tuning for Enhancing Machine Learning Performance of Deep Brain Stimulation Parameter Configurations Quantified by Conformal Wearables

Authors: *R. C. LEMOYNE[1], T. J. MASTROIANNI[2];
[1]Independent, Independent, Running Springs, CA; [2]Cognition Engin., Pittsburgh, PA

Abstract: Deep brain stimulation provides substantial therapeutic intervention for the treatment of movement disorder symptoms, such as Parkinson's disease. The amalgamation of machine learning and conformal wearables equipped with inertial sensors supplement the utility of deep brain stimulation. Conformal wearables can elucidate the response to an assortment of deep brain stimulation parameter configurations with the objective quantification of the tremor response through the resultant inertial sensor signal data. The confluence with machine learning enables a pathway to computationally automate diagnostics of an assortment of deep brain stimulation parameter configurations. However, further evolution for this amalgamation of machine learning and conformal wearables equipped with inertial sensors for deep brain stimulation is realized through the consideration of hyperparameter tuning that modifies the performance of the respective machine learning algorithm. Therefore, the research objective is to ascertain the influence of hyperparameter tuning for the enhancement of machine learning performance based on the quantified response from a series of deep brain stimulation parameter configurations that are quantified by conformal wearables with inertial sensors.

Disclosures: R.C. LeMoyne: None. **T.J. Mastroianni:** None.

Poster

121. Parkinson Disease: Biomarkers

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 121.20

Topic: C.03. Parkinson's Disease

Support: Department of Defense Award number W81XWH-06-067
Seedlings Foundation
Helen Graham Foundation

Title: Identification of novel autoantibody signatures related to non-motor symptoms in individuals with high-risk of Parkinson's disease

Authors: *S. GARNETT[1], N. D. ANUAR[2], K. L. MAREK[3], P. E. MORRIS[2], M. MULLINS[1], J. M. BLACKBURN[1];
[1]Integrative Biomed. Sci., Univ. of Cape Town, Cape Town, South Africa; [2]Sengenics Corp., Kuala Lampur, Malaysia; [3]Yale Univ. Sch. Med., New Haven, CT

Abstract: Parkinson's disease (PD) is a neurodegenerative disease with unknown etiopathogenesis, characterized by the degeneration of dopaminergic neurons in the substantia nigra. There is currently no established molecular test available to diagnose PD. Hyposmia, a decreased sense of smell, is thought to be an early indicator of PD, while dopamine transporter (DAT) imaging correlates with PD striatal dopamine levels. Current treatments are invasive, so an accurate diagnosis is required. Recently detection of immunological changes indicates a potential autoimmune component in the disease development. Autoantibodies show great potential as markers for diagnosis and prognosis and can often be detected years before clinical

manifestation. A panel of diagnostic biomarkers would allow for effective detection, classification, and treatment of PD before irreversible damage is done. Recent studies using an immunome protein array identified 38 autoantibodies that differentiate PD from healthy controls and 16 autoantibodies that could stratify elderly individuals into healthy, intermediate and unhealthy groups.
Using samples from Parkinson-associated risk study (PARS), we aimed to identify autoantibody biomarkers for the early diagnosis of PD from a cohort of 145 samples. These consisting of hyposmic (HYP) (n=96) and normosmic (n=49) participants, further classified based on DAT deficit (n=38) with or without phenoconversion (n=17). Serum samples were assayed to detect autoantibodies on the KREX-based Immunome protein microarray, which contains more than 1600 natively folded proteins that expose non-linear conformational epitopes.
Negative control filtering reduced the protein number analyzed to 402, after which random forest classification identified 116 autoantibodies as biomarkers for stratifying the groups. The diagnostic ability of the biomarkers was evaluated using ROC analysis. Consequently, 22 biomarkers can identify the HYP DAT deficit group that photoconverted with a sensitivity of 90.5% and specificity of 70.6%. Amongst the identified biomarkers, there are proteins involved in immune regulation, protein degradation (RNF7), cell death (RIPK1) and vitamin D regulation (VDR), all potentially involved in PD
With a complex aetiology such as PD it is unlikely to find individual biomarkers to classify the progression of the disease. These biomarker signatures are, however, able to identify early PD, thereby opening up the ability for early treatment and monitoring disease prognosis. With a larger sample pool and longitudinal monitoring, these signatures may become more refined and perhaps identify disease and progression subclasses.

Disclosures: **S. Garnett:** A. Employment/Salary (full or part-time):; Sengenics Corporation. **N.D. Anuar:** A. Employment/Salary (full or part-time):; Sengenics Corporation. **K.L. Marek:** A. Employment/Salary (full or part-time):; The Michael J. Fox Foundation. **P.E. Morris:** A. Employment/Salary (full or part-time):; Sengenics Corporation. **M. Mullins:** None. **J.M. Blackburn:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Sengenics Corporation.

Poster

122. Functional Architecture and Circuits in the Visual Cortex of Non-Human Primates I

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 122.01

Topic: C.04. Movement Disorders other than Parkinson’s Disease

Support: 2E31642-22-114

Title: Discrimination and characterization of abnormal cortical activities for working memory of restless legs syndrome patients based on explainable machine learning

Authors: *M. KIM[1], J. HUH[1], H. KIM[1], P. SEO[1], K.-Y. JUNG[2], K. KIM[1];
[1]Yonsei university, Wonju-Si, Korea, Republic of; [2]Seoul Natl. Univ. Hosp., Seoul, Korea, Republic of

Abstract: Introduction: Restless Legs Syndrome (RLS) is neurological disorder characterized by an urgent need to move the legs and an unpleasant sensation in the legs which disturb patients' sleep. The patients in RLS usually complain cognitive deficits due to deprivation of sleep. However, the neurophysiological basis for the cognitive function in RLS is not sufficiently discovered. Here we propose a method for the discrimination of RLS based on 3D-convolutional neural networks (CNNs) and single-trial event-related potential (ERP) during a visual working memory task. In addition, we tried to identify the most relevant features discriminating RLS patients from normal control using an explainable machine learning approach. **Method:** Nine drug-naïve RLS patients and 13 healthy normal controls participated in the study. EEG were recorded in a 20-10 system 19 channels while the subjects were performing 200 trials of modified Sternberg's working memory task. During the retrieval phase, the target number between 0-9 was presented to determine whether the number has ever been presented in the encoding phase. Each single-trial ERP was segmented according to the target onset (0-900 ms). Cortical source activities within 50 ms windows were reconstructed using sLORELTA and projected onto two-dimensional images (60 x 60) using Mollweide projection. Thus, three-dimensional (3D) data (60 x 60 x 18) were generated for the input to 3D CNN classifier which is trained to determine whether the input is from a RLS patient or a normal control. Leave-one-subject-out cross-validation (LOOCV) was used for the performance evaluation. After successful training, layer-wise relevance propagation (LRP) was applied to identify the most crucial features for the decision of the classifier. **Results:** Average classification accuracy was 97.91 ± 3.58% (obtained from 22 repetition of LOOCV). The critical cortical features identified by LRP included left superior frontal and right inferior frontal regions (300-500 ms), left lingual gyrus (150-450 ms) and left precuneus (350-450 ms). **Conclusion:** The proposed method could successfully discriminate RLS patients from normal controls based on single-trial cortical activities. The critical cortical regions to predict RLS were identified explainable machine learning approach. We showed that RLS patients can be classified with high accuracy based on single-trial cortical activities during performing working memory task. An explainable machine learning approach could be successfully applied to identify the cortical areas critical for the classification, which are expected to play important roles for the working memory task.

Disclosures: M. Kim: None. **J. Huh:** None. **H. Kim:** None. **P. Seo:** None. **K. Jung:** None. **K. Kim:** None.

Poster

122. Functional Architecture and Circuits in the Visual Cortex of Non-Human Primates I

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 122.02

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: KIST Grant 2E31642-22-114
NRF Grant 2022R1A6A3A13068868

Title: Classification and characterization of idiopathic rapid eye movement sleep behavior disorder patients by single-trial event related potential during visuospatial attention based on explainable machine learning

Authors: *H. KIM[1], M. KIM[1], J. HUH[1], P. SEO[1], J.-S. SUNWOO[2], K.-Y. JUNG[2], K. KIM[1]; [1]Yonsei Univ., Wonju, Korea, Republic of; [2]Seoul Natl. Univ. Hosp., Seoul, Korea, Republic of

Abstract: Introduction: Idiopathic REM sleep behavior disorder (iRBD) is an early sign of synucleinopathies, including Parkinson's disease, dementia with Lewy bodies, and multiple system atrophy. An early detection is important to slow down the progression of the neurodegenerative disease. iRBD is known to be associated with visuospatial impairments, especially visual perception. The study aims to develop an efficient algorithm for the classification of iRBD patients by using single-trial event-related potential (ERP) during visuospatial attention task based on deep neural networks.**Methods**: Sixty-channel electroencephalograms recorded from 45 drug-naive iRBD patients and normal controls each while performing Posner's cueing task were used in this study. Cortical source activities were reconstructed using weighted minimum norm estimation. The single-trial ERPs were averaged within every 50 ms time-interval from target onset to 800 ms for all subjects. The cortical activities were projected onto 2D image using Mollweide projection. Finally, the dimension of constructed input data for classification was 120x120x16 three-dimensional volumes (2D space x time). In this study, we address a three-dimensional convolutional neural network to distinguish iRBD patients from normal controls. Five-fold cross-validation was adopted to evaluate the subject-independent performance of the classifier. Layer-wise relevance propagation was applied to produce heatmaps that indicate the relevance of temporal and topographical characteristics for predicting iRBD patients from normal controls.**Results**: The mean classification accuracy achieved by the proposed classifier through overall cross-validation was 100.0 ± 0.0% for training data and 70.08 ± 3.95% for testing data. The critical spatiotemporal features included superior frontal gyrus, left postcentral gyrus within 200-400 ms following target onset when predicting iRBD patients from normal controls correctly.**Discussion**: The main goal of the study is to investigate spatiotemporal characteristics of cortical activities which helps to discriminate iRBD patients from normal controls based on explainable machine learning approach. The prefrontal cortex activity in an early phase of ERP may play an important role in visuospatial processing and may reflect deficits of visuospatial attention in iRBD patients. In addition, the proposed algorithm could successfully predict iRBD patients from normal controls based on single-trial cortical activities with high accuracy. The findings may contribute to design a classifier which generalizes to unseen subjects for different tasks in neuroimaging.

Disclosures: H. Kim: None. **M. Kim:** None. **J. Huh:** None. **P. Seo:** None. **J. Sunwoo:** None. **K. Jung:** None. **K. Kim:** None.

Poster

122. Functional Architecture and Circuits in the Visual Cortex of Non-Human Primates I

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 122.03

Topic: C.06. Neuromuscular Diseases

Title: Spinal Muscular Atrophy CNS organoids unravel developmental disease signatures reverted by peptide oligonucleotide conjugates

Authors: *P. RINCHETTI[1], I. FARAVELLI[2], M. TAMBALO[4], S. MANCINELLI[4], L. MAPELLI[5], A. D'ANGELO[7], M. RIZZUTI[7], E. D'ANGELO[6], N. BRESOLIN[3], G. P. COMI[2], F. LOTTI[1], S. E. PRZEDBORSKI[1], S. LODATO[4], M. NIZZARDO[3], S. CORTI[3];
[1]Columbia Univ., New York, NY; [2]Univ. of Milan, Milano, Italy; [3]Univ. of Milan, Milan, Italy; [4]Humanitas Res. Hosp., milan, Italy; [5]Dept of Brain and Behavioral Sci., [6]Brain and Behavioral Sci., Univ. of Pavia, Pavia, Italy; [7]IRCCS Fndn. Ca' Granda Ospedale Maggiore Policlinico, milan, Italy

Abstract: Spinal Muscular Atrophy (SMA) is a neuromuscular disease and the leading cause of genetic death during childhood, due to mutations in the Survival Motor Neuron (SMN) gene that encodes SMN protein, which plays a pivotal role in RNA processing. Although, SMN is ubiquitously expressed, motor neurons are the most vulnerable neuronal type to this disease, with a resulting clinical phenotype of progressive muscular atrophy. Many preclinical/clinical studies have led to the development of several therapeutic strategies. However, these approaches are efficacious only if administered in the early stages of the disease. Unravelling prenatal and pre-symptomatic SMA features is crucial to explore the therapeutic window and increase drug efficacy. It is necessary to understand SMN's role in reliable biological models to further optimize the available treatments and facilitate the development of novel compounds. A major scientific advance in disease modeling has been the generation of organoids, which can self-assemble and self-organize to resemble features of the developing CNS. Using 3D human CNS organoids, we successfully recapitulate SMA pathology.We derived iPSC lines from SMA type 1 patients and healthy controls and generated cerebral organoids. By developing a novel modified differentiation method using small molecules, we also derived spinal cord organoids (SCOs). Results showed that SMA-SCOs exhibited a significant alteration in their neurofilament elongation. Single cell transcriptomic analysis of SCOs revealed drastic changes and key disease features in gene expression of motor neurons, as well as in additional neuronal and precursor subtypes. Electrophysiological studies in both cerebral and spinal cord organoids were performed to investigate circuit function and activity. Results showed that control organoids had a higher basal spike frequency compared to the affected ones, but the SMA-SCOs were more responsive to the glutamatergic stimuli. Different therapeutic strategies developed to restore the levels of SMN have received FDA/EMA approval. They are based either on *SMN2* splicing correction exploiting antisense oligonucleotides (ASOs) and small molecules or full-length *SMN1* gene replacement. Here, we demonstrated that disease features were restored by treatment with newly developed peptide-conjugated ASO increasing SMN levels.We demonstrated that organoids can be exploited as a platform for modelling disease pathogenic mechanisms and test potential therapeutic approaches. We confirmed that the observed phenotypes in the SMA organoids were ameliorated using existing therapeutic applications.

Disclosures: **P. Rinchetti:** None. **I. Faravelli:** None. **M. Tambalo:** None. **S. mancinelli:** None. **L. Mapelli:** None. **A. D'Angelo:** None. **M. Rizzuti:** None. **E. D'Angelo:** None. **N. Bresolin:** None. **G.P. Comi:** None. **F. Lotti:** None. **S.E. Przedborski:** None. **S. Lodato:** None. **M. Nizzardo:** None. **S. Corti:** None.

Poster

122. Functional Architecture and Circuits in the Visual Cortex of Non-Human Primates I

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 122.04

Topic: C.06. Neuromuscular Diseases

Title: Development of Antisense Oligonucleotide Targeting Calpain 2

Authors: M. LEINDERS[1], *J. COHEN[1], J. KLEE[1], E. MIZERAK[1], T. MARTIANEZ CANALES[2], S. DEKKERS[2], F. VAN VEEN[2], M. ELAND[2], M. HEMBURY[2], R. REDIS[2], M. BLANCA TORROBA[2], R. DE WIT[2], S. DE MUNNIK[2];
[1]Amylyx Pharmaceuticals, Inc, Cambridge, MA; [2]Charles River Labs., Leiden, Netherlands

Abstract: Evidence supports axonal degeneration, first characterized by Augustus Waller in the 1850s, as one of the critical pathways underlying pathology in ALS and other neurodegenerative diseases and axonopathies. Calpain 2 (*CAPN2*) may be one of the critical effectors in the axonal degeneration pathway. The experimental goal was to develop antisense oligonucleotides (ASOs) with the ability to knockdown *CAPN2*. ASOs targeted to *CAPN2* were applied to human glutamatergic neurons and levels of *CAPN2* expression were evaluated by qPCR. Fifteen ASO candidates were identified with at least 30% knockdown of *CAPN2* in the human glutamatergic cell line. The lead *CAPN2* ASO reduces gene expression by approximately 74%. ASOs targeting *CAPN2* were successfully created and show concentration-dependent knockdown. Additional studies on the ability of *CAPN2* ASOs to reduce axonal degeneration in multiple models, including models of vincristine- and colchicine-induced axonal degeneration, is currently under evaluation.

Disclosures: **M. Leinders:** A. Employment/Salary (full or part-time):; Amylyx Pharmaceuticals, Inc. **J. Cohen:** A. Employment/Salary (full or part-time):; Amylyx Pharmaceuticals, Inc. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Amylyx Pharmaceuticals, Inc. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Amylyx Pharmaceuticals, Inc. **J. Klee:** A. Employment/Salary (full or part-time):; Amylyx Pharmaceuticals, Inc. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Amylyx Pharmaceuticals, Inc. **E. Mizerak:** A. Employment/Salary (full or part-time):; Amylyx Pharmaceuticals, Inc. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and

pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Amylyx Pharmaceuticals, Inc - Pending Grant. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Amylyx Pharmaceuticals, Inc - Stock Options. **T. Martianez Canales:** A. Employment/Salary (full or part-time):; Charles River Laboratories. **S. Dekkers:** A. Employment/Salary (full or part-time):; Charles River Laboratories. **F. van Veen:** A. Employment/Salary (full or part-time):; Charles River Laboratories. **M. Eland:** A. Employment/Salary (full or part-time):; Charles River Laboratories. **M. Hembury:** A. Employment/Salary (full or part-time):; Charles River Laboratories. **R. Redis:** A. Employment/Salary (full or part-time):; Charles River Laboratories. **M. Blanca Torroba:** A. Employment/Salary (full or part-time):; Charles River Laboratories. **R. de Wit:** A. Employment/Salary (full or part-time):; Charles River Laboratories. **S. de Munnik:** A. Employment/Salary (full or part-time):; Charles River Laboratories.

Poster

122. Functional Architecture and Circuits in the Visual Cortex of Non-Human Primates I

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 122.05

Topic: C.06. Neuromuscular Diseases

Title: Autophagy is a potential early adaptive response in the neuromuscular disorder of hemochromatosis.

Authors: *Y. KIM[1], V. V. DHORAJIA[2], L. ZENG[3], R. CHENG[3], J. KIM[3];
[1]Physical Therapy and Kinesiology, [2]Biomed. Engin. and Biotech., [3]Biomed. and Nutritional Sci., Univ. of Massachusetts Lowell, Lowell, MA

Abstract: Hereditary hemochromatosis (HH) is a rare genetic disease mainly caused by uncontrolled iron absorption and overload, which results in multiple organ dysfunction, including liver cirrhosis, cardiomyopathy, and neurological disorders. HH also affects the neuromuscular system, as characterized by movement disorder, muscle weakness, and/or fatigue. However, the underlying mechanism of neuromuscular impairments is still unclear. As mitochondria are key for muscle function, this study sought to explore mitochondrial capacity and related molecular systems in the skeletal muscle of Hfe-deficient mice, an established mouse model of HH. Although systemic iron levels were significantly elevated in Hfe deficiency, we observed a mild iron overload in the skeletal muscle of Hfe-deficient mice as compared to age-matched control wild-type mice. While mitochondrial oxidative capacity (e.g., PGC-1α; mitochondrial biogenesis marker) did not change, there was a trend of the enhanced autophagy flux (e.g., LC3II/I) in the Hfe-deficient skeletal muscle. These results suggest that autophagy could play a significant role in the skeletal muscle homeostasis in HH. There was no evidence of oxidative stress (e.g., 4-HNE) in the skeletal muscle of Hfe-deficient mice. Collectively, our results suggest that autophagy could support mitochondrial capacity as well as skeletal muscle health at pre-pathological HH, likely young age. Future studies are warranted to explore how

mitochondrial biogenesis and turnover are regulated along with the autophagy system in the development of neuromuscular disorders in hemochromatosis at an advanced age.

Disclosures: **Y. Kim:** None. **V.V. Dhorajia:** None. **L. Zeng:** None. **R. Cheng:** None. **J. Kim:** None.

Poster

122. Functional Architecture and Circuits in the Visual Cortex of Non-Human Primates I

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 122.06

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: The Nemours Foundation
NIGMS (P20 GM103446)

Title: Ataxia and failure to thrive in mice with genetic deletion of the Na,K-ATPase beta1-subunit in cerebellar granule cells

Authors: Z. LI[1], K. SPERLE[1], E. TOKHTAEVA[3], O. VAGIN[3], ***S. A. LANGHANS**[2]; [2]Nemours Children's Hlth. - Delaware, [1]Nemours Children's Hlth. - Delaware, Wilmington, DE; [3]David Geffen Sch. of Med., UCLA, Los Angeles, CA

Abstract: The Na,K-ATPase is a ubiquitously expressed integral membrane protein that carries out Na^+ extrusion and K^+ uptake across the plasma membranes of most animal cells to maintain intracellular ion homeostasis, to control cell volume, and to restore the resting membrane potential in excitable cells. The loss of the ion-pumping function of Na,K-ATPase due to mutations in its catalytic α-subunit are known to be associated with several complex neurological disorders including rapid-onset dystonia-parkinsonism (RDP), alternating hemiplegia of childhood (AHC), familial hemiplegic migraine (FHM), cerebellar ataxia with areflexia, pes cavus, optic atrophy and sensorineural hearing loss (CAPOS) syndrome. The Na,K-ATPase also has pump-independent functions: the α-subunit acts as a signaling scaffold, and the auxiliary β-subunit isoforms, β_1 and β_2, serve as cell adhesion molecules. In recent years, significant effort has been made to unravel the physiological relevance of pump-independent functions of Na,K-ATPase and especially those of its β-subunits. Progress has been made in epithelial cells to demonstrate the role of the β_1-subunit in tight junction formation and epithelial polarization, but still very little is known about cell-specific functions of the β_1-subunit in neuronal cells. To explore physiological roles of the β_1-subunit in neurons, we have taken advantage of cerebellar granule cells, that unlike most cells, express two β-subunit isoforms, β_1 and β_2 (also known as AMOG or Adhesion Molecule On Glia) and generated mice with targeted deletion of the β_1-subunit in these cells. Heterozygous knockout mice had no apparent phenotype, had a normal life span (> 2 years), and were indistinguishable from control mice (homozygous or heterozygous floxed without Cre, wildtype with or without Cre). In contrast, homozygous knockout mice presented with symptoms (around weaning age, independent of sex, N > 25, male and female

each) consistent with cerebellar ataxia such as wobbly gait, asynergic movements, dysmetria, and tremor that progressed with age. Overall, homozygous β_1 knockout mice also had a shortened life span when compared to their control littermates, possibly due to a general failure to thrive. This phenotype was profoundly distinct from that of mice with deletion of the β_2 isoform, suggesting that the β_1-subunit of Na,K-ATPase plays an isoform-specific unique role in cerebellar granule cell function and cerebellar development.

Disclosures: Z. Li: None. **K. Sperle:** None. **E. Tokhtaeva:** None. **O. Vagin:** None. **S.A. Langhans:** None.

Poster

123. Functions of Glia and Non-Neuronal Cells in Stroke

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 123.01

Topic: C.09.Stroke

Support: NIH R01 NS44025
NIH R01 HL139685
NIH R21 NS098514

Title: Sphingosine-1-phosphate receptor 2 contributes to short-term and long-term injury after neonatal arterial focal stroke

Authors: *Y. FUKUZAKI, M. LECUYER, J. FAUSTINO, Z. S. VEXLER;
Neurol., UCSF, San Francisco, CA

Abstract: Background: Neonatal arterial ischemic stroke is common—1 per 2,300-5,000 births—and causes long-term neurological deficits, including cerebral palsy and neurodevelopmental disabilities. It has become apparent that developmental stage of the brain at the stroke onset plays a key role in the pathophysiology of injury, with neuroinflammation as a major injury modulator (Fernandez-Lopez et al. 2012, Fernandez-Lopez et al. 2014, Hagberg et al. 2015). In adult stroke models attenuation of sphingosine-1-phosphate (S1P)/S1P receptor 2 (S1PR2)-mediated signaling at the immune-neurovascular axis was shown neuroprotective. However, the effects of S1PR2 in neonatal stroke are unknown.
Methods: Postnatal day 9 global S1PR2 deletion (KO) and HET mice were subjected to a transient 3h middle cerebral artery occlusion (tMCAO). Specific S1PR2 inhibitor JTE-13 was administered to a subset of WT mice (2.5 μg/μl). Cytokine/chemokine multiplex analysis and flow cytometry were examined 72h after tMCAO. Behavior tests and histological outcomes during acute and long-term injury phases.
Results: At 24h after tMCAO, Open Field test revealed differences between KO and HET: total traveling distance was unchanged in KO compared to naïve KO but not HET and WT. Accumulation of number of leukocytes recruited to the injury site was attenuated in KO following tMCAO. The number of NeuN+ cells in ischemic-Core was 15.8% higher in KO than

in HET, along with the number of non-engulfed neurons 12.6%. The number of CD68+ and cleaved caspase-3+ cells in the core as well as extent of astrocytic glial scar in the penumbra were not different between groups, whereas caspase-dependent spectrin fragmentation was attenuated in KO. Pharmacological inhibition of S1PR2 significantly attenuated injury volume 72h after tMCAO. Anxiety index at 2 weeks was reduced in injured KO, and tissue loss was apparent in both groups but the remaining tissue volume was significantly larger in KO than in HET. Density of microglia associated with the vessels was higher in KO than in HET in 24h and 2 weeks. Neurofilament enwrapped by MBP+ myelin was higher in contra-KO than in contra-HET in motor cortex, and FoxP2+ projection neuron was lower in ipsi-HET than in ipsi-KO at 2 weeks.
Conclusions: Cumulatively, disruption of S1PR2 protects from neonatal stroke.

Disclosures: **Y. Fukuzaki:** None. **M. Lecuyer:** None. **J. Faustino:** None. **Z.S. Vexler:** None.

Poster

123. Functions of Glia and Non-Neuronal Cells in Stroke

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 123.02

Topic: C.09.Stroke

Support: AHA predoctoral fellowship

Title: Retinoid X receptors rejuvenate microglia in aged brains and prevent cognitive declines after ischemic stroke

Authors: *S.-M. TING, G. SUN, L. OBERTAS, J. ARONOWSKI;
Neurol., Univ. of Texas Hlth. Sci. Center, Houston, Houston, TX

Abstract: Ischemic stroke is the fifth-leading cause of death and a leading cause of disability in the United States. The majority of stroke victims are over 65 years of age. Moreover, elderly stroke patients have worse and less reversible neurological deficits and higher mortality than younger adults. One potential reason is the age-related dysfunctions of microglia (MΦ), the brain-resident macrophages. After ischemic stroke, these cells, together with blood-derived macrophages, remove dead cells and tissue debris, release trophic factors and promote brain repair. However, the aged MΦ may fail to be as effective in this process, thereby being less effective in mediating recovery after stroke. Retinoid-X-receptors (RXR) are pleiotropic transcription factors. Our earlier studies suggest that RXR activation plays critical roles in priming MΦ toward the “reparative” phenotype with enhanced phagocytic/trophic functions. Randomization and blinding were used to provide scientific rigor. To show that RXR activation reverses age-related MΦ dysfunctions, we harvested MΦ from the brains of aged (18-20 months old) C57BL6 mice to assess their gene expressions (via RT-qPCR) and phagocytic ability (via functional assay). As attempt to rejuvenate these aged MΦ, the cells were treated with RXR activator - bexarotene. We found that RXR activations converted MΦ toward “reparative”

phenotype, with increased trophic factors production, reduced pro-inflammatory phenotype, and enhanced phagocytic capacity. To single out the role of RXR in MΦ to post-stroke recovery, we employed myeloid-specific RXRα knockout (Mac-RXR-KO) aged mice. In these mice, RXRα was knocked out only in phagocytes (mostly microglia/macrophages). Both male and female aged (18-20 months old) Mac-RXR-KO mice and their littermate controls (RXR^{LoxP}) were subject to reversible MCA/CCAo to induce ischemic stroke. Bexarotene or vehicle control was injected intraperitoneally 24 hours after stroke and then once a day for 7 days. Since cognitive functions are important indices for post-stroke recovery in aging subjects, we evaluated the spatial learning and long-term memory of these mice using Barnes maze test started 21 days after stroke. We found that bexarotene improved both spatial learning (memory retention) and long-term memory in control genotype mice but not in Mac-RXR-KO mice, suggesting the beneficial effects of bexarotene include RXR signaling in microglia/macrophages. Our data suggest that RXR may be a potential target to reverse age-related microglial dysfunctions and improve post-stroke cognitive functions.

Disclosures: S. Ting: None. **G. Sun:** None. **L. Obertas:** None. **J. Aronowski:** None.

Poster

123. Functions of Glia and Non-Neuronal Cells in Stroke

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 123.03

Topic: C.09.Stroke

Support: AHA Grant 14SDG18730034
NIH Grant RO1NS107853

Title: Is Histone Deacetylase 3 a Key Regulator of Intracerebral Hemorrhage Induced Neuroinflammation?

Authors: *N. WATSON, F. BONSACK, S. SUKUMARI RAMESH;
Pharmacol., Augusta Univ., Augusta, GA

Abstract: Secondary brain injury is a leading cause of neurological deficits after intracerebral hemorrhage (ICH), a severe stroke subtype. Stimulation of the immune system at the site of a brain hemorrhage, characterized by microglial activation, leads to neuroinflammation and secondary brain damage. We previously reported that ICH results in the hypoacetylation of histone H3, suggesting a novel role of histone acetylation in the pathophysiology of ICH. Moreover, both a broad-spectrum and class 1 histone deacetylase inhibitor (HDACi) improved acute neurological outcomes in a mouse model of ICH. However, the isoform-specific role of histone deacetylases (HDACs) in the pathophysiology of ICH remains unknown. Our central hypothesis is that a class I HDAC isoform, HDAC3 is a critical molecular regulator of neurological outcomes after ICH. To this end, genetic knockdown of HDAC3 in a macrophage cell line significantly attenuated hemin-induced release of TNF-α and IL-6 compared to a

control. In contrast, the genetic knockdown of both HDAC1 and HDAC2 significantly augmented hemin-induced release of TNF-α from cells without an effect on IL-6. To extend this observation further, we have now generated microglia-specific HDAC3 conditional knockout using Cre-Lox technology. Our preliminary studies indicate improved neurobehavioral outcomes in HDAC3 flox/flox: Cx3cr1 CreER post-ICH compared to experimental control, implicating an unexplored role of HADC3 in ICH-induced neuroinflammation.

Disclosures: **N. Watson:** None. **F. Bonsack:** None. **S. Sukumari Ramesh:** None.

Poster

123. Functions of Glia and Non-Neuronal Cells in Stroke

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 123.04

Topic: C.09.Stroke

Support: NS099531
NS109459
NS101960

Title: Tenascin-c inhibition differentially curtails post-stroke toll-like receptor signaling

Authors: *B. CHELLUBOINA[1], A. CHOKKALLA[1,2], S. L. MEHTA[1], K. MORRIS-BLANCO[1], R. VEMUGANTI[1,2,3];
[1]Neurolog. Surgery, Univ. of Wisconsin, Madison, WI; [2]Cell. and Mol. Pathology Grad. Program, Madison, WI; [3]William S. Middleton Veterans Admin. Hosp., Madison, WI

Abstract: We recently demonstrated the role of stroke-induced tenascin-C (TNC) in ischemic pathogenesis. TNC activates toll-like receptor (TLR) -4 dependent neuroinflammation. However, TNC's role in post-stroke TLR signaling induction and sex differences remains unknown. Therefore, we investigated the sex differences in the TLR signaling after stroke in conjunction with TNC knockdown. Male and female C57BL/6 mice were subjected to transient MCAO and injected (i.v.) with either TNC siRNA or a negative (non-targeting) siRNA at 5 min after reperfusion. Infarct volume (T2-MRI) and TLR signaling (mouse-specific TLR signaling array) were evaluated at 3 days of reperfusion. The TNC siRNA treated cohort showed significantly less post-stroke brain damage than the sex-matched negative siRNA treated cohort. TNC inhibition also significantly reduced the post-stroke TLR signaling. The results demonstrated that the TNC knockdown in males, but not females, show a downregulation of the myeloid differentiation primary response protein 88 (MyD88)-dependent pathway.

Disclosures: **B. Chelluboina:** None. **A. Chokkalla:** None. **S.L. Mehta:** None. **K. Morris-Blanco:** None. **R. Vemuganti:** None.

Poster

123. Functions of Glia and Non-Neuronal Cells in Stroke

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 123.05

Topic: C.09.Stroke

Support: NS114336

Title: The role of CXCR2 blockade in post-stroke remyelination

Authors: *E. FONT BELMONTE, D. REN, J. D. HINMAN;
Neurol., UCLA, Los Angeles, CA

Abstract: Subcortical white matter ischemic injury is a common age-related pathology that increases the risk of stroke, cognitive impairment, and death. White matter damage is associated with immune cell infiltration, axonal degeneration, and ultimately myelin loss. After the lesion, the oligodendrocyte progenitor cells (OPCs) migrate to the border lesion, but they fail to differentiate into myelin-producing oligodendrocytes (OLs). Therefore, strategies to drive post-stroke remyelination are key therapeutic targets for brain repair in ischemic white matter disease. We hypothesized that vascular expression of the migratory chemokine CXCL5 signals through the CXCR2 receptor to cause restriction of OPCs within the vascular niche and blocks their differentiation into functional OLs. The chemokine receptor CXCR2 drives OPC migration through the vascular niche in embryonic development. One of the CXCR2 ligands, CXCL5, is increased by white matter ischemia and is up-regulated in chronically injured brain blood vessels. Thus, the CXCL5-CXCR2 signaling axis is a potential target for stroke recovery. To test this hypothesis, we used an established model of subcortical white matter ischemia induced by stereotactic injection of L-NIO, a NOS inhibitor that causes vasoconstriction, into the white matter underneath the forelimb sensorimotor cortex resulting in a focal white matter stroke. CXCR2 signaling was blocked using CXCR2 antiserum at 1, 24, and 48 hours after the stroke (n= 14) versus non-specific IgG control (n=10). We used both females and males that were pseudo-randomly assigned to control or treated groups to have a similar ratio in each group. Stroke lesion size was measured at 7d post-stroke and the extent of remyelination was measured by peri-infarct myelin basic protein immunoreactivity at 30d post-stroke.To specifically test the role of CXCR2 inhibition in OPCs, we developed PDGFRα-CreRT/CXCR2-fl/fl mice, in which CXCR2 expression is deleted in OPCs after Cre induction. Phenotyping of PDGFRα-CreRT/CXCR2-fl/fl mice after stroke demonstrates robust OPC response to stroke as previously observed. These findings suggest an important role for modulating CXCR2 signaling as a therapeutic strategy for brain repair in ischemic white matter disease.

Disclosures: E. Font Belmonte: None. **D. Ren:** None. **J.D. Hinman:** None.

Poster

123. Functions of Glia and Non-Neuronal Cells in Stroke

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 123.06

Topic: C.09.Stroke

Support: NIH R01NS104117
NINDS R01109221

Title: Intranasally administered elovanoid precursors provide neuroprotection by regulating the expression of microglia and neuroinflammatory gene expression

Authors: *M. REID[1], S.-H. HONG[2], P. K. MUKHERJEE[1], A. OBENAUS[3], L. KHOUTOROVA[1], K. SHELVIN[1], N. DESAI[1], B. JUN[1], L. S. BELAYEV[1], N. G. BAZAN[1]; [1]Neurosci. Ctr. of Excellence, Louisiana State Univ. Hlth. Sci. Ctr., New Orleans, LA; [2]Mcgovern Med. Sch., Univ. of Texas Hlth. Sci. Ctr. at Houston, Houston, TX; [3]Pediatrics, Univ. of California, Irvine, Irvine, CA

Abstract: Ischemic stroke causes alterations in homeostatic signaling that lead to neuronal death and tissue loss. We have previously shown a novel class of lipid mediators, Elovanoids (ELVs), to provide neuroprotection when administered after middle cerebral artery occlusion (MCAo). The neuronal specific elongase enzyme ELOVL4 (elongation of very-long-chain fatty acids–4) is responsible for the conversion of DHA into very-long-chain (≥C28) PUFAs (VLC-PUFAs,n-3) which are precursors for ELVs.We aim to assess the neuroprotection and changes in gene expression that occur when ELV precursor C-32:6 and C-34:6 are administered intranasally (IN) after MCAo. Male Sprague Dawley rats received 2h of the MCAo. Treatments with C-32:6, C-34:6 (1µg/µl, 20 µg per rat), or vehicle were administered at 1, 24, and 48h after onset of MCAo. The neurobehavioral composite battery was performed on days 1, 2, 3, and/or 7. Ischemic core and penumbra were computed from T2WI on day 7 followed by immunohistochemistry. In the separate group of rats, RT-qPCR was used to determine expression of genes that have been shown to be dysregulated following stroke including genes associated with inflammatory signaling, apoptosis, cellular homeostasis, and astrocyte and microglia activation when treated with VLC-PUFAs. Physiological variables showed no significant differences among groups. No adverse behavioral side effects were observed after the administration of our treatments. Treatments with C-32:6 and C-34:6 improved behavioral function on days three by (41% and 20%) and seven by (45% and 24%); T2WI total lesion volumes were reduced by (87% and 61%), respectively, compared to the vehicle on day 7. In the ischemic penumbra, C-32:6 and C-34:6 decreased $TMEM119^+$ microglia by (38% and 29%), increased $NeuN^+$ neurons by (87% and 110%), reduced IgG staining by (54% and 25%), and increased the number of $SMI\text{-}71^+$ vessels by (50% and 26%). In the core, C-32:6 and C-34:6 reduced $TMEM119^+$ microglia by (12% and 15%), increased $NeuN^+$ neurons by (251% and 89%) and increased the number of $SMI\text{-}71^+$ vessels by (31% and 70%). RT-qPCR data indicated a decrease in the expression of genes related to microglial activation and neuroinflammation and an increase in pro-homeostatic genes. We demonstrated that IN treatment with C-32:6 and C-34:6 protected the ischemic penumbra, decreased infarct volume, increased neurogenesis, and decreased microglial activation by affecting genes specific to neuroinflammatory signaling. We are currently exploring the conversion of the fatty acids to ELVs and the molecular mechanisms involved.This study was supported by NIH, NINDS grant R01NS104117, and R01109221 (NGB and LB).

Disclosures: **M. Reid:** None. **S. Hong:** None. **P.K. Mukherjee:** None. **A. Obenaus:** None. **L. Khoutorova:** None. **K. Shelvin:** None. **N. Desai:** None. **B. Jun:** None. **L.S. Belayev:** None. **N.G. Bazan:** None.

Poster

123. Functions of Glia and Non-Neuronal Cells in Stroke

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 123.07

Topic: C.09.Stroke

Support: CONACYT, México

Title: Agmatine atenuattes cognitive and motor deficits after acute thrombotic stroke

Authors: *M. L. MIRANDA-MOSQUEDA, C. GÓMEZ-ACEVEDO;
Pharmacol., Natl. Autonomous Univ. of Mexico, México, Mexico

Abstract: OBJECTIVE To propose a new effective neuroprotective pharmacological option against cerebrovascular events, and their consequences. Stroke represents a global health problem; it is the third cause of death and the first of disability in older adults including loss of independence and a considerable hospital expense. The probability of suffering an acute stroke increases after suffering a transitory event, since 1 in 3 people will evolve to such a degree, even half of them within 12 months after the transitory event. The ischemic type of stroke represents between 70 and 85% of cases, consists of a transient or permanent reduction in CBF caused by an embolus or a thrombus and involves irreversible cell damage, triggering various biochemical mechanisms known as Ischemic Cascade. Agmatine is a biogenic amine that has been found in a variety of food. Recently, various benefits of Agmatine have been described in the treatment of CNS conditions, which have been attributed to its multiple interactions in inflammatory processes (inhibition of metalloproteases and NF-κB, increase of eNOS, etc). **METHODS** **Bilateral carotid thrombosis (BCT):** Induction of thrombus formation by application of FeCl3 on the common carotid arteries, two events 32 days apart. **Animals:** 4-month-old CD1 mice, light-dark cycle 12-12, food and water ad libitum. **Burrowing test:** Performance measurement in the burrowing task, sensitive to hippocampal damage. **NDSS test:** Assessment of neurobehavioral deficits, scale analogous to NIHSS. **Quantification of the Infarct area:** tetrazolium chloride (TTZ) staining sensitive to mitochondrial activity. **Treatment:** The animals were administered with Agmatine 100mg/kg or saline solution (SS)15 min after the second surgery corresponding to the BCT model. **CONCLUSIONS** Our histological and behavioral results show neuroprotective effects reflected in the decrease of neurological deficits, infarct area and changes in excavation behavior, this allows us to propose a pharmacological alternative to attenuate reperfusion injury and those damages caused by repeated acute stroke events.

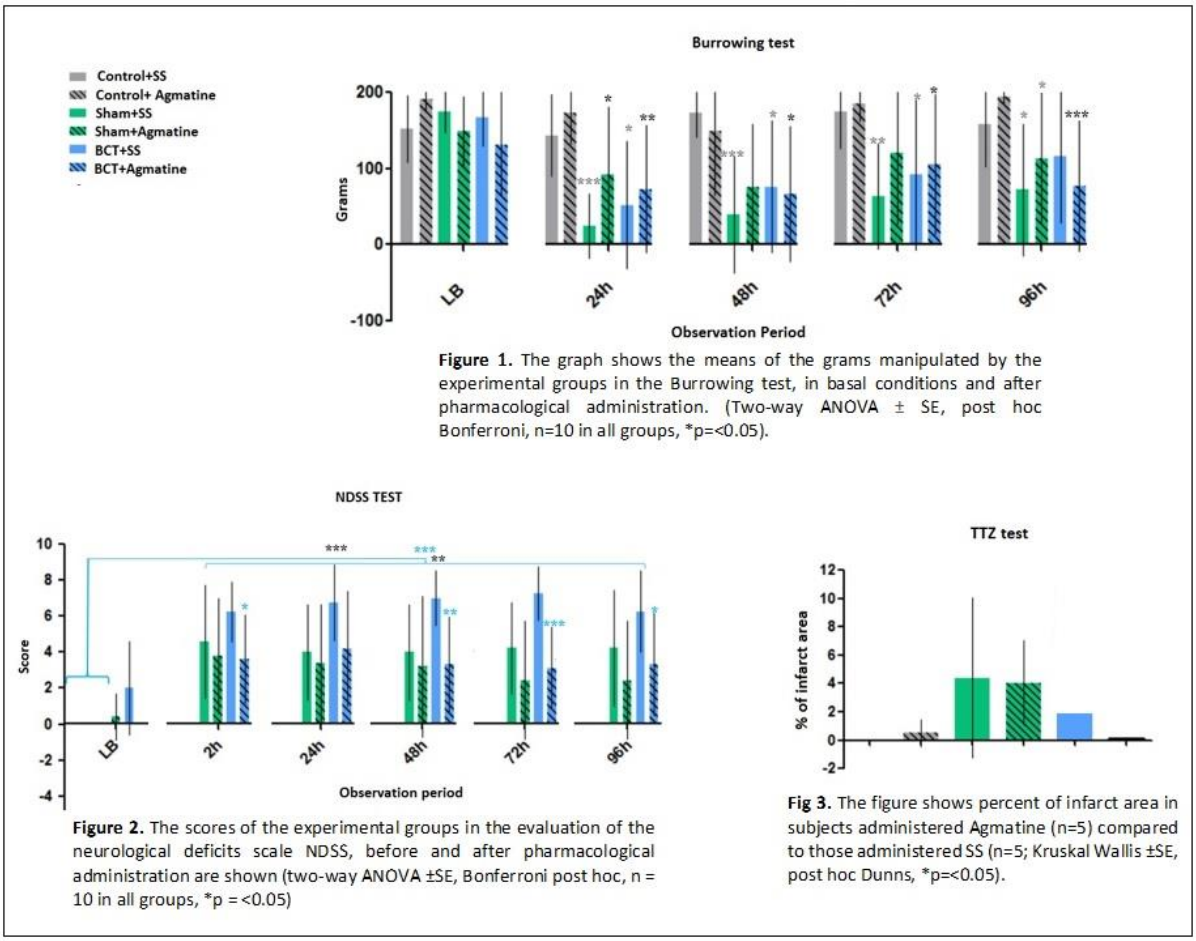


Figure 1. The graph shows the means of the grams manipulated by the experimental groups in the Burrowing test, in basal conditions and after pharmacological administration. (Two-way ANOVA ± SE, post hoc Bonferroni, n=10 in all groups, *p=<0.05).

Figure 2. The scores of the experimental groups in the evaluation of the neurological deficits scale NDSS, before and after pharmacological administration are shown (two-way ANOVA ±SE, Bonferroni post hoc, n = 10 in all groups, *p = <0.05)

Fig 3. The figure shows percent of infarct area in subjects administered Agmatine (n=5) compared to those administered SS (n=5; Kruskal Wallis ±SE, post hoc Dunns, *p=<0.05).

Disclosures: M.L. Miranda-Mosqueda: None. **C. Gómez-Acevedo:** None.

Poster

123. Functions of Glia and Non-Neuronal Cells in Stroke

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 123.08

Topic: C.09.Stroke

Support: NIH R01NS117906

Title: Metformin protects primary mouse astrocytes and neurons from oxidative injury by regulating the activity of the pyruvate dehydrogenase complex

Authors: *A. RAHMAN[1], Y. ZHANG[2], S. SHARMA[1], S. RAHMAN ARCHIE[1], T. ABBRUSCATO[3];
[1]Pharmaceut. Sci., Texas Tech. Univ. Hlth. Sci. Ctr., Amarillo, TX; [2]Pharmaceut. Sci., Texas

tech university Hlth. Sci. Ctr., Amarillo, TX; [3]Pharmaceut. Sci., Texas Tech. University, Hlth. Sci. Ctr., Amarillo, TX

Abstract: Background: Previous evidence has shown the protecting role of metformin on mouse astrocytes and neuronal damage and investigations support possibly repurposing this agent for alleviating stroke injury. Immediate after stroke, a rapid transition from aerobic to anaerobic conditions promotes oxidative metabolism in the ischemic brain. Altered pyruvate dehydrogenase complex (PDHC) and pyruvate dehydrogenase kinase (PDK2) controls oxidative metabolism after stroke. In addition, the level of lactate dehydrogenase (LDH) and LDH/PDHC can serve as important risk markers for ischemic stroke. Previous studies support that PDC-PDK-LDH plays a vital role in metabolic reprogramming and brain injury. Oxygen-glucose deprivation (OGD) in primary astrocytes and neurons is a widely accepted *in vitro* model for stroke and a means to model oxidative injury. Objective: We aimed to investigate the modulatory effect of different doses of metformin (10 and 100 μM) pretreatment on the PDK-PDH-LDH pathway in mouse astrocytes and neurons exposed to OGD. Method: The primary astrocytes and neurons were isolated and cultured from the cerebral cortices of one day old pups and from E16 or E17 embryos (CD-1 Mice), respectively. We determined the expression of associated proteins in mouse astrocytes using Western blot analysis. Results: Experiments support that 4 hours of OGD induces around a two-fold increased activity of PDK2, PPDH, LDH and 2.5-fold reduced activity of PDHC compared to control in astrocytes. 100 μM of metformin pretreatment significantly reduces the activity of PDK2, PPDH, LDH, LDH/PDHC and increased the activity of PDHC ($p<0.05$, paired t-test). A similar trend was observed in cultured neurons exposed to OGD. OGD induces a 1.5-fold increased activity of PDK2, PPDH, LDH, and decreased activity of PDHC compared to control. 10 and 100 μM of metformin significantly reduces the expression of PDK2, PPDH, and LDH and increased the activity of PDHC in a dose-dependent manner. Conclusion: Together these results suggest that metformin alleviates oxidative damage of primary mouse astrocytes and neurons after OGD conditions by the PDK-PDH-LDH pathway. Repurposing metformin for stroke injury to counteract injurious cellular pathways may provide a novel means to reduce stroke injury and promote neuronal recovery. Future studies will test the effects of metformin during OGD exposure.

Disclosures: A. Rahman: None. **Y. Zhang:** None. **S. Sharma:** None. **S. Rahman Archie:** None. **T. Abbruscato:** None.

Poster

123. Functions of Glia and Non-Neuronal Cells in Stroke

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 123.09

Topic: C.09.Stroke

Support: R15 AG059142
F31NS124302
University of Mississippi Graduate Student Council Research Grant

Title: Uncovering the IGF-1 Signaling Mechanisms Responsible for Neuroprotection Following Stroke

Authors: *C. HAYES[1], N. MORGAN[1], B. ASHMORE[1], K. THOMAS[3], A. VIJAYASANKAR[1], M. DE LEON[2], J. MARSHALL[1], N. ASHPOLE[1];
[1]Univ. of Mississippi, Oxford, MS; [2]Biomolecular Sci., Univ. of Mississippi, Houston, TX; [3]Tougalooo, Tougaloo, MS

Abstract: Strokes are a leading cause of mortality and disability worldwide; thus, there is a dire need for new, effective pharmacotherapeutics that can be administered to reduce the burden of disease post-insult. Clinical findings have shown that IGF-1 levels and post-stroke functional outcomes exhibit a positive relationship. Importantly, the administration of exogenous IGF-1 in rodent models of ischemic stroke attenuates neurological damage and functional deficits following stroke. Ongoing stroke damage after the initial insult is primarily induced by increased extracellular glutamate causing substantial neuronal death, increased neuro-inflammation, and greater tissue loss. Evidence from our laboratory has shown that reductions of the IGF-1 receptor (IGF-1R) in astrocytes reduces their ability to buffer excitotoxic levels of glutamate and a reduction in glutamate machinery. Based on this, we proposed that loss of astrocytic IGF-1 signaling could modulate the extent of stroke damage. Considering neurons also express the IGF-1R, it is likely that IGF-1 protects neurons by directly modulating the neurons. Our hypothesis is that the functional regulation of both neurons and astrocytes by IGF-1 is critical to minimize damage in ischemic stroke. To address this, we first conducted in vitro experiments to determine if the inhibition of IGF-1R in astrocytes altered neuroprotection from glutamate-induced toxicity. Moreover, we utilized novel inducible astrocyte-specific or neuron-specific transgenic mouse models to reduce IGF-1R in specific cell populations in the adult brain. One to three months following knockout, mice were subjected to photothrombosis to induce ischemic stroke, and we subsequently analyzed the extent of tissue damage and sensorimotor dysfunction. Moreover, we also investigated the systemic inflammatory and brain proteomic changes three hours following stroke. Our in vitro results provided evidence that the inhibition of IGF-1R in astrocytes exacerbated neuronal death in the presence of toxic glutamate levels. Additionally, we see that astrocyte knockout mice have a smaller infarct volume compared to wildtype controls and neuronal knockouts. A similar trend was also observed in immediate sensorimotor deficits following stroke. Overall, our findings provide a foundation for the development of pharmacological interventions that can target astrocyte mechanisms of protection to combat stroke damage.

Disclosures: C. Hayes: None. **N. Morgan:** None. **B. Ashmore:** None. **K. Thomas:** None. **A. Vijayasankar:** None. **M. De Leon:** None. **J. Marshall:** None. **N. Ashpole:** None.

Poster

123. Functions of Glia and Non-Neuronal Cells in Stroke

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 123.10

Topic: C.09.Stroke

Support: Seed Funding Grant, Touro University System

Title: Role of microglia during postnatal brain development after neonatal intraventricular hemorrhage (IVH): A Stem Cell + Pharmacologic Treatment Strategy

Authors: *G. VINUKONDA[1], Y. LIAO[2], F. HU[2], M. S. WOLIN[3], M. S. CAIRO[2], E. F. LA GAMMA[4];
[1]Pediatrics, Cell biology &Anatomy, [2]Pediatrics, [3]Physiol., [4]Pediatrics, Biochem. & Mol. Biol., New York Med. Col., Valhalla, NY

Abstract: Intraventricular hemorrhage (IVH) is a common complication of premature neonates and is associated with white matter injury, neurodevelopmental and cognitive disabilities. Currently no effective treatment is available. Extravasated red blood cells (RBC) hemolyze and release cytotoxic byproducts: free hemoglobin and iron, that elicit cytokine influx and free radical generation which contribute to tissue damage. After IVH, microglia are key regulators of anti-oxidant responses and phagocytic hematoma debris removal. M1 microglia infiltrate, secrete pro-inflammatory cytokines and generate free radicals accelerating tissue damage and suppresses transition to protective M2 microglia phenotype. Our RNA sequencing data and INGENUITY pathway analysis revealed that Fc-receptor mediated phagocytosis by macrophages with multiple modified signaling molecules were involved in IVH. Therefore, we studied "*living therapy*" (unrestricted somatic stem cells: USSCs) alone and combined with sulforaphane (SFN; antioxidant) and deferoxamine (DFN; iron chelator) for effects on microglia mediated pathologies. We used our rabbit model of IVH and evaluated the effects of treatment on microglial spatial distribution, phenotype changes, and density gradient in the developing forebrain. After IVH, we found densely populated resting Iba-1^+ microglia in the borders of the ventricles and choroid plexus. These microglia were highly proliferative with amoeboid morphology and infiltrated deep into areas of the brain parenchyma. Cell density experiments showed reduced infiltrated microglia in USSC treated compared with untreated IVH pups ($p<0.05$ both comparisons, n=5 each group). Combined treatment with SFN-DFN to reestablish heme-iron homeostasis significantly reduced iron and hemoglobin ($p<0.0$, n=5 each group). This reduction was associated with a significant increase of superoxide enzyme levels that aid in removal of free radicals ($p<0.05$, n=5 each group). Immunostaining using an oxidative marker 8-hydroxy-2'-deoxyguanosine (8-OHD) exhibited significantly lower numbers of 8-OHD positive cells compared with nontreated IVH pups. In this study the USSC treatment alone suppressed microglial infiltration and oxidative stress. SFN-DFN treatment reduced hemoglobin and iron accumulation and further attenuated inflammation and free radical production. Together the data suggests that the possible beneficial effect of combined treatment is additive or even synergistic. The goal would be to minimize accelerants of tissue destruction by focusing on categorical repair processes that will enable innate recovery of the developing injured brain.

Disclosures: G. Vinukonda: None. **Y. Liao:** None. **F. Hu:** None. **M.S. Wolin:** None. **M.S. Cairo:** None. **E.F. La Gamma:** None.

Poster

123. Functions of Glia and Non-Neuronal Cells in Stroke

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 123.11

Topic: C.09.Stroke

Support: Applebaum Foundation Inc Grant
Department of Neurology, Miller School of Medicine

Title: Regulation of glial cells and inflammatory markers in the hippocampus and the cortex following intra-arterial stem cell therapy in a canine model of ischemic stroke

Authors: *R. THAKKAR, D. OJEDA, D. YAVAGAL;
Neurol., Miller Sch. of Medicine, Univ. of Miami, Miami, FL

Abstract: Stroke is the 2nd leading cause of death globally. Despite the current standard of care for stroke, more than 50% of stroke survivors are chronically disabled, leading to more than $46 billion in annual economic burden in the US alone. It is therefore imperative to develop novel therapies for stroke. Preclinical studies in the past two decades have shown promise in cell therapies for stroke. One such approach, intra-arterial (IA) delivery of Mesenchymal Stem Cells (MSCs), is minimally invasive making it attractive for clinical translation. Recent studies from our lab have shown the safety and efficacy of IA-MSC treatment in rodent and canine ischemic stroke models. These studies from our group have established the precise timing and effective dosage of IA-MSC therapy that leads to improved stroke outcomes. It is believed that IA-MSCs exert their protective effects by mediating anti-inflammatory actions. However, this mechanism is not very well studied, specifically in the large animal brain. This gap in the field is crucial for effective translation of cell-based therapies to the clinic. Therefore, in this study we determined the expression pattern of microglia, astrocytes, and the Nod-like receptor 3 (NLRP3) inflammasome pathway markers in the large animal canine brain following IA MSC therapy after ischemic stroke. Immunohistochemistry staining and immunofluorescence imaging of the canine brain cortex and hippocampus were performed to determine the expression of inflammatory markers. Sequence identity and match was pre-determined using BLAST software to confirm antigenic specificity for the rare canine research model. Numerical quantification identified the expression patterns of GFAP, Iba1, NLRP3, Apoptosis-associated speck-like protein containing a CARD domain (ASC), Caspase1, and Interluekin-1beta at different doses of IA-MSCs (10, 20, and 40 million) at 30 days post-stroke. Results from this study showed a significant dose-dependent reduction in glial cell activation in the canine hippocampus and the cortex. This was accompanied by significantly decreased expression of the NLRP3 inflammasome and IL1β cytokine following IA-MSC therapy. These novel findings help us understand inflammation in the canine brain after stroke. Our data further reveal how IA-MSC therapy mediates its action via inflammatory changes. Overall, this approach contributes to developing more robust and engineered IA-MSCs therapies for stroke patients, leading to more effective translation.

Disclosures: **R. Thakkar:** A. Employment/Salary (full or part-time):; University of Miami. **D. Ojeda:** A. Employment/Salary (full or part-time):; University of Miami. **D. Yavagal:** A. Employment/Salary (full or part-time):; University of Miami.

Poster

123. Functions of Glia and Non-Neuronal Cells in Stroke

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 123.12

Topic: C.09.Stroke

Support: NIH R01NS112642

Title: Cofilin inhibition improves cognitive deficit & protects against hemorrhagic brain injury in mice

Authors: *G. BAHADER[1,2], M. ALI[1], D. A. ALMARGHALANI[3], Q. ALHADIDI[4], Z. A. SHAH[5];
[1]Univ. of Toledo, Toledo, OH; [2]Medicinal and Biol. Chem., The university of Toledo, Toledo, OH; [3]Dept. of Pharmacol. & Exptl. Therapuetics, The Univ. of Toledo, Toledo, OH; [4]Pharm., Al-Yarmook Univ. Col., Baqubah, Iraq; [5]Medicinal & Biol. Chem., Univ. of Toledo Col. of Pharm. and Pharmaceut. Sci., Toledo, OH

Abstract: Intracerebral Hemorrhage (ICH) is a devastating subtype of stroke representing a major cause of long-term disability worldwide. Cofilin, an actin-binding & severing protein, has been identified as a stress-activated protein that plays a major role in microglial cell activation & neuronal apoptosis. In our previous studies, we demonstrated that knocking down cofilin mitigates ICH-induced injury & improves neurobehavioral parameters via combating oxidative stress & neuroinflammation. In the current study, we investigated the efficacy of a first-in-class small-molecule cofilin inhibitor (CI) in an ICH mouse model. Male mice were subjected to an intrastriatal stereotaxic injection of collagenase to induce ICH. Subsequently, a single intravenous injection of CI (10, 25, 50, 100 mg/kg in 4 cohorts) or vehicle was administered 3 hours following the injury & continued every 12 hours for the total duration of the study. A battery of neurobehavioral tests was performed starting from day 1 after ICH & up to 7 days. Sensory& locomotor performance was measured using grip strength, rotarod, & neurologic deficit scores. Spatial learning & memory were measured on days 4 to 7 following ICH using the T-maze test. Animals were sacrificed on day 7 after ICH & several assays were performed, including Western blotting, real-time PCR, & immunohistochemistry. Our results showed that treatment with CI significantly reduced the hematoma volume & improved the neurobehavioral tasks compared to the vehicle. Furthermore, CI-treated mice exhibited lower glial cell activation, neuroinflammatory, endoplasmic reticulum stress, & apoptotic markers. The expression level of pre- & postsynaptic proteins, synaptophysin & postsynaptic density 95, was also increased in the CI-treated animals, translating to an improvement in cognitive functions. Altogether, these results confirm the potential role of cofilin as a novel therapeutic target for the treatment of ICH.

Disclosures: G. Bahader: None. **M. Ali:** None. **D.A. Almarghalani:** None. **Q. Alhadidi:** None. **Z.A. Shah:** None.

Poster

123. Functions of Glia and Non-Neuronal Cells in Stroke

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 123.13

Topic: C.09.Stroke

Support: UC DDC

Title: Genetic mimicry: discovery of stroke-mediated axonal regenerative therapeutics via functional genomics

Authors: *J. AN[1], B. TOH[1], J. T. WANG[3], R. DAMOISEAUX[2], J. D. HINMAN[1];
[1]Dept. of Neurology, David Geffen Sch. of Med., [2]Mol. Screening Shared Resource, CNSI, UCLA, Los Angeles, CA; [3]Dept. of Neurobio., Stanford Univ., Stanford, CA

Abstract: Ischemic stroke injury results in characteristic and stereotypic degeneration of axons driving a critical barrier to functional neurologic recovery. The molecular mechanisms regulating stroke-mediated axonal degeneration are unclear. By investigating the genetic mechanisms of stroke surviving cortical neurons, we can exploit molecular pathways promoting axonal regeneration and unlock therapeutic strategies to drive neuronal survival and repair. To address this objective, we used a knockout genetic mouse model of delayed Wallerian degeneration (*Sarm1*-null) in a unique model of subcortical stroke injury that predominantly damages axons. Combining retrograde neuronal tracing after stroke with MACS-FACS capture and transcriptional profiling of surviving stroke-injured cortical neurons in wild-type versus knockout models, we identified stroke-induced activation of genetic programs driving neuronal differentiation, axonogenesis, and synaptogenesis in stroke-injured neurons in *Sarm1*-null mice. The top 150 differentially expressed up-regulated genes and the top 150 up- and down-regulated genes were inputted into CLUE-IO to identify 2428 compounds with similar transcriptional profiles across 9 cell lines. Compounds with CMap enrichment scores ≥ 90 were filtered for blood-brain barrier permeability. This curated list of 18 small molecule candidates were subjected to an automated screening approach in E17 primary murine cortical neurons. After 48 hours of drug exposure at sub-nanomolar concentrations, five out of 18 compounds significantly increased neurite outgrowth compared to control neurons. HL017, an androgen receptor antagonist, showed sub 100nM mean neurite outgrowth of 276% with peak outgrowth of 460% at 95pM, compared to control (p<0.0001, two-way ANOVA). HL013, a serotonin receptor agonist, showed sustained outgrowth across sub 100nM concentrations with peak outgrowth of 345% at 95pM (p<0.0001). HL004, a topoisomerase inhibitor, and HL009, an ATPase inhibitor, both demonstrated significant sustained outgrowth across sub 100nM doses (p<0.0001, p<0.0001). HL012, an ATPase inhibitor, displayed steady outgrowth across sub 50nM doses (p<0.0001). Importantly, promotion of neurite outgrowth was independent of pharmacologic class and effective even in the presence of *Sarm1*, implying a novel mechanism regulating axonal growth. This functional *in silico*/chemical genomics screen validates a druggable

axonogenesis profile that can be recapitulated *in vitro* and harnessed for therapeutics *in vivo* to drive functional neurologic recovery.

Disclosures: J. An: None. **B. Toh:** None. **J.T. Wang:** None. **R. Damoiseaux:** None. **J.D. Hinman:** None.

Poster

123. Functions of Glia and Non-Neuronal Cells in Stroke

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 123.14

Topic: C.09.Stroke

Support: DST Purse
ICMR

Title: N-acetyl cysteine ameliorates mitochondrial dysfunction in ischemic injury via attenuating drp-1 mediated mitochondrial autophagy.

Authors: *M. ALI, S. PARVEZ;
Jamia hamdard, Jamia hamdard, NEW DELHI, India

Abstract: Background and Purpose
Ischemic reperfusion (I/R) injury causes a wide array of functional and structure alternations of mitochondria, associated with oxidative stress and increased the severity of injury. Despite the previous evidence for N-acetyl L-cysteine (NAC) provide neuroprotection after I/R injury, it is unknown to evaluate the effect of NAC on altered mitochondrial autophagy forms an essential axis to impaired mitochondrial quality control in cerebral I/R injury. **Methods** Male wistar rats subjected to I/R injury were used as transient Middle Cerebral Artery Occlusion(tMCAO)model. After I/R injury, the degree of cerebral tissue injury was detected by infarct volume, H&E staining and behavioral assessment. We also performed mitochondrial reactive oxygen species and mitochondrial membrane potential by flow cytometry and mitochondrial respiratory complexes to evaluate the mitochondrial dysfunction. Finally, we performed the western blotting analysis to measure the apoptotic and autophagic marker. **Results** We found that NAC administration significantly ameliorates brain injury, improves neurobehavioral outcome, decreases neuroinflammation and mitochondrial mediated oxidative stress. We evaluated the neuroprotective effect of NAC against neuronal apoptosis by assessing its ability to sustained mitochondrial integrity and function. Further studies revealed that beneficial effects of NAC is through targeting the mitochondrial autophagy via regulating the GSK-3β/Drp1mediated mitochondrial fission and inhibiting the expression of beclin-1 and conversion of LC3, as well as activating the p-Akt pro-survival pathway. **Conclusion**Our results suggest that NAC exerts neuroprotective effects to inhibit the altered mitochondrial changes and cell death in I/R injury via regulation of p-GSK-3β mediated Drp-1 translocation to the mitochondria.

Disclosures: M. Ali: None. **S. Parvez:** None.

Poster

123. Functions of Glia and Non-Neuronal Cells in Stroke

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 123.15

Topic: C.09.Stroke

Support: Swedish Research Council
The Swedish Brain Foundation
The Swedish Stroke Foundation
T. Söderberg's Foundations
Swedish Society for Medical Research
The Friebe Foundation
Deutsche Forschungsgemeinschaft

Title: Complement C3a treatment modulates astrocyte reactivity, stimulates cortical connectivity and accelerates recovery after ischemic stroke

Authors: *M. PEKNA[1], A. STOKOWSKA[1], M. ASWENDT[2], D. ZUCHA[3], F. WIETERS[2], J. MORAN SUAREZ[1], A. L. ATKINS[1], Y. LI[1], M. MITEVA[1], J. LEWIN[1], D. WIEDERMANN[4], M. DIEDENHOFEN[4], Å. TORINSSON NALUAI[1], P. ABAFFY[3], L. VALIHARCH[3], M. KUBISTA[3], M. HOEHN[5], M. PEKNY[1];
[1]Univ. of Gothenburg, Univ. of Gothenburg, Gothenburg, Sweden; [2]Univ. Hosp. Cologne, Univ. of Cologne, Koeln, Germany; [3]Czech Acad. of Sci., Prague, Czech Republic; [4]Max Planck Inst. for Metabolism Res., Cologne, Germany; [5]Res. Ctr. Juelich, Juelich, Germany

Abstract: Despite advances in acute care, ischemic stroke remains a major cause of serious long-term disability. Novel approaches targeting both neuronal and glial responses are needed to enhance recovery and improve long-term outcome. The complement C3a receptor (C3aR) is a regulator of inflammation with roles in neurodevelopment, neural plasticity and neurodegeneration. Using mice lacking C3aR (*C3aR*$^{-/-}$) and mice overexpressing C3a in the brain, we uncovered two opposing effects of C3aR signaling on functional recovery after ischemic stroke: inhibition in the acute phase and facilitation in the later phase. Peri-infarct astrocyte reactivity was increased and density of microglia reduced in *C3aR*$^{-/-}$ mice 21 days after stroke, C3a overexpression led to the opposite effects. Pharmacological treatment of wild-type mice with intranasal C3a starting 7 days after stroke accelerated recovery of motor function and attenuated astrocyte reactivity without enhancing microgliosis. C3a treatment stimulated global white matter reorganization, increased peri-infarct structural connectivity and upregulated *Igf1* and *Thbs4* in the peri-infarct cortex. Thus, C3a treatment from day 7 after stroke exerts positive effects on astrocytes and neuronal connectivity while avoiding the deleterious consequences of C3aR signaling during the acute phase. Intranasal administration of C3aR agonists within convenient therapeutic time window holds translational promise to improve outcome after ischemic stroke.

Disclosures: **M. Pekna:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Holder of United States patent "C3a receptor agonists for use against ischemic brain injury, stroke, traumatic brain injury, spinal cord injury and neurodegenerative disorders" (US 11,266,715). **A. Stokowska:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Holder of United States patent "C3a receptor agonists for use against ischemic brain injury, stroke, traumatic brain injury, spinal cord injury and neurodegenerative disorders" (US 11,266,715).. **M. Aswendt:** None. **D. Zucha:** None. **F. Wieters:** None. **J. Moran Suarez:** None. **A.L. Atkins:** None. **Y. Li:** None. **M. Miteva:** None. **J. Lewin:** None. **D. Wiedermann:** None. **M. Diedenhofen:** None. **Å. Torinsson Naluai:** None. **P. Abaffy:** None. **L. Valiharch:** None. **M. Kubista:** None. **M. Hoehn:** None. **M. Pekny:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Holder of United States patent "C3a receptor agonists for use against ischemic brain injury, stroke, traumatic brain injury, spinal cord injury and neurodegenerative disorders" (US 11,266,715)..

Poster

123. Functions of Glia and Non-Neuronal Cells in Stroke

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 123.16

Topic: C.09.Stroke

Support: RF1NS119872
AG042189

Title: Intraperitoneal, but not intracerebroventricular, IGF1 treatment improves ischemic stroke-induced affective and cognitive behaviors in acyclic middle-aged female rats

Authors: *Y. EL-HAKIM[1], K. MANI[2], N. SAMIYA[3], F. SOHRABJI[4];
[1]Texas A&M Hlth. Sci. Ctr., Bryan, TX; [2]Neurosci. and Exptl. Therapeut., Texas A & M Univ., Bryan, TX; [3]Texas A&M Univ. Syst. Hlth. Scien Neurosci. and Exptl. Therapeut., College Station, TX; [4]Neurosci. and Exptl. Therapeut., Texas A&M Univ. Syst. Hlth. Scien Neurosci. and Exptl. Therapeut., Bryan, TX

Abstract: Stroke is the leading cause of long-term disability and a risk factor for dementia. Hence stroke therapies are urgently needed to improve the quality of life for stroke survivors, especially women who are at a greater risk for stroke after menopause. Our previous studies have modeled this population using acyclic middle-aged female rats. This group has lower circulating levels of the peptide hormone Insulin-like Growth Factor (IGF-1) and display worse outcomes after a stroke than young adult female rats. ICV administration of IGF-1 to this group decreases infarct volume, improves sensory motor performance and reduces cytokine levels in the ischemic hemisphere. Despite this neuroprotection, icv IGF1 treatment did not reduce peripheral inflammation or improve cognitive decline and depressive behaviors in the chronic phase of

stroke. In view of the evidence that stroke induces gut dysbiosis, and that gut dysfunction is implicated in depressive and cognitive behaviors, we hypothesize that, unlike icv IGF-1 treatment, which is restricted to the brain, systemic (i.p.) IGF1 treatment would repair the gut, attenuate peripheral cytokine levels and improve long-term behavior outcomes. Acylic middle-aged Sprague Dawley female rats (9-11 mos) were subjected to endothelin-1 induced middle cerebral artery occlusion (MCAo) or sham operation. Animals received i.p. IGF1 injections 4h and 24h post MCAo, or icv infusions, while controls received vehicle. Sensory motor tests, blood and gut samples were acquired pre and post MCAo. Animals were terminated either in the acute phase (2d) or chronic phase (30d). The latter group was also subject to tests of cognition and depressive-like behavior. In contrast to icv treatment, i.p.-IGF-1 did not reduce infarct volume or acute sensory motor impairment but significantly attenuated circulating levels of IL-17, TNFα, and IFNg and reduced post stroke gut dysmorphology, by preserving villus:crypt ratio and attenuating crypt hyperplasia. In addition, i.p. IGF1 treatment attenuated the post stroke cognitive deficits as assessed by the Barnes Maze assay and Novel Object Recognition Test as well as depressive outcomes in the burrowing assay. Since long term disability after stroke is correlated with elevated levels of peripheral cytokines, our data suggest that systemic IGF1 may be a better therapeutic option for long term cognitive and depressive behaviors after stroke.

Disclosures: Y. El-Hakim: None. **K. Mani:** None. **N. samiya:** None. **F. Sohrabji:** None.

Poster

123. Functions of Glia and Non-Neuronal Cells in Stroke

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 123.17

Topic: C.09.Stroke

Support: RFAG042189 to FS
AARF-21-849749 to DS
F31 NS118970 to TEB

Title: Sex differences in cognitive function after stroke and its treatment with Mir20a-3p in middle-aged Sprague Dawley rats

Authors: *D. SAMPATH[1], T. BRANYAN[1], K. MARKOWSKY[1], R. GUNDA[1], N. SAMIYA[2], J. M. SINGER[1], F. SOHRABJI[3];
[1]Texas A&M Univ. Syst. Hlth. Scien Neurosci. and Exptl. Therapeut., Bryan, TX; [2]Texas A&M Univ. Syst. Hlth. Scien Neurosci. and Exptl. Therapeut., College Station, TX; [3]Neurosci. and Exptl. Therapeut., Texas A&M Univ. Syst. Hlth. Scien Neurosci. and Exptl. Therapeut., Bryan, TX

Abstract: Introduction: Stroke is a leading risk factor for dementia. Our previous studies show that the small non-coding RNA, mir20a-3p, is neuroprotective for stroke and reduces sensory-motor impairment in the acute phase (Branyan et al., 2021). In this study, we used a battery of

tests to assess the integrated functioning of affective and cognitive circuits in the chronic phase of stroke as well as the impact of mir20a-3p. **Methodology:** Middle-aged females and males were subject to ischemic stroke using endothelin-1 injected adjacent to the left middle cerebral artery (MCA). Mir20a-3p mimic or scrambled oligo was administered i.v. 4h, 24h after stroke and at 60d post stroke. Long-term cognitive changes were assessed by contextual fear conditioning (CFC) and the novel object recognition test (NORT). **Results:** Both males and females showed significant sensory-motor impairment due to stroke in the acute phase, which was attenuated by Mir20a-3p treatment. Cognitive function was assessed by cued and contextual fear conditioning, evaluated by percent freezing during acquisition, retrieval, and extinction of fear memory. When measured 30, 60 and 100d after stroke, retrieval of fear memory was significantly reduced over time in sham and stroke males and females. However, linear regression analysis revealed that among females, the rate of decline of fear memory was significantly accelerated in the stroke group that received scrambled oligo treatment, while the rate of decline in the Mir20a-3p group was similar to the sham group, indicating a protective effect of this drug. Surprisingly, stroke+ scrambled treated male rats did not show an accelerated decline. Evaluation of fear extinction after reconditioning at 100 days post MCAo did not show sustained stroke or treatment related effects in either sex. Declarative memory, assessed by NORT, showed a significant decline of declarative memory in all groups of females at 30 days after stroke; however, sham and MCAo+mir20a-3p treated animals' cognitive performance on this test recovered when measured at 100 days, while the deficit persisted in MCAo+scrambled treated females. Male rats did not show any change in performance due to stroke or its treatment at comparable time points of testing. Hyperintensities in the forebrain of T2 weighted MRI images were similar in vehicle-treated males and females but were decreased in mir20a-3p treated females compared to males. **Conclusion:** Although acute sensory-motor impairment is seen to a similar extent in males and females, stroke significantly affected cognitive function in females but not males. Moreover, mir20a-3p treatment abrogated this effect of stroke in females

Disclosures: D. Sampath: None. **T. Branyan:** None. **K. Markowsky:** None. **R. Gunda:** None. **N. samiya:** None. **J.M. Singer:** None. **F. Sohrabji:** None.

Poster

123. Functions of Glia and Non-Neuronal Cells in Stroke

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 123.18

Topic: C.09.Stroke

Support: Xunta de Galicia - IN607A2018/3, IN607D2020/09, IN606A-2021/015
Science Ministry of Spain - RTI2018-102165-B-I00, RTC2019-007373-1
INTERREG Atlantic Area - EAPA_791/2018_NEUROATLANTIC
INTER-REG V A España Portugal (POCTEP) - 0624_2IQBIONEURO_6_E
Instituto de Salud Carlos III, Sara Borrell Program - CD21/00166
Instituto de Salud Carlos III, Miguel Servet Program - CPII17/00027
Instituto de Salud Carlos III, iPFIS contract - IFI18/00008

Title: Tweak as a promising therapeutic target in intracerebral hemorrhage

Authors: *D. ROMAUS-SANJURJO, J. PÍAS-PELETEIRO, A. CUSTODIA, M. ARAMBURU-NÚÑEZ, D. ÁLVAREZ-RAFAEL, A. OURO, T. SOBRINO;
Hlth. Res. Inst. of Santigao de Compostela, Santiago de Compostela, Spain

Abstract: Background: Endothelial function (EF) has an important role in intracerebral hemorrhage (ICH). Cellular (circulating endothelial progenitor cells, EPCs) and molecular markers (soluble TWEAK, sTWEAK) are positively associated with the endothelial function (EF). Therefore, we conducted a translational study focused on testing the role of the EF and EPCs and sTWEAK levels on the outcome of patients with acute ICH. Then, we investigated whether recombinant TWEAK treatment induces EPCs mobilization, angiogenesis processes and hematoma reduction in a rat model of ICH. **Methods:** Forty-six patients with primary ICH were recruited within 24 hours of the symptom onset (clinical study); while SD rats, undergoing a collagenase-induced ICH, were randomized into 3 experimental groups: 1) control group treated with PBS, 2) TWEAK 50 group (50 µg/kg TWEAK), and 3) TWEAK 150 group (150 µg/kg TWEAK) (preclinical study). In patients, both FMD and ICH volume were measured, whereas hematoma volume was measured in rats as primary endpoints. EPCs levels were measured by flow cytometry. Serum levels of sTWEAK from patients were quantified by ELISA. In the preclinical study, several functional tests were performed to assess the neurological and functional outcome; moreover, angiogenesis in the perihematoma area was studied by immunohistochemistry. **Results:** Circulating EPCs levels at admission, and serum levels of sTWEAK at admission and 24 h were strongly associated to EF measured by FMD (all $p<0.0001$). Moreover, FMD was independently associated with good functional outcome at 12 months (modified Rankin scale <3) ($p=0.047$) as well as to residual lesion volume ($p=0.045$). ICH rats from the TWEAK 50 group showed higher levels of circulating EPC within the first 28 days compared to control group (all $p<0.01$). Moreover, hematoma volume was significantly reduced only in the TWEAK 50 group at 28 days ($p<0.05$). No effects were observed in the neurological and functional recovery. Immunohistochemistry analysis revealed a greater angiogenesis in the perihematoma area as well as increased cell proliferation in the subventricular zone in both groups treated with TWEAK. **Conclusion:** These results showed that EF play an important role in the recovery of ICH patients. Furthermore, preclinical results showed that the treatment with recombinant TWEAK emerges as a potential therapeutic option in ICH, laying the foundations for future clinical trials using TWEAK.

Disclosures: D. Romaus-Sanjurjo: None. **J. Pías-Peleteiro:** None. **A. Custodia:** None. **M. Aramburu-Núñez:** None. **D. Álvarez-Rafael:** None. **A. Ouro:** None. **T. Sobrino:** None.

Poster

123. Functions of Glia and Non-Neuronal Cells in Stroke

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 123.19

Topic: C.09.Stroke

Support: American Heart Association AHA Award Number: 20CDA35310828

Title: NLY01 decreases chronic neuroinflammation, infarct volume, and behavioral deficits in a mouse model of ischemic stroke

Authors: *K. PRESCOTT, J. T. HOLSTEN, R. L. BRIMBERRY, T. C. PETERSON;
Univ. of North Carolina Wilmington, Wilmington, NC

Abstract: Approximately 2.7% of all adults in the United States have had a stroke. The most common treatment for ischemic stroke is the use of recombinant tissue plasminogen activator, but with a limited treatment, it is effective in less than 3% of the population. Reducing the pro-inflammatory cytokines TNF, IL-1α, and C1q released by microglia after stroke has been shown to reduce neurotoxic reactive astrocytes (nRAs) after injury. NLY01 is a glycogen-like peptide-1 receptor (GLP1R) agonist that crosses the blood-brain barrier and inhibits microglia from releasing these cytokines which reduces nRAs. We hypothesize that NLY01 will reduce microglial activation, nRA formation, reduce infarct volume, and reduce behavioral deficits after ischemic stroke. To examine how NLY01 would affect the neuroinflammatory response and reduce neurotoxic astrocytes following ischemic stroke, a distal medial cerebral artery occlusion (dMCAO) was performed on female C57BL/6J mice. NLY01 was administered 4 hours after surgery using retro-orbital injection and every 48 hours for 7 days using an intraperitoneal injection. Mice were administered 0 mg/kg (n = 12), 1 mg/kg (n = 11), 3 mg/kg (n = 11), or 15 mg/kg (n = 7) of NLY01 following stroke, and the brain was extracted 7 days post-stroke. A separate experiment was performed to examine the functional benefits of NLY01 treatment following stroke. A photothrombotic stroke was induced over the motor cortex in female C57BL/6J mice, prior to similar administration of 0 mg/kg (n = 11), 1(n = 11), 3 mg/kg (n = 11), or 15 mg/kg (n = 12) of NLY01. Behavior assessments included the grid walk, rotating beam, and tapered beam. Brains were extracted 30 days post-stroke. A One-way ANOVA was performed to examine group differences in astrocyte coverage, microglial coverage and infarct size. No differences were found in the inflammatory response or infarct size 7 days post stroke. The 0 mg/kg group had a thinner cortex than the 1- ($p < .001$) and 3 mg/kg ($p < .0001$) groups. The 1- ($p = .02$) and 3 mg/kg ($p = .002$) groups had less macrophage coverage in the peri-infarct area than the 0 mg/kg group. The 3 mg/kg ($p = .01$) had less astrocyte coverage than the 0 mg/kg group. Compared to the 0 mg/kg group, the 1 and 3- mg/kg group performed better on the rotating beam ($p < .001$, $p = .015$; respectively) and the tapered beam ($p < .001$; both) two days after stroke and the grid walk task ($p = .02$, $p = .03$; respectively) 14 days after stroke. This suggests that NLY01 can reduce neuroinflammation and improve behavioral deficits when administered after stroke. NLY01 may also be effective in other neurological disorders and injuries where glial cells and nRAs exacerbate neuronal damage, such as Parkinson's Disease.

Disclosures: K. Prescott: None. **J.T. Holsten:** None. **R.L. Brimberry:** None. **T.C. Peterson:** None.

Poster

123. Functions of Glia and Non-Neuronal Cells in Stroke

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 123.20

Topic: C.09.Stroke

Title: Aging and Smoking Exacerbates Post-Stroke Complement Driven Neuroinflammation

Authors: *C. COUCH;
Microbiology and Immunol., Med. Univ. of South Carolina, Charleston, SC

Abstract: Following ischemic stroke, complement-dependent neuroinflammation, initiated by natural IgM binding to reperfused endothelium, exacerbates secondary injury and worsens acute and chronic outcomes. We have shown that a complement inhibitor (B4Crry), that targets specifically to the ischemic penumbra, inhibits complement activation leading to improved outcomes following murine ischemic stroke. However, while multiple neuroprotective agents have shown beneficial effects in rodent models of stroke, they have failed to translate in the clinic, a likely explanation being that there has been inadequate assessment of functional outcomes in stroke models, as well the use of young healthy animals that are not representative of clinical cohorts. We investigated the impact of age and smoking comorbidities on acute outcomes after stroke and assessed whether increased complement activation contributes to a worsened outcome with these comorbidities. Following hypoxia, brain endothelial cells (b.End3) exposed to serum from cigarette smoke (CS)-exposed mice had higher levels of IgM and C3d deposition compared to cells exposed to naïve serum. After middle cerebral artery occlusion, aged and CS-exposed mice had significantly worse neurological deficits and mortality compared to aged mice. B4Crry reduced mortality and motor deficits in aged and aged+CS exposed mice, and there was a higher effect size in comorbid animals. Age and/or CS exposure resulted in larger infarct volumes and increased levels of C3d deposition and microglial activation compared to young adults, but aged/CS-exposed animals treated with B4Crry fared comparable to young adults. The pro-inflammatory effects of aging and smoking contribute to worse stroke outcomes, and these effects are mitigated by complement inhibition.

Disclosures: C. Couch: None.

Poster

123. Functions of Glia and Non-Neuronal Cells in Stroke

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 123.21

Topic: C.08. Ischemia

Title: Neuroprotective effect of macrophage migration inhibitory factor(MIF) in ischemic stroke mice model

Authors: *B. JANG, J. KIM, M. KIM, S. LEE, D. KIM;
Rehabil. Med., Asan Med. Ctr., Seoul, Korea, Republic of

Abstract: Objective: Macrophage migration inhibitory factor(MIF) is multifunctional immune cytokine which is known to play neuroprotective role in in vitro ischemic stroke models, however the neuroprotective effect in vivo model is not yet clear. This study aimed to investigate if the MIF promotes neurological recovery in vivo stroke mice model. **Methods:** The group was allocated to sham vehicle, sham MIF, MCAO vehicle, MCAO MIF. Transient middle cerebral artery occlusion (tMCAO) is performed to male mice in MCAO groups. Vehicle and MIF was administered through intracerebroventricular route. We evaluated the neurological functional scale, and rotarod test, and T2-weighted magnetic resonance imaging. As secondary outcome, the expression level of microtubule-associated protein 2 (MAP2), Bcl2, brain-derived neurotrophic factor (BDNF) was measured by western blot assay. **Results:** The neurological scale was significantly higher in MCAO MIF group compared to MCAO vehicle group (Figure 1). MCAO vehicle group exhibited significantly poorer performance on the rotarod test than MCAO MIF group (Figure 2). MCAO MIF group had significantly reduced total infarct volume compared with MCAO vehicle group in T2-weighted MRI image (Figure 3). Expression levels of BDNF, Bcl2, and MAP2 tend to be higher in MCAO MIF group than MCAO vehicle group. **Conclusion:** This study suggests that MIF has neuroprotective effect on in vivo ischemic stroke model. MIF seems to facilitate neurological recovery, and protect the brain tissue from ischemic injury. This offers possibility of future novel therapeutic agents for stroke patients.
Figure 1. Neurological scale
Figure 2. Rotarod latency
Figure 3. Infarction volume

Disclosures: B. Jang: None. **J. Kim:** None. **M. Kim:** None. **S. Lee:** None. **D. Kim:** None.

Poster

123. Functions of Glia and Non-Neuronal Cells in Stroke

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 123.22

Topic: C.08. Ischemia

Support: CIHR
CCNA

Title: Acute minocycline treatment inhibits microglia activation, reduces infarct volume, and provides variable improvement in post-stroke cognitive impairment in rats

Authors: *S. J. MYERS[1], V. AGAPOVA[1], S. V. PATEL[1], B. L. ALLMAN[1], L. A. SPOSATO[2], S. N. WHITEHEAD[1];
[1]Anat. and Cell Biol., [2]Clin. Neurolog. Sci., Univ. of Western Ontario, London, ON, Canada

Abstract: Approximately two-thirds of stroke patients experience cognitive impairment, but the underlying mechanisms that drive post-stroke cognitive decline are not well understood. Microglia play a critical role in mediating the post-stroke inflammatory response. The acute

microglia response may be neuroprotective, but an accumulation of chronically activated pro-inflammatory microglia can be harmful and is associated with cognitive decline. More specifically, microglia activation in the brain's white matter has been associated with executive dysfunction. Minocycline is a tetracycline derivative that readily crosses the blood-brain barrier and has been shown to effectively inhibit microglia activation. Using minocycline, this study aimed to assess the relationship between white matter microglia activation and cognitive decline in a rat model of ischemic stroke. Nine-month-old male wildtype Fischer 344 rats received an injection of endothelin-1 into the right dorsal striatum to induce a transient focal ischemic stroke. Minocycline or saline was administered twice per day for 4 days post-stroke. To assess striatal-based learning and cognitive flexibility (an important component of executive function) rats were tested using an operant conditioning-based set-shifting task. Further, to assess hippocampal-based spatial learning and memory, rats were tested on the Morris water maze. Brains were harvested at 28 days post-stroke for histological analysis of infarct volume and white matter pathology. Infarct volume was measured in NeuN stained tissue and revealed minocycline treatment significantly reduced infarct size. Further immunohistochemical analyses showed that minocycline treatment decreased the area coverage of activated microglia (OX6+) in the major white matter tracts and in the infarct region. Conversely, the area coverage of total microglia (Iba1+) remained consistent between treatment groups. Contrary to our prediction, minocycline treatment did not alter cognitive flexibility but improved striatal-dependent learning in a subset of animals in the set-shifting task. Moreover, minocycline treatment impaired hippocampal-dependent spatial learning in a subset of animals but did not affect hippocampal-based memory, highlighting the complex nature of the post-stroke microglial response. To date, no therapeutic approach has been successful at preventing post-stroke cognitive decline. This study expands our understanding of post-stroke microglia activation and its relationship with cognitive impairment.

Disclosures: S.J. Myers: None. **V. Agapova:** None. **S.V. Patel:** None. **B.L. Allman:** None. **L.A. Sposato:** None. **S.N. Whitehead:** None.

Poster

123. Functions of Glia and Non-Neuronal Cells in Stroke

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 123.23

Topic: C.09.Stroke

Support: NIH Grant NS44025
NIH Grant HL139685

Title: Effects of acute cerebral ischemia-reperfusion in neonatal mice on microglial and neuronal proteome in CD11brGFP-NFLrRFP RiboTag mice.

Authors: *E. DI MARTINO[1], J. FAUSTINO[1], S. GADAGKAR[2], H. BOUTEJ[3], J. KRIZ[3], Z. S. VEXLER[1];

[1]Neurol., Univ. of California San Francisco, San Francisco, CA; [2]CERVO Brain Res. Ctr., [3]Psychiatry and Neurosciences, Laval Univ., Quebec City, QC, Canada

Abstract: Background: Stroke during the perinatal period is as frequent as in the elderly. Brain maturation stage at the time of injury depicts the mechanisms of neurological damage, causing long-term functional and cognitive deficits. We previously reported that microglial cells serve as endogenous neuro- and neurovascular protectants (Fernandez-Lopez et al *J.Neurosci* 2016). **Aim:** To understand the role of neuronal-microglial interplay in the neonatal brain post ischemia-reperfusion. **Methods:** Unsexed 9-10 day old CD11brGFP RiboTag and NFLrRFP RiboTag pups underwent 3h middle cerebral artery occlusion (tMCAO) and were sacrificed 6h (NFLrRFP) or 24h (Cd11brGFP) after reperfusion. Pups were perfused with saline, and the injured region and corresponding region in the contralateral hemisphere as well as cortex from naive pups were collected. Tissue from n=6/sample was pulled together and ribosomes were isolated using anti-RFP (for NFL) or anti-FLAG (for CD11b) beads. Proteomics analysis was performed using LC-MS and peptide libraries were generated. Focus was on peptides with fold change >2 and Z<0.05. **Results:** Compared to naïve CD11brGFP RiboTag pups, we observed upregulation of peptides from several classes in injured regions, including peptides involved in cell growth and morphology (Plec, Myh10), locomotion and cell adhesion (Fn1, Fgb, Fgg), angiogenesis, cell activation and inflammation (Ccr1, C3, C8a, Lcn2, Vim, S100a9), and downregulation of peptides involved in ATP-dependent activity (Rpa1, Rpa2), cell reproduction and cell cycle (Dlg1), lipid binding and several metabolic pathways (Pdha1). Preliminary results on NFLrRFP samples show upregulation of peptides involved in response to stress (Sod1), membrane trafficking and transport (Gpm6a, Apoa1), and downregulation of peptides linked to DNA metabolism, cytoskeletal structure and pathways involved with laminin and myosin organization (Myo18a, Myl6, Lmna) in injured samples compared to controls. **Summary:** Our on-going studies suggest a rapid downregulation of neuronal physiological functions after neonatal stroke and rapid upregulation of microglial inflammatory signalling in response to injury.

Disclosures: E. Di Martino: None. **J. Faustino:** None. **S. Gadagkar:** None. **H. Boutej:** None. **J. Kriz:** None. **Z.S. Vexler:** None.

Poster

123. Functions of Glia and Non-Neuronal Cells in Stroke

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 123.24

Topic: C.09.Stroke

Support: NIH Grant NS111590

Title: Systemic transfer of astrocytic mitochondria improves functional recovery after intracerebral hemorrhage by enhancing neuronal antioxidant defense and neuroplasticity.

Authors: R. TASHIRO, **D. OZAKI**, J. BAUTISTA-GARRIDO, G. SUN, L. OBERTAS, J. ARONOWSKI, *J. JUNG;
The Univ. of Texas Hlth. Sci. Ctr. At H, The Univ. of Texas Hlth. Sci. Ctr. At H, Houston, TX

Abstract: We recently demonstrated that astrocytes release functional mitochondria (Mt) that can enter microglia, where promote their healing phenotype that assists in hematoma resolution and neurological recovery after intracerebral hemorrhage (ICH). However, relevant neuroprotective mechanism by astrocytic Mt transfer into neurons in brain after ICH is unclear. In this study, we found that ICH causes an elevated oxidative damage via a robust increase in superoxide generation and this coincides with loss of the mitochondrial enzyme manganese superoxide dismutase (Mn-SOD). Systemically transplanted astrocytic Mt that upon entering brain, restored Mn-SOD levels in the neurons and reduced neurological deficits in the mice subjected to ICH. Using an *in vitro* ICH-like injury model in cultured neurons, we found that astrocytic Mt upon entering neurons prevented superoxide-induced oxidative stress and cell death by restoring neuronal Mn-SOD levels, while at the same time promoted neurite extension by upregulating synaptogenesis-related gene expression. Moreover, we found that Mt genome-encoded small peptide humanin (HN) that is normally abundant in Mt, could simulate Mt transfer-mediated protective effect on neuronal Mn-SOD expression, oxidative stress, and neuroplasticity under ICH-like injury *in vitro*. Our study suggests that adoptive astrocytic Mt transfer promotes neuronal Mn-SOD-mediated anti-oxidative defense and neuroplasticity in the brain, which enhance functional recovery following ICH.

Disclosures: R. Tashiro: None. **D. Ozaki:** None. **J. Bautista-Garrido:** None. **G. Sun:** None. **L. Obertas:** None. **J. Aronowski:** None. **J. Jung:** None.

Poster

123. Functions of Glia and Non-Neuronal Cells in Stroke

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 123.25

Topic: C.09.Stroke

Support: NRF 2021R1A2C2006110
NRF 2021M3E5D9021364
NRF 2019R1A5A2026045

Title: Role of Arginase 1 expressed in infiltrating macrophages in the formation of fibrotic scar and the functional recovery in photothrombotic stroke mice

Authors: *H. KIM[1], H. PARK[1], Y. SEO[1], X. JIN[1], S. GENISCAN[1], Y. OH[1], B. KIM[1,2];
[1]Biomed. Sci., Ajou Univ. Sch. of Med., Suwon, Korea, Republic of; [2]Neurol., Ajou univ, Suwon, Korea, Republic of

Abstract: Ischemic stroke causes devastating neurological deficits with limited functional recovery. Excessive post-stroke inflammation may in part contribute to secondary damages to

peri-infarct neural tissue. Arginase-1(Arg1) is a marker of M2-type immune cells that play a role in the resolution of inflammation and tissue repair. However, distinctive roles of Arg1 in post-stroke inflammation have not been fully elucidated. The present study sought to determine the functional influence of Arg1 in a photothrombotic stroke model in mice. Arg1 expression increased in a time-dependent manner at the outer region of the infarction core. Most Arg1 positive cells were Iba1+ inflammatory cells. The majority of Arg1 positive cells were colocalized with YFP positive cells in LysM-cre::Rosa26-eYFP mice, indicating that Arg1 is expressed predominantly in infiltrating macrophages, not in resident microglial cells. We generated LysM-cre::$Arg1^{fl/fl}$ mice to deplete Arg1 specifically in infiltrating macrophages following stroke (Arg1 cKO mice). In this line, the number of Arg1 positive cells was sharply reduced by more than 90% in the infarcted tissue. Behavioral analysis revealed that Arg1 cKO mice showed improved recovery in skilled walking (ladder walking) at 4 weeks after stroke compared to control $Arg1^{fl/fl}$ mice. At this time point, the expression of fibrosis marker fibronectin was significantly decreased at the periphery of the lesion. Moreover, astrocytes were found in Arg1 cKO mice within the fibronectin positive infarct core, where astrocytes were completely excluded in $Arg1^{fl/fl}$ mice, indicating that Arg1 in infiltrating macrophages may play a role in developing fibrotic scars following stroke. Intriguingly, expression of the excitatory presynaptic marker vglut2 was evidently restored in the peri-infarct region compared to $Arg1^{fl/fl}$ mice, implying the potential influence of the fibrotic microenvironment on post-stroke synapse remodeling. We are now evaluating how Arg1 regulates the post-stroke inflammatory microenvironment using a cytokine PCR array.

Disclosures: H. Kim: None. **H. Park:** None. **Y. Seo:** None. **X. Jin:** None. **S. Geniscan:** None. **Y. Oh:** None. **B. Kim:** None.

Poster

123. Functions of Glia and Non-Neuronal Cells in Stroke

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 123.26

Topic: C.09.Stroke

Support: Joe and Marie Field Family Foundation

Title: Elucidating the role and underlying mechanism of astrocytic P2Y1R neuroprotection in an in vitro model of ischemic stroke

Authors: *G. SPAGNUOLO, L. M. IACOVITTI;
Vickie & Jack Farber Inst. for Neurosci., Thomas Jefferson Univ., Philadelphia, PA

Abstract: Earlier studies have found that in a model of traumatic brain injury (TBI), activated microglia transformed astrocytes into a neuroprotective phenotype by downregulating the purinergic receptor P2Y1R, resulting in the rescue of TBI-injured neurons. However, this mechanism has not been fully elucidated and little is known of its relevance to other forms of

injury. Thus, in this study, we sought to determine the underlying mechanism and its potential role in the *in vitro* model of ischemic injury from oxygen-glucose deprivation (OGD). We cultured neurons from mixed sex embryonic (E) day 14 Sprague-Dawley rats and astrocytes and microglia from mixed sex postnatal (PN) day 1-5 Sprague-Dawley rats. We first showed that indeed blocking P2Y1R receptors on astrocytes with the P2Y1R antagonist MRS 2179 significantly improved neuronal viability after OGD. To further explore the critical role of this receptor, we co-cultured neurons, astrocytes, and microglia and found a downregulation of astrocytic P2Y1R at both the RNA and protein level and enhanced neuronal survival after OGD. If, however, microglia were eliminated from the culture or cultures were treated with the tetracycline antibiotic minocycline to inhibit microglial reactivity, astrocytic P2Y1R remained unchanged. We next explored the upstream events leading to microglial reactivity. Since neurons dying from OGD release ATP, we added exogenous ATP to a culture of astrocytes and microglia and found a similar downregulation of astrocytic P2Y1R, implicating neuronally released ATP as the trigger for microglial reactivity. Once reactive, microglia are known to release a variety of cytokines and growth factors that act upon other cell types. We are currently exploring which microglial cytokines and growth factors downregulate astrocytic P2Y1R and events downstream of the receptor which promote neuronal survival after OGD, including possible effects on the NfKB/Akt pathway. Finally, we further showed that in aged astrocytes, P2RY1 is not downregulated after OGD, suggesting a loss of this neuroprotective mechanism during the aging process that may negatively impact neuronal survival. Our hope is that by decreasing or blocking astrocytic P2Y1R, there is potential for improvement in neuronal survival after cerebral ischemia, even in the aged brain.

Disclosures: G. Spagnuolo: None. **L.M. Iacovitti:** None.

Poster

123. Functions of Glia and Non-Neuronal Cells in Stroke

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 123.27

Topic: C.09.Stroke

Support: American Heart Association (957277),
Neuroscience Program, College of Medicine, Department of Chemistry and Biochemistry, John G. Kulhavi Professorship in Neuroscience, and E. Malcolm Field and Gary Leo Dunbar endowed Chair in Neuroscience at Central Michigan University
Partially by the Student Research & Creative Endeavors Grant received by Arjun P. from the Office of Research and Graduate Studies at Central Michigan University.

Title: Delivery of CRISPR/Cas9 to Knockout Notch, GSK-3β, and BMP Pathways in Adult Rat Astrocytes

Authors: *A. POUDEL[1,2,5], E. A. NISPER[2,5], B. SRINAGESHWAR[1,2,5], R. C. SCHALAU[1], I. Y. SMITH[1], S. A. SCHWIND[1], S. M. PATEL[2], N. DAY[1], K. N. JACOB[1], L. K. BOLEN[1], A. M. UPRETY[1,3], O. SMITH[1], M. J. KING[2], G. L. DUNBAR, Sr.[1,3,5], A. SHARMA[4], J. L. BAKKE[2], J. ROSSIGNOL[2,1,5];
[1]Program of Neurosci., [2]Col. of Med., [3]Dept. of Psychology, [4]Dept. of Chem. and Biochem., Central Michigan Univ., Mount Pleasant, MI; [5]Field Neurosciences Inst. Lab. for Restorative Neurol., Saginaw, MI

Abstract: In stroke, disruption in blood flow in the circle of Willis deprives brain tissues of oxygen eventually killing the neurons and causing neuroinflammation. The neuroinflammation activates astrocytes for defensive functions, also called reactive astrocytes. Previous studies have shown that inhibition of Notch, GSK-3 β, and BMP pathways in astrocytes can convert them into functional neurons. In this study, genes that regulate the above-mentioned pathways (such as *Hes5*, *NF-kB1*, and *Blc2* for Notch; *NLRP3 inflammasome* for GSK-3β and *Smad1,5, and 8/9* for BMP) were knocked out using the CRISPR/Cas9 gene-editing tool *in-vitro* using reverse lipofection with Lipofectamine CRISPRMAX Cas9 transfection reagent in adult rat brain-derived astrocytes. Six days following transfection, proteins were extracted from astrocytes, and western blot analysis was performed. The results showed a significant reduction in the expression of Nfkb1, Smad1, Smad5, and Smad9 protein suggesting the knockout of *Nfkb1* genes in the Notch pathway and *Smad1, Smad5,* and *Smad9* genes in BMP pathways. MTT toxicity assay was performed in transfected astrocytes after 6 days and the results showed the gene knockout was not detrimental to the astrocytes. In parallel, we also complexed the sgRNA with the G4 70/30 PAMAM dendrimers to improve the transfection efficiency and stability of the sgRNA, and to protect sgRNA from degradation. MTT assay was performed to determine the toxicity of dendrimers sgRNA complex to cells. Our results showed that G4 70/30 PAMAM dendrimers-sgRNA complex was successfully formed and stable over 24 hours when measured at 260nm UV absorbance. The goal of this preliminary study was to analyze the feasibility of using dendrimers to deliver CRISPR/Cas9 in hypoxia astrocytes (mimicking stroke brain) and via intraperitoneal injection in stroke rats for knocking-out genes involved in the different pathways described above to re-program astrocytes to neurons near the stroke infarct area. As a proof of concept, male and female rats were intraperitoneally (IP) injected one time with G4 90/10 PAMAM dendrimers tagged with Cy5.5 dye at 100μg/mL concentration. After 24 hours of injection, rats were euthanized. Brains slices imaging revealed the presence of G4 90/10 dendrimers in rat brain suggesting that dendrimer crosses BBB following IP injections. Once again, the dendrimers were found to be safe and this suggests using the CRISPR/Cas9 plasmid-dendrimer complex in future experiments to edit the genes and the pathways to potentially convert the astrocytes to neuroblasts in stroke would be a potential avenue of research.

Disclosures: A. Poudel: None. **E.A. Nisper:** None. **B. Srinageshwar:** None. **R.C. Schalau:** None. **I.Y. Smith:** None. **S.A. Schwind:** None. **S.M. Patel:** None. **N. Day:** None. **K.N. Jacob:** None. **L.K. Bolen:** None. **A.M. Uprety:** None. **O. Smith:** None. **M.J. King:** None. **G.L. Dunbar:** None. **A. Sharma:** None. **J.L. Bakke:** None. **J. Rossignol:** None.

Poster

123. Functions of Glia and Non-Neuronal Cells in Stroke

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 123.28

Topic: C.09.Stroke

Support: CCSG P30 CA060553
NIH R25 NS070695
NIH T32 GM142604
NIH R35 HL155652

Title: Neutrophils recruitment and migration in the cortex is regulated Platelet Endothelial Cell Adhesion Molecule (PECAM/CD31) in experimental ischemic stroke and can be modulated for positive outcomes on infarct size

Authors: N. A. NADKARNI[1], E. ARIAS[1], M. HAYNES[1], R. FANG[2], H. F. ZHANG[2], W. A. MULLER[1], A. BATRA[1], ***D. SULLIVAN**[1];
[1]Northwestern Univ., Chicago, IL; [2]Northwestern Univ., Evanston, IL

Abstract: Background: Ischemic stroke is a leading cause of morbidity and mortality in the world. The infiltration of neutrophils (PMNs) post-stroke has been implicated as the first mediator of inflammatory damage. However, blockade of PMN transendothelial migration (TEM) in preclinical studies has not translated to meaningful clinical outcomes, possibly due to an incomplete understanding of PMN recruitment patterns. PECAM is a known regulator of leukocyte recruitment and diapedesis and functions downstream from previous target therapies. To examine PMN recruitment both spatially and temporally, PECAM function was disrupted in a preclinical ischemic stroke model.
Methods: LysM-eGFP and CatchupIVM mice were used to track myeloid leukocytes and PMNs, respectively. To simulate cerebral ischemia-reperfusion injury, control mice and mice treated with PECAM blocking antibodies were subject to transient middle cerebral artery occlusion (tMCAO) model. Brain slices were collected at 24 h or 72 h time points post-reperfusion. Wide-field confocal microscopy and flow cytometry were used to spatial resolve PMN and leukocyte infiltration patterns in relation to the vasculature. To map PMN infiltration in an unbiased manner, a custom-made automated process was created to detect PMN position.
Results: Leukocyte infiltration throughout the infarct was not uniform over time. At 24 h post-stroke, a majority of infiltrating leukocytes were PMNs. Treatment with function blocking anti-PECAM antibodies disrupted the TEM process and resulted in more PMNs inside vessels. Notably, PECAM blockade also shifted the distribution of PMNs to the cortical surface compared to controls (72% compared to 89%,). At 72 h, roughly 50% of the myeloid cells recruited cells were PMN. In control mice, leukocytes were distributed throughout the cortex and subcortex. At 72 h, disrupting PECAM function again significantly restricted PMN infiltration to the cortex compared to control (51% compared to 69%). Infarct size was significantly reduced in PECAM blocked mice compared to control at both 24 h and 72 h. The total number of PMNs recruited was not modulated by PECAM blockade at 24 h or 72 h.
Conclusions: Leukocyte TEM and infiltration post-stroke progressed with marked spatiotemporal heterogeneity. Disrupting TEM with PECAM function blocking antibodies restricted PMN infiltration to the cortex at both early and later time points. This finding suggests that TEM occurs primarily at the cortical surface. The reduction of stroke size in PECAM treated

mice suggests the potential therapeutic benefit of regulating the timing and pattern of infiltrating PMNs after stroke.

Disclosures: **N.A. Nadkarni:** None. **E. Arias:** None. **M. Haynes:** None. **R. Fang:** None. **H.F. Zhang:** None. **W.A. Muller:** None. **A. Batra:** None. **D. Sullivan:** None.

Poster

124. Brain Injury: Molecular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 124.01

Topic: C.10. Brain Injury and Trauma

Title: Cortical Brain Injury Causes Retrograde Degeneration of Afferent Basal Forebrain Cholinergic Neurons via the p75NTR

Authors: *S. DASGUPTA[1], L. E. MONTROULL[2], W. J. FRIEDMAN[3];
[1]Rutgers, The State Univ. of New Jersey, Rutgers, The State Univ. of New Jersey, Newark, NJ; [2]Rutgers, The State Univ. of NJ, Newark, NJ; [3]Rutgers Univ., Rutgers, The State Univ. of NJ - Newark, Newark, NJ

Abstract: Basal forebrain cholinergic neurons (BFCNs) extend long projections to multiple targets in the brain to regulate cognitive functions and are compromised in numerous neurodegenerative disorders. To assess how injury to the target region of these neurons affects their viability *in vivo*, we are using the Fluid Percussion Injury (FPI) model to test the effects of injury at the cortex on the afferent BFCNs. Our studies show significantly fewer BFCNs ipsilateral to the injury compared to the contralateral side of the brain 7 and 14 days after the injury, an effect which is absent in p75 knockout mice. These results suggest a retrograde degenerative effect of the cortical injury on the projecting BFCNs through p75NTR. Basal forebrain survival, growth, synaptic maintenance, and apoptosis is governed primarily by neurotrophins (NT). Treatment of BFCN neurons with mature NTs promote survival via the Trk family of receptors, while pro-neurotrophins (pro-NT) trigger apoptosis via p75NTR. Interestingly BFCNs express all the neurotrophin receptors throughout life and may access NTs locally or from their targets such as cortex, hippocampus and amygdala. We have observed an induction of proBDNF and proNGF in the cortex and hippocampus after cortical FPI, both in WT and p75KO mice, suggesting that the induction of these factors my contribute to BFCN degeneration. To determine the effects of NT and proNT signaling directly on BFCN viability and function, we are using microfluidic and filter chamber cultures to segregate BFCN soma and axons *in vitro* allowing for compartmentalized treatment with pro/mature NTs. Our studies show that stimulation of BFCN axon terminals with proNGF which is a ligand for p75NTR, elicits retrograde degeneration of the axons and cell death of these neurons *in vitro*. Moreover, exposure of these neurons to mature or proNTs in the axonal or soma compartments may activate specific signaling mechanisms with different functional consequences. The knowledge of how pro or

mature NTs affect axonal integrity and BFCN survival will shape our understanding of the role of NTs in BFCN development and in conditions of neurodegeneration.

Disclosures: S. Dasgupta: None. **L.E. Montroull:** None. **W.J. Friedman:** None.

Poster

124. Brain Injury: Molecular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 124.02

Topic: C.10. Brain Injury and Trauma

Title: Isoform ratios of different neurotrophic proteins following mild traumatic brain injury-evidence to support more specific assessment and reporting

Authors: *V. KRISHNAN MUTHAIAH[1], K. KALIYAPPAN[1], J. I. MCPHERSON[1], J. LEDDY[2], K. E. PERSONIUS[1];
[1]Rehabil. Sci., [2]Orthopaedics, Univ. at Buffalo, Buffalo, NY

Abstract: Title: Isoform ratios of different neurotrophic proteins following mild traumatic brain injury -Evidence to support more specific assessment and reporting.
Authors: Vijaya Prakash Krishnan Muthaiah, Kathiravan Kaliyappan, Jacob I. McPherson, John J. Leddy, Kirkwood E. Personius
Brain-Derived Neurotrophic Factor (BDNF) is expressed in a precursor or pro-form (32kDa) which must be cleaved to achieve the mature form (14kDa). The receptor, tyrosine kinase B (TrkB) also exists in multiple isoforms including full length (FL-TrkB) (140kDa) and truncated (t-TrkB) (85-90kDa) subtypes. m-BDNF binds preferentially to the TrkB receptor while the p75 receptor has a higher affinity for pro-BDNF. Furthermore, the union of mature-BDNF (m-BDNF) and FL-TrkB triggers positive downstream mechanisms including cell growth, differentiation, and synaptic plasticity whereas activation of t-TrkB by m-BDNF acts as a dominant-negative to favorable downstream processes. Despite the difference in preferential binding and overall effects between BDNF and TrkB subtypes, expression of these proteins has been largely described as positive indicators within mild traumatic brain injury (mTBI) literature. Here, we sought to determine the ratios of expressed pro-BDNF to m-BDNF and t-TrkB to FL-TrkB within the cortex and hippocampus following mild traumatic brain injury (mTBI).
Adult male rats underwent mTBI or sham (control) procedure. On post-injury day (PID) 1, 3, 7, or 14 mTBI animals were sacrificed for protein analysis. Sham animals were sacrificed at PID 3. Protein analyses were performed using western blot (n=4 per group). After normalizing results to beta-actin, ratios were obtained by dividing the signal density of T-TrkB by FL-TrkB and pro-BDNF by m-BDNF for each set of samples. Ratios within each sample were then averaged. Within the cortex and hippocampus, the ratio of the negative or inactive isoforms of TrkB and BDNF to the full-length or mature forms was substantial across groups and time points. Ratios of t-TrkB to FL-TrkB ranged from 3.07 to 5.18 within the cortex and 3.43 to 5.82 within the hippocampus. Ratios of pro-BDNF to m-BDNF ranged from 1.62 to 2.41 within the cortex and

1.15 to 1.88 within the hippocampus.
Previous reports have presented TrkB and BDNF expression as favorable to recovery from m-TBI. However, our work indicates that the negative isoforms of TrkB and BDNF predominate following m-TBI. Ratios of TrkB and BDNF isoforms with conflicting functions reveal that future work should specifically assess each subtype since they induce opposing downstream effects.

Disclosures: V. Krishnan muthaiah: None. **K. Kaliyappan:** None. **J.I. McPherson:** None. **J. Leddy:** None. **K.E. Personius:** None.

Poster

124. Brain Injury: Molecular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 124.03

Topic: C.10. Brain Injury and Trauma

Support: Mark Diamond Research Fund, University at Buffalo

Title: Neurotrophic protein expression within the brainstem following mild traumatic brain injury

Authors: *J. I. MCPHERSON[1], V. P. K. MUTHAIAH[1], K. KALIYAPPAN[1], J. J. LEDDY[2], K. E. PERSONIUS[1];
[1]Rehabil. Sci., [2]Orthopaedics, Univ. At Buffalo, Buffalo, NY

Abstract: The brainstem houses many vital functions in vertebrate animals. Neurotrophic proteins and their receptors are active following mild traumatic brain injury (mTBI). Brain Derived Neurotrophic Factor (BDNF) has received much attention due to its role in neuroplasticity. Pro-BDNF binds preferentially to the p75 receptor while mature BDNF (m-BDNF) has a high affinity to the TrkB receptor. TrkB also exists in multiple isoforms including full length (FL-TrkB) and truncated (t-TrkB) subtypes. In adults, the p75 receptor emerges in response to injury and when activated may lead toward cellular dysfunction or death. FL-TrkB activation, however, favors cellular proliferation and synaptic plasticity while t-TrkB acts as a dominant negative receptor. The presence of these proteins has not been assessed within the brainstem following mTBI. Here, we sought to determine the extent to which neurotrophic protein and associated receptor expression is affected within the brainstem following mTBI. Adult male rats underwent mTBI or sham (control) procedure. Behavioral function was measured by the modified neurologic severity scale (mNSS). At post-injury day (PID) 1, 3, 7, or 14 mTBI animals (n=5 per time point) were sacrificed for protein analysis. Sham animals (n=5) were sacrificed at PID 3. Expression of p75, TrkB, and BDNF were quantified via western blot and protein localization was assessed within the medulla using immunohistochemistry. Within the brainstem, p75 expression increased at PID 1 vs. sham animals ($p=0.0129$, one-way ANOVA, n=4). T-TrkB and pro-BDNF expression were increased at PID 7 and 14 compared to

sham animals (p=0.002-0.038, one-way ANOVA, n=4). FL-TrkB and m-BDNF expression were increased at PID 7 (p=0.033-0.044, one-way ANOVA, n=4). The ratio of t-TrkB:FL-TrkB was substantial across groups and time points (2.62-3.98), suggesting a limited positive downstream impact. Pro-BDNF:m-BDNF ratios, while more modest, still favored the more negative isoform (1.24-1.57). Evidence of apoptotic cell death (via TUNEL labeling) was present within the medulla. Additional NeuN experiments revealed cell death occurring within a subset of neurons within the medulla. mNSS scores returned toward negligible score by PID 7-14.
Significant biochemical changes were observed within the brainstem following mTBI. While mNSS scores improved by PID 7-14, biochemical responses persisted. Despite the assertation that mTBI produces "mild" injury, evidence of cell death was observed in the medulla. Ratios of TrkB and BDNF isoforms with conflicting functions suggest that future work should specifically assess for each subtype since they induce opposing downstream effects.

Disclosures: J.I. McPherson: None. **V.P.K. Muthaiah:** None. **K. Kaliyappan:** None. **J.J. Leddy:** None. **K.E. Personius:** None.

Poster

124. Brain Injury: Molecular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 124.04

Topic: C.10. Brain Injury and Trauma

Support: Fight for Sight / Glaucoma UK Small Grant Award - 24GUK
Welsh Clinical Academic Training Award
Sêr Cymru Programme of the Welsh Government
Tweedy Bequest
Zebra Biologics, materials support
Fujifilm Wako Pure Chemical, materials support

Title: Brain-derived neurotrophic factor released from blood platelets prevents dendritic atrophy of lesioned adult central nervous system neurons

Authors: *A. WANT[1], X. NAN[1], P. S. DISTEFANO[2], R. M. LINDSAY[2], Y. A. BARDE[1], J. E. MORGAN[1];
[1]Cardiff Univ., Cardiff Univ., Cardiff, United Kingdom; [2]Zebra Biologics, Concord, MA

Abstract: In humans and other primates, blood platelets contain high concentrations of BDNF due to the expression of the *BDNF* gene in megakaryocytes. By contrast mice, typically used to investigate the impact of CNS lesions, have no demonstrable levels of BDNF in platelets. Here, we explore potential contributions of platelet BDNF with two well-established CNS lesion models using mice engineered to express *Bdnf* under the control of a megakaryocyte-specific promoter. In these animals, mean serum BDNF levels were 23.8, SD ± 10.4 ng/ml, close to those determined in primates. Using a highly sensitive, mature BDNF-specific ELISA, BDNF levels

were found to be detectable in wild-type (WT) animals at 6.7, SD ± 2.4 pg/ml. In WT mouse serum, BDNF presumably derives from non-neuronal cells including skeletal muscle. Retinal explants prepared from mice engineered to contain BDNF in platelets were labelled using DiOlistics and dendritic integrity of retinal ganglion cells (RGCs) assessed after 3 days by Sholl analysis. The results were compared with those obtained from retinae of WT animals as well as with WT explants supplemented with BDNF or the TrkB agonist, ZEB85. An optic nerve crush (ONC) model was also used, with the dendrites of RGCs similarly assessed 7 days post injury in mice containing BDNF in platelets and compared with WT animals. In retinal explants, mice expressing BDNF in platelets showed robust preservation of dendrite complexity, similar to that seen with BDNF- and ZEB85-supplemented media. The Sholl areas under curve (AUC) were 1776, SD ± 924.9, 1733 ± 833.0, 1763 ± 909.0 vs 1451 ± 809.3 in the WT control group (p=<0.001). Repeat experiments with 6 retinas per group failed to reveal differences in cell survival based on counts of RBPMS+ cells, with all 4 groups showing roughly 15% loss. In ONC, we also observed a robust neuroprotective effect on the dendrites of the RGCs in the platelet BDNF mouse, with Sholl AUC significantly higher compared to WT (2775 SD ± 1371 and 2033 SD ± 1179, p=0.008), with no significant difference in the contralateral eye controls. Repeat experiments with 5 mice per group found no difference in cell survival, with both showing approximately 50% loss. In summary, our results reveal that platelet BDNF has a strong neuroprotective effect on the dendrite complexity of RGCs in both an *ex vivo* and *in vivo* model, suggesting that platelet BDNF is likely to be a significant neuroprotective factor in primates.

Disclosures: A. Want: None. **X. Nan:** None. **P.S. DiStefano:** A. Employment/Salary (full or part-time):; Zebra Biologics. **R.M. Lindsay:** A. Employment/Salary (full or part-time):; Zebra Biologics. **Y.A. Barde:** None. **J.E. Morgan:** None.

Poster

124. Brain Injury: Molecular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 124.05

Topic: C.10. Brain Injury and Trauma

Support: CURE/DoD Funding #W81XWH-15-2-0069

Title: Unique hilus astrocyte morphology and gliosis following CCI brain injury: a predictive phenotype for post traumatic epilepsy?

Authors: *J. BROWNING[1], E. K. G. BASSOS[2], H. SONTHEIMER[3], S. ROBEL[4], P. J. VANDEVORD[5], M. THEUS[6], M. L. OLSEN[7];
[1]Sch. of Neurosci., [2]Biomed. Sci. and Pathobiology, Virginia Tech., Blacksburg, VA; [3]Sch. of Med. and Res. Inst., Virginia Tech. Sch. of Neurosci., Roanoke, VA; [4]Fralin Biomed. Res. Inst., Virginia Tech. Carilion Res. Inst., Roanoke, VA; [5]Biomed. Engin., Virgina Tech. Univ., Blacksburg, VA; [6]Translational Biology, Medicine, and Hlth. Grad. Program, Blacksburg, VA; [7]Virginia Tech. Neurosci. PhD Program, Blacksburg, VA

Abstract: Traumatic brain injury (TBI) is the most common cause of acquired epilepsy. To date nearly all research has focused on neurons and treatments almost exclusively address neuronal dysfunction. Yet, the field has identified other potential underlying causes that individually decrease seizure threshold, including astrogliosis**.** The present study aimed to investigate astrocyte morphological changes related to gliosis in the hilus of the hippocampus following controlled cortical impact (CCI) injury in CD31 outbred mice. Astrocyte morphology was evaluated four months following a moderate CCI injury (2.0 mm depth, 200 ms dwell, 5 ms/sec velocity, 3 mm flat impactor tip). Continuous twenty-four hour EEG recording with video monitoring was used to evaluate spontaneous seizure activity in these mice (2 months - 4 months). Immunohistochemistry using GFAP staining was performed on 50 μ;m hippocampal brain sections, followed by confocal imaging (20X, 40X) followed by Imaris analysis to determine the volume occupied by reactive astrocytes in the hilus and their morphology. It was found that CCI mice had a significant increase in the amount of GFAP coverage in the hilus, and the astrocytes within the hilus took on an elongated shape, not previously described. Astrocytes within the hilus were more prolated and less oblate in shape in the ipsilateral hemisphere relative to control mice, the extent to which may be related to spontaneous seizures. Ongoing studies are aimed at identifying if this cellular phenotype correlates with seizures post CCI injury.

Disclosures: J. Browning: None. **E.K.G. Bassos:** None. **H. Sontheimer:** None. **S. Robel:** None. **P.J. VandeVord:** None. **M. Theus:** None. **M.L. Olsen:** None.

Poster

124. Brain Injury: Molecular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 124.06

Topic: C.10. Brain Injury and Trauma

Support: MUSC SCORE U54DA016511
Alzheimer's Association AARF-16-443277
MUSC VA IK6
MUSC VA BX004471
MUSC VA BX000347
NIH RF1NS083559
NIH RO1NS104573

Title: Long-term Use of Fish Oil Exaggerates Secondary Disease Progression Following Repetitive Mild Brain Injury

Authors: J. TOMBERLIN[1], J. KURTZ[1], E. KARAKAYA[1], P. COURSON[1], S. BEYAZ[2], A. ERGUL[1], O. ALBAYRAM[1];
[1]Pathology and Lab. Med., Med. Univ. of South Carolina, Charleston, SC; [2]Cold Spring Harbor Lab., Cold Spring Harbor, NY

Abstract: Traumatic brain injury (TBI) is a leading cause of disability and mortality in the US, a prerequisite for chronic traumatic encephalopathy (CTE), and a major environmental risk factor for Alzheimer's disease and related dementias. While the initial damage is irreversible in TBI, secondary insults contribute to long-term sequelae in a reversible manner. Importantly, the environmental risk factors and that contribute to the secondary sequelae after TBI are poorly understood. While previous studies suggest that long-term consumption of saturated-high fat diet (HFD) aggravates the disease progression of TBI, long-term effects of unsaturated-HFD in secondary disease development after TBI remain largely unexplored. Here, we discovered that the novel *cyclic* unsaturated [45% Fat Kcal Diet Fish Oil] HFD intervention model in mice exacerbates age-dependent disease progression after brain injury, without inducing metabolic changes, such as body weight and blood glucose increases, associated with obesity. Unsaturated-HFD (Fish Oil) (n=18) and matched-purified (n=23) control diet was used in male 8-week-old C57BL/6J mice. After 2 weeks of *cyclic* dietary intake and baseline evaluation of behavior, animals subjected to repetitive mild TBI (rmTBI;7 mild injuries in 9 days) or sham injury followed by behavioral and pathological assay at 6-months after injuries. Notably, novel *cyclic* Fish Oil HFD intervention significantly induced neurodegeneration in the cortex accompanied with learning deficits and sensorimotor incompetency at 6-months after rmTBI, assessed by Morris water maze & accelerated rotarod respectively. Additionally, lipidomic analysis revealed altered fatty acid content in the neocortex of Fish Oil HFD animals compared to controls, specifically an increase in eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) content. Finally, an assessment of lipid peroxidation using the MDA assay revealed higher levels of peroxidation in Fish Oil HFD animal neocortex, possibly due to the increased presence of EPA & DHA in the brain. Our study is significant to address a major gap in knowledge regarding the role and molecular mechanisms by which long-term usage of Fish Oil content leads to the progression of secondary insults to the development of cognitive impairment following TBI and has the potential to facilitate the development of much needed preventive and disease modifying strategies. Future studies aim to investigate the differential effects of DHA- and EPA-rich diets and their therapeutic interventions on cerebrovascular disorders, such as vascular contributions to cognitive impairment and dementia (VCID).

Disclosures: J. Tomberlin: None. **J. Kurtz:** None. **E. Karakaya:** None. **P. Courson:** None. **S. Beyaz:** None. **A. Ergul:** None. **O. Albayram:** None.

Poster

124. Brain Injury: Molecular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 124.07

Topic: C.10. Brain Injury and Trauma

Support: Sigma Xi

Title: Treatment with young blood plasma following rmTBI in mice ameliorates neurodegenerative pathology

Authors: *R. E. BARKEY[1], R. E. TAPP[2], A. PERLBERG[3], S. NEFF[4], J. M. FLINN[4]; [1]George Mason Univ., Centreville, VA; [2]George Mason Univ., Fairfax, VA; [3]Psychology, George Mason Univ., Chantilly, VA; [4]Psychology, George Mason Univ., Fairfax, VA

Abstract: This study investigated the efficacy of young blood plasma injections for the immediate and delayed treatment of behavioral and neuropathological effects of repetitive mild traumatic brain injury (rmTBI) in mice. mTBIs are the most common form of TBI, among which rmTBI patients have greater difficulty recovering from injury as well as an increased likelihood of developing neurodegenerative diseases later in life. The behavioral and neurological deficits that occur following rmTBI are similar to those that occur during other neurodegenerative diseases. As previous studies have shown treatment with young blood plasma is effective at reducing neurodegenerative and inflammatory responses in aged mice and Alzheimer's type mice, treatment with young blood plasma may also be effective in reducing similar pathology in rmTBI mice. Beginning at 8 weeks of age, C57Bl/6J mice received either a total of 5 mTBIs or a sham procedure at 48 hour intervals. Young blood plasma was collected via terminal cardiac extractions from 8-week-old C57Bl/6J mice. One group of mice began treatment with young blood 24 hours after the final injury; a second group began plasma treatment 30 days after the final injury. Mice received either 150µL of plasma or 150µL of saline via tail vein injections once every 48 hours for a total of 16 injections over 4.5 weeks. Following the completion of the plasma treatment, mice underwent behavioral testing in Morris water maze (MWM), Open Field (OF), Elevated Zero Maze (EZM), and nesting. Brains were analyzed following behavioral testing using cresyl-violet/Luxol FastBlue (CV-LFB) staining, and western blot analysis for inflammation markers. Preliminary results in immediate treatment mice show TBI saline mice had fewer platform crosses than all other groups ($p = .026$) and plasma-treated mice had more platform crosses ($p = .037$) in probe trials. TBI mice built nests faster than sham mice ($p = .022$), with higher quality nests built at a 2-hour measurement, but overall built lower quality nests compared to sham mice after 16 hours ($p = .063$). In OF, TBI-plasma mice had the most entries into the center ($p = .05$). In EZM, TBI mice spent less time in open arms ($p = .004$). CV-LFB staining revealed plasma mice had higher cell density in the corpus callosum ($p = .002$) and entorhinal cortex ($p < .001$). A significant injury*treatment interaction was found in the infralimbic region ($p = .049$) and the dentate gyrus ($p = .05$) with TBI saline mice having reduced cell density and TBI-plasma mice returning to sham levels. Overall, this study demonstrates that treatment with young blood plasma after rmTBI ameliorates neuronal loss and may rescue behavioral deficits related to neurodegeneration.

Disclosures: R.E. Barkey: None. **R.E. Tapp:** None. **A. Perlberg:** None. **S. Neff:** None. **J.M. Flinn:** None.

Poster

124. Brain Injury: Molecular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 124.08

Topic: C.10. Brain Injury and Trauma

Support: NIH Grant T32 AG071474
NIH Grant T32 GM007250
VA Grant W81XWH2210129

Title: Traumatic brain injury accelerates pathology in a mouse model of Alzheimer's disease

Authors: *S. BARKER[1,4,5,6], M.-K. SHIN[2,4,5,6], E. VÁZQUEZ-ROSA[2,4,5,6], K. FRANKE[5], C. J. CINTRÓN-PÉREZ[2,4,5,6], P. SRIDHARAN[3,4,5,6], L. GAN[7], A. PIEPER[2,4,5,6];
[1]Pathology, [2]Psychiatry, [3]Neurosci., Case Western Reserve Univ., Cleveland, OH; [4]Harrington Discovery Inst., Cleveland, OH; [5]Geriatric Res. Educ. and Clin. Ctr., Louis Stokes Cleveland VA Med. Ctr., Cleveland, OH; [6]Inst. for Transformative Mol. Med., Case Western Reserve Univ. Sch. of Med., Cleveland, OH; [7]Helen and Robert Appel Alzheimer's Dis. Res. Institute,, Weill Cornell Med., New York City, NY

Abstract: A single traumatic brain injury (TBI) increases the risk of developing Alzheimer's disease (AD) by 50% and accelerates onset of cognitive decline by 3-4 years. Additionally, TBI is the leading environmental risk factor for AD and the third overall risk factor behind genetics and aging. Unfortunately, the underlying mechanism of this relationship is not understood, and there are no treatments that protect patients from accelerated AD after TBI. We recently reported that tau, a microtubule binding protein essential for neuronal health, is acetylated after TBI at lysines 274 and 281. Acetylated tau is also elevated in AD, and we found that acetylated tau was significantly more elevated in brains of AD patients with a history of TBI, compared to AD alone and healthy controls. Acetylation impairs microtubule binding, resulting in pathological tau mislocalization to the soma. Additionally, acetylation increases tau aggregation. Therefore, we hypothesize that tau acetylation mediates the increased risk for AD after TBI. To study this phenomenon, we determined an intensity of TBI that accelerates AD-like pathology and cognitive impairment in 5XFAD mice, a mouse model of AD. Our unique multimodal TBI produces a complex and rigorously reproducible brain injury resulting acute axonal degeneration and neurobehavioral impairment and persisting chronically with blood-brain barrier degradation and neurodegeneration. This clinically relevant model of TBI also produces the same systemic metabolic alterations that have been reported in TBI patients. Importantly, application of this TBI model to young 5xFAD mice causes learning deficits that are not seen in either sham-injured 5xFAD mice or in wild type littermates. We plan to use this model of TBI-accelerated AD to test whether pharmacologically reducing or genetically blocking tau acetylation can prevent the accelerated onset of AD after TBI.

Disclosures: S. Barker: None. **M. Shin:** None. **E. Vázquez-Rosa:** None. **K. Franke:** None. **C.J. Cintrón-Pérez:** None. **P. Sridharan:** None. **L. Gan:** None. **A. Pieper:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); holds patents related to P7C3 compounds.

Poster

124. Brain Injury: Molecular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 124.09

Topic: C.10. Brain Injury and Trauma

Support: NIH Grant RF1 NS114359
Departmental R&D

Title: Suppression of mortality by anesthetic preconditioning in a Drosophila melanogaster (fruit fly) model of traumatic brain injury (TBI) is a quantitative trait that can be subjected to a genome wide association study (GWAS).

Authors: D. JOHNSON-SCHLITZ[1], D. A. WASSARMAN[2], ***M. PEROUANSKY**[3]; [1]Anesthesiol., [2]Med. Genet., Univ. of Wisconsin, Madison, WI; [3]Univ. of Wisconsin Madison Dept. of Anesthesiol., Univ. of Wisconsin Madison Dept. of Anesthesiol., Madison, WI

Abstract: Long-term disability and death following TBI represent major healthcare challenges lacking effective pharmacological treatment despite intense research. Since cellular and molecular responses to damage are likely to be similar across tissues and evolutionarily conserved, we are investigating TBI using a fruit fly model that replicates key characteristics of TBI known from mammalian models[1] while providing experimental flexibility and an extensive genetic toolbox. We discovered that exposure of flies to the anesthetics isoflurane (ISO) and sevoflurane (SEVO) prior to TBI substantially reduces early mortality and extends lifespan in standard laboratory fly strains,[2] phenomenologically reproducing protection from ischemic damage referred to as anesthetic preconditioning (AP). Mechanistic understanding of AP would provide new therapeutic avenues for TBI. In this study, we test the hypothesis that the efficacy of AP is determined by genetic factors.We used inbred and fully sequenced fly lines from the Drosophila Genetic Reference Panel (DGRP) identified by RAL followed by a number.[4] We induced TBI in 1-8 days-old flies from 50 DGRP lines using a High-Impact Trauma (HIT)[1] device with or without pre-treatment with ISO using the Serial Anesthesia Array (SAA).[3] Mortality 24 h after TBI is expressed as the Mortality Index (MI_{24}) based on which we calculated the effect size of AP from the standardized mean difference = $(MI_{24}^{untreated} - MI_{24}^{preconditioned}) / S_{pooled}$ where the MI_{24} is the mean value, and S_{pooled} is the pooled standard deviation for the two groups ($\sqrt{[(SD_1^2 + SD_2^2)/2]}$). The effect size (Hedge's *g*) ranged from -0.28 (RAL324) to 1.62 (RAL509) i.e. the effect of pre-treatment varied continuously from a small increase to a large suppression of the MI_{24}. This distribution indicates that AP is a quantitative trait that is suitable for GWAS analysis. Our experimental system allows deep investigation of the genetic basis of the protective effect of anesthetics in the context of TBI, which is difficult to impossible to execute using mammalian models because of animal welfare concerns (which deprives investigators of an unanesthetized control group) and cost. Our studies will inform the TBI community of candidate targets for drug development.References: 1. R. Katzenberger et al. *PNAS* 2013; 2. J. Fischer et al. *Anesth. Analg.* 2018; 3. Z. Olufs et al. *Sci. Rep.* 2018; 4. T. Mackay et al. *Nature* 2012

Disclosures: D. Johnson-Schlitz: None. **D.A. Wassarman:** None. **M. Perouansky:** None.

Poster

124. Brain Injury: Molecular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 124.1

Topic: C.10. Brain Injury and Trauma

Support: NIH 1 R15 GM132937-01

Title: Behavioral Responses in Drosophila melanogaster Following Traumatic Brain Injury

Authors: P. BOSS, G. ORME, L. CHEN, S. PARK, Y. ZHANG, *A. CROCKER;
Middlebury Col., Middlebury, VT

Abstract: Over 1.5 million people in the US are affected by a traumatic brain injury (TBI) annually, with over 5.3 million currently living with a TBI-related disability. To study this increasing health concern, we used *Drosophila melanogaster* (fruit fly). Previous work demonstrated that fruit flies show many of the hallmarks of traumatic brain injury including increased glial markers and evidence of cellular injury. To expand on this work we used the Drosophila Genetics Reference Panel (DGRP) to identify natural variations in the behavioral effects of TBI. Using a circular arena groups of 16 flies either male or female were video tracked for 10 minutes following a TBI induced through the high impact trauma (HIT) method. We hypothesized that concussed flies will have a greater loss of phototaxis, slower mean velocity, and less mean distance traveled throughout the ten-minute video than control flies, across all DGRP lines. We also hypothesized that there will be variation across these lines in all measures. We also hypothesized that adding a second stressor (heat) following TBI will produce variability across lines in coping mechanisms with the new stressor. We split our analysis into motor stress responses and social stress responses. Motor stress response consisted of thigmotaxis measures, mean velocity, total distance traveled, and zone transitions. Social stress responses consisted of the mean distance between subjects, the number of body contacts, and the total time in contact with another subject. We found variation in each of these measures along with all lines increasing velocity and distance traveled in response to a second stressor but by different magnitudes. We also found that some of these measures were sexually dimorphic. Future work will focus on using this variation to perform a genome-wide association study in order to determine genes that may be playing a role in stress responses and motor deficits following TBI.

Disclosures: P. Boss: None. **G. Orme:** None. **L. Chen:** None. **S. Park:** None. **Y. Zhang:** None. **A. Crocker:** None.

Poster

124. Brain Injury: Molecular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 124.11

Topic: C.10. Brain Injury and Trauma

Support: NIH Grant GM083889
NIH Grant R01MH104632
NIH Grant R01MH107305
Emory Score Pilot Grant

Title: Age- and sex-dependent emergence of long-term brain deficits in a Drosophila head trauma model

Authors: *C. YE[1], J. BEHNKE[1], K. MOBERG[2], J. Q. ZHENG[2];
[1]Cell biology, [2]Cell Biol., Emory Univ., Atlanta, GA

Abstract: Emerging evidence suggests that women, especially older women, have a greater risk of suffering neurological defects and behavioral dysfunction after head-directed injuries compared to men. However, very little is known concerning the cellular and molecular mechanisms underlying the age and sex differences in head injury response. In this study we take advantage of the tractable model organism, *Drosophila melanogaster*, to investigate age- and sex-dependent emergence of long-term brain deficits after head trauma. Our group developed the **H**ead **I**mpact **FL**y **I**njury model (HIFLI) model, which enables delivery of mild repetitive headfirst impacts to multiple (10-15 at a time) awake and unrestrained adult flies. We showed that young flies (3-5 days old) subjected to our mild and nonlethal injuries immediately exhibited concussive-like behaviors such as temporary uncoordinated and seizure-like movements but recovered within minutes. However, these injured flies progressively developed impaired startle-induced climbing and brain degeneration throughout their lifetime. We observed substantially worse injury recovery, sensorimotor decline, and brain pathology in flies injured at older ages (2 and 4 weeks of age), indicating that aging increases vulnerability to mild head injury. Importantly, these deficits were more profound in females than in males, and were most prominent in females in the oldest injury cohort (injury at 4 weeks of age). Next, we investigated changes in cellular activity in response to injury. Head impacts elicit an acute elevation in neuronal activity only in female flies, and temperature-dependent suppression of neuronal activity abrogates the effects of injury. Finally, we determined that the size difference between male and female flies neither affects injury severity nor contribute to the observed sex-different injury response. Together, our findings validate *Drosophila* as a suitable model system for investigating the long-term effects of head trauma, suggest an increased vulnerability in females and older adults for head trauma-induced brain dysfunction and degeneration, and indicate that early altered neuronal excitability may be a key mechanism linking mild brain trauma to chronic degeneration.

Disclosures: C. Ye: None. **J. Behnke:** None. **K. Moberg:** None. **J.Q. Zheng:** None.

Poster

124. Brain Injury: Molecular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 124.12

Topic: C.10. Brain Injury and Trauma

Title: Elucidating the role of hormesis and ellagic acid on motor abilities and lifespan after traumatic brain injury

Authors: *M. M. MENDOZA, T. A. TOGASHI, E. GIANG, R. E. HARTMAN;
Loma Linda Univ., Loma Linda, CA

Abstract: Ellagic acid is a type of polyphenol, or secondary metabolite that protects plants against environmental insults (e.g., ultraviolet light, extreme temperatures, and predators). Previous studies have demonstrated that dietary consumption of polyphenols generally elicit health benefits. They are mildly toxic chemicals that do not kill our cells, but rather bolster cellular resilience through activating endogenous antioxidant and anti-inflammatory pathways. This process, known as hormesis, may explain some of their beneficial effects, and also imply that a high enough dose will ultimately become detrimental. Although our lab has demonstrated neuroprotective effects of ellagic acid and related compounds in humans, rodents, and flies, we have yet to systematically determined minimal, optimal, and maximum dosages. The current study utilizes a high-throughput *Drosophila* model of traumatic brain injury (TBI) and shows that low doses of ellagic acid are associated with extending lifespan and increasing climbing abilities. However, high doses have negative consequences that are sex and injury dependent. High doses in females, for example, reduced lifespan but did not further exacerbate the reduction in lifespan associated with a blunt-force traumatic injury. High doses in males, however, had little effect on control fly lifespan, but significantly exacerbated the negative effects of injury on lifespan. These data further highlight the importance of determining optimal dose in all future experimental explorations of polyphenol efficacy. Future studies will determine the biochemical pathways activated and/or inhibited at various doses.

Disclosures: M.M. Mendoza: None. **T.A. Togashi:** None. **E. Giang:** None. **R.E. Hartman:** None.

Poster

124. Brain Injury: Molecular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 124.13

Topic: C.10. Brain Injury and Trauma

Support: NIH Grant R01NS115815
NIH Grant K23NS101036
Barrow Neurological Foundation
Chuck Noll Foundation

Title: Age and sex-based differences in physiologic, molecular and functional performance after murine traumatic brain injury

Authors: *S. P. RAIKWAR[1], A. RANI[1], S. AHMAD[1,2], S. W. CARLSON[4], P. M. KOCHANEK[5,6], V. A. VAGNI[5], K. L. FELDMAN[5], J. S. CATAPANO[2], S. MIHALJEVIC[1], J. RULNEY[1,7], K. KARAHALIOS[1,8], M. F. WATERS[1,3], A. F. DUCRUET[1,2], R. M. JHA[1,2,3]; [1]Translational Neurosci., [2]Neurosurg., [3]Neurol., Barrow Neurolog. Institute, SJHMC, Dignity Hlth., Phoenix, AZ; [4]Neurosurg., Univ. of Pittsburgh, Sch. of Med., Pittsburgh, PA; [5]Critical Care Medicine, Safar Ctr. for Resuscitation Res., UPMC Children's Hosp. of Pittsburgh, Univ. of Pittsburgh Sch. of Med., Pittsburgh, PA; [6]Clin. and Translational Sci. Inst., Univ. of Pittsburgh Sch. of Med., Pittsburgh, PA; [7]Univ. of Arizona Col. of Med., Tucson, AZ; [8]Uniformed Services Univ. of the Hlth. Sci., Bethesda, MD

Abstract: In clinical traumatic brain injury (TBI), advanced age and female sex prognosticate morbidity, mortality, and a slower recovery trajectory. Few preclinical studies have specifically evaluated the impact of aging and sex differences on cerebral blood flow (CBF) and neurodegeneration in translational models of TBI. We subjected age matched old (15-19 months), and adult (12 weeks) male and female mice (n=6/group) to the clinically relevant controlled cortical impact (CCI) model of TBI (left parietal cortex, velocity=5.0m/s, dwell time=50ms, depth=1.2mm). Pre- and post-TBI laser speckle contrast imaging (LSCI) measured acute and chronic surface hemodynamic changes in CBF. Cognitive and motor function tests evaluated sex specific differences at multiple timepoints. Neuroinflammation and neurodegeneration markers were evaluated by immunofluorescence on 3 and 21d post-TBI. No significant differences were observed in pre-TBI LSCI CBF either ipsilaterally or contralaterally between old males and females [range: 304-371 (AU)]. There was an immediate reduction in CBF 15-min post TBI that was greater on the ipsilateral vs contralateral hemisphere in both sexes (Ipsilateral: 77.68% female vs 68.18% male; contralateral: 31.80% female, vs 29.09% male; all $p<0.05$ pre-vs post-TBI, ipsilateral). This persisted at 24h but by 72h CBF was only impaired ipsilaterally (49.53% male and 37.3% female: all $p<0.05$ pre- vs post-TBI). LSCI assessments of CBF in adult mice is ongoing. Despite no differences in acute CBF, functional outcome varied between sexes post-TBI. Although both sexes had long-term spatial memory deficits in Morris water maze at 21d post-TBI (naïve vs male TBI $p=0.017$; naïve vs female TBI $p=0.009$), effect sizes were markedly more pronounced in females. In females both adult and aged mice had impaired motor function (d14, Rotarod, adult $p<0.05$ naïve vs post-TBI; aged $p<0.0001$ naïve vs post TBI). In contrast, only aged males had impaired motor coordination (7d, beam balance, $p<0.001$ pre- vs post-TBI) and working memory (10d, novel object recognition index, $p=0.0071$ naïve vs post-TBI). Neuropathological assessment is ongoing; preliminary analyses suggest both sex and age-based differences in microglial and astrocytic responses, neuronal loss, and expression of SUR1-TRPM4, and AQP4 at 72h and Tau and β-amyloid at 21d post TBI. We conclude that TBI-induced physiologic, molecular, and functional differences in an age- and sex-specific manner. This lays a foundation to develop novel precision biomarkers and targeted therapies that appropriately endotype TBI patients for age and sex.

Disclosures: S.P. Raikwar: None. **A. Rani:** None. **S. Ahmad:** None. **S.W. Carlson:** None. **P.M. Kochanek:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Chuck Noll

Foundation for Brain Injury Research. **V.A. Vagni:** None. **K.L. Feldman:** None. **J.S. Catapano:** None. **S. Mihaljevic:** None. **J. Rulney:** None. **K. Karahalios:** None. **M.F. Waters:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Barrow Neurological Foundation. **A.F. Ducruet:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Barrow Neurological Foundation. **R.M. Jha:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; R01NS115815, K23NS101036, Barrow Neurological Foundation, Chuck Noll Foundation for Brain Injury Research. F. Consulting Fees (e.g., advisory boards); Biogen.

Poster

124. Brain Injury: Molecular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 124.14

Topic: C.10. Brain Injury and Trauma

Support: NS104282-01A1

Title: Clip antagonism improves meningeal macrophages and neurobehavioral outcomes after traumatic brain injury in a sex-dependent manner.

Authors: *L. VENKATASAMY[1], S. BEEVERS[1], V. ARISMENDI[1], R. P. TOBIN[2], M. K. NEWELL-ROGERS[3], L. A. SHAPIRO[1];
[1]Texas A&M Univ. Syst. Hlth. Scien Neurosci. and Exptl. Therapeut., Bryan, TX; [2]Div. of Surgical Oncology, Dept. of Surgery, Anschutz Med. Campus, Univ. of Colorado Sch. of Medicine,, Aurora, CO; [3]Texas A & M University, Med. Physiol., Temple, TX

Abstract: Background:Traumatic brain injury (TBI) can lead to an increased risk of long-term disease including, depression, cognitive impairment, and Alzheimer's disease (AD), that may be linked to the immune response. Therapeutic options are limited, and outcomes may be improved by better understanding of the effects of biological sex on the immune response after TBI. Full-length CD74 contributes to innate immune signaling, and MHC II-associated invariant peptide (CLIP), a cleavage product of CD74, is involved in the transition from an innate to an adaptive immune response. Depletion of CD74, or CLIP antagonism, were previously shown to prevent the secondary neurodegeneration in male mice given a fluid percussion injury (FPI) model of TBI. The meninges serve as an interface between the brain and the immune system and can be compromised by TBI. Here, we examined the influence of CLIP-antagonism on the meningeal immune response to FPI at 1- and 15-days post-injury and examined the influence of CLIP-antagonism on neurobehavioral outcomes after FPI, including assessment of sex as a biological

variable. Hypothesis:CLIP antagonism after FPI will reduce the early meningeal immune response and differentially improve the long-term neurobehavioral impairment in male and female mice. Methods:FPI was induced in C57BL/6 mice, as previously described. Mice were injected (1 mg/kg, i.p.) with our CLIP antagonist peptide (CAP) at 30 mins after FPI or sham FPI. Vehicle animals (Veh) received only DMSO. We utilized male mice for flow cytometry 1 and 15 days after FPI. Object location test (OLT), Novel object recognition test (NORT) and pattern separation test (PST), beginning 32 days after FPI were performed in male and female mice. Results:CAP significantly reduced the number of meningeal CD11b+ cells at 15 days post-FPI. In female and male mice, FPI induced significant deficits in OLT, NORT and PST, that were mostly improved by CAP treatment. In the OLT, male sham and male FPI + Veh performed significantly worse than females. In the PST, the male FPI mice exhibited significant impairment in latency to first visit the novel object compared to female FPI mice, and this difference was ameliorated in CAP treated FPI mice. Conversely, in NORT, male sham mice explored the novel object significantly more than the female sham mice, and the FPI + CAP male mice moved at a significantly faster velocity than the FPI + CAP female mice. Thus, in response to FPI, male and female mice have varied cognitive impairment and respond differentially to CAP. Together, the results suggest that CLIP antagonism after FPI can reduce meningeal macrophages concomitant with improved neurobehavioral performance.

Disclosures: L. Venkatasamy: None. **S. Beevers:** None. **V. Arismendi:** None. **R.P. Tobin:** None. **M.K. Newell-Rogers:** None. **L.A. Shapiro:** None.

Poster

124. Brain Injury: Molecular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 124.15

Topic: C.10. Brain Injury and Trauma

Support: NIH/NIGMS 2U54GM104942-03

Title: The impact of exercise on traumatic brain injury recovery is both intensity- and sex-dependent.

Authors: *J. T. IVEY, B. WHITE, R. VELAZQUEZ-CRUZ, R. OLIVERIO, Z. M. WEIL, K. KARELINA;
Neurosci., West Virginia Univ., Morgantown, WV

Abstract: With 2.8 million incidents reported every year, traumatic brain injury (TBI) is among the most common causes of death and disability in the United States. Quiet rest has long been recommend for individuals after TBI. However, this approach has been criticized as both lacking supporting evidence for its efficacy and potentially depriving those undergoing it from beneficial social and physical activity. Practice guidelines are increasingly moving away from rest and towards a more active recovery regimen. We previously reported that exercise after experimental

brain injury in mice reduces inflammation, stimulates neurogenesis and aids in cognitive recovery. Here, we aimed to expand on our earlier findings by assessing sex differences in TBI outcomes after varying intensities of treadmill exercise. Beginning 3 days after controlled cortical impact (CCI) or sham injury, male and female Swiss Webster mice underwent forced treadmill exercise for 10 days in one of four conditions: sedentary, low, moderate, or high intensity. We then performed Barnes maze cognitive function assessment and found interesting sex differences such that low and moderate, but not high-intensity exercise improved spatial cognition, whereas the female mice show better outcomes after high intensity exercise. Following functional assessment we processed brain tissue for lesion volume, axon degeneration, and microglial activation. There was no significant effect of exercise intensity on lesion volume in females, however, among males lesion volume was progressively reduced after low and moderate intensity exercise compared to sedentary mice, but remained large in the high intensity group. Silver staining showed that exercise had no effect on the axonal damage in either sex. Preliminary data also indicate that low intensity exercise reduces the number of activated microglia in the ipsilateral hippocampus in both sexes. In a separate cohort, we are currently examining the glutathione levels of the peri-lesional tissue to determine the impact of exercise on oxidative stress. Taken together, these data build on our previous report that the neuroprotective effects of exercise are intensity-dependent. Importantly, we now have preliminary evidence that this effect is also sex-dependent and are working towards uncovering the mechanisms by which exercise can improve outcomes in male and female TBI survivors.

Disclosures: J.T. Ivey: None. **B. White:** None. **R. Velazquez-Cruz:** None. **R. Oliverio:** None. **Z.M. Weil:** None. **K. Karelina:** None.

Poster

124. Brain Injury: Molecular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 124.16

Topic: C.10. Brain Injury and Trauma

Support: Sylvan Adams Sports Institute, Tel Aviv University, Tel Aviv, Israel
The Dr. Miriam and Sheldon G. Adelson Chair and Center for the Biology of Addictive Diseases
Ari and Regine Aprijaskis Fund

Title: The Influence of Aerobic Exercise on Learning and Memory Following TBI in Mice

Authors: L. TSEITLIN[1], L. BIKOVSKI[1,2], B. RICHMOND- HACHAM[1], S. SCHREIBER[3], ***C. G. PICK**[1];
[1]Tel Aviv Univ., Tel Aviv Univ., Tel Aviv, Israel; [2]Sch. of Behavioral Sci., Netanya Academic Col., Netanya, Israel; [3]Psychiatry, Tel Aviv Sourasky Med. Ctr., Tel Aviv, Israel

Abstract: The profound benefits of physical activity are well known, and there is a growing body of information about the positive effect it has on memory and cognition. Studies have shown that exercise, particularly aerobics, promote neuronal repair and synaptic regeneration, prevent neuroinflammation, facilitate recovery from brain injury, and decrease the risk of neurodegenerative diseases. Traumatic brain injury (TBI) is the most common neurological condition in individuals under 50 years of age and is considered a risk factor for neurodegenerative disorders such as Alzheimer's and Parkinson's. TBI patients suffer from behavioral, neurological, and mental impairments, both short and long-term.Our working hypothesis is that post-TBI aerobic exercise would significantly affect the brain, improve mice's performance in behavioral tests, and increase neuronal survival and regeneration. The present study aims to measure the impact of brain injury and running on learning and memory in mice, moreover to find the most effective therapeutic window for starting a running protocol post-TBI.ICR mice will be divided into four groups of at least ten mice (Control, TBI, Control + Aerobic Exercise, TBI + Aerobic Exercise). Starting at three different time points post-TBI, mice will exercise on a treadmill for two weeks. We will use three behavioral tests, novel object recognition for visual memory, Y-maze for spatial memory, and elevated plus-maze for anxiety-like behavior. In addition, for neuronal survival and regeneration we will harvest the brains of these mice and perform immunohistochemical staining for NeuN and Doublecortin as well as western blot to quantify the levels of BDNF.Our lab's preliminary findings suggest that a running protocol starting 48h/7d/13d after TBI significantly decreases the visual and spatial memory deficits induced by the brain injury.

Disclosures: L. Tseitlin: None. **L. Bikovski:** None. **B. Richmond- Hacham:** None. **S. Schreiber:** None. **C.G. Pick:** None.

Poster

124. Brain Injury: Molecular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 124.17

Topic: C.10. Brain Injury and Trauma

Support: UMMC Department of Anesthesiology Internal Funding

Title: Influences of diet on stress responses in a rodent model of juvenile traumatic brain injury

Authors: *A. M. SMITH[1], Z. J. WARFIELD[1], A. A. HULITT[2], S. JOHNSON[2], B. E. GRAYSON[3], C. DOS SANTOS E SANTOS[4];
[1]Dept. of Neurol., Univ. Of Mississippi Med. Ctr., Flowood, MS; [2]Tougaloo Col., Jackson, MS; [3]Dept. of Neurol., [4]Dept. of Anesthesiol., Univ. of Mississippi Med. Ctr., Jackson, MS

Abstract: Traumatic brain injury (TBI) is one of the leading causes of death for children in the United States, and juveniles are more likely to sustain TBIs than most other age groups. Furthermore, many children consume diets that are high in saturated fats and refined sugars.

Therefore, the goal of the current study was to identify a potential relationship between high-fat diet consumption and TBI on hypothalamic-pituitary-adrenal (HPA) axis function in dealing with stress in juvenile rats. In the present study, male juvenile Long-Evans rats were fed either a combination of a high-fat diet with a high-fructose corn syrup solution or a standard chow diet. On post-natal day 30, subjects sustained either a sham TBI or a TBI via the Closed-Head Injury Model of Engineered Rotational Acceleration (CHIMERA). Subjects participated in a trial of the elevated plus maze either 1 day post-injury or 4 days post-injury. One group of subjects also participated in a trial of the open field test 4 days post-injury, while a separate group underwent an acute restraint stress test 7 days post-injury. All subjects were euthanized 7 days post-injury, and brain and blood plasma samples were collected for use in QRT-PCR, immunohistochemistry, and corticosterone or adrenocorticotropic hormone (ACTH) assays. Neither consumption of a high-fat diet nor TBI resulted in significant changes to behaviors in the elevated plus maze. In contrast, TBI subjects spent significantly longer periods of time resting and significantly less time ambulatory in the open field test compared to sham subjects. Further, subjects who sustained a TBI and also consumed a high-fat diet spent the lowest percentage of time in the center of the open field. In addition, TBI subjects who participated in the acute restraint stress test had significantly lower plasma corticosterone levels compared to sham subjects, but plasma ACTH levels were not significantly altered by diet or TBI. In addition, QRT-PCR showed significantly lower expression of NR3C1, NR3C2, and CRHR2 in the hypothalamus of TBI subjects compared to sham subjects. These results offer evidence that TBI and high-fat diet consumption can cause HPA axis dysfunction, which can result in the presence of more anxiety-like behaviors.

Disclosures: **A.M. Smith:** None. **Z.J. Warfield:** None. **A.A. Hulitt:** None. **S. Johnson:** None. **B.E. Grayson:** None. **C. Dos Santos E Santos:** None.

Poster

124. Brain Injury: Molecular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 124.18

Topic: C.10. Brain Injury and Trauma

Support: Internal Start Up

Title: Pediatric Mild Traumatic Brain Injury Impact on Signal Circuit Maturation and Seizure Threshold During Postnatal Brain Development

Authors: *R. R. CORRIGAN[1], T. BEDROSIAN[1,2];
[1]Abigail Wexner Res. Inst., The Steve and Cindy Rasmussen Inst. for Genomic Med., Columbus, OH; [2]Dept. of Pediatrics, The Ohio State Univ., Columbus, OH

Abstract: Traumatic brain injury (TBI) even mild (mTBI) in severity is known to increase development of post-traumatic epilepsy up to 8-fold (doi: 10.3171/2017.2.PEDS16585);

however, there is currently a general lack of early-life TBI paradigms using rodent models to study post-traumatic epileptogenesis (doi: 10.1089/neu.2018.6127). Collectively, this has led to a major gap in the field's knowledge surrounding how pediatric TBI lends to long-term consequences, such as epileptogenesis. It is my hypothesis that early life mTBI disrupts the timing of critical developmental processes such as circuit formation and transduction that will ultimately prime the cortical microenvironment towards seizure activity when challenged later in life. Male and female postnatal day (pnd) 7 wildtype mice underwent a mild weight drop TBI or sham injury paradigm, adopted from a previous lab. We implemented microarray electrode array (MEA) field recording of acute brain slices placed on a 64-multielectrode probe to detect electrical transduction changes at 1 day post injury (dpi), 1-week or 3-week post injury (pnd 8, 14, or 28, respectively). Spike generation over a period of 10 minutes in injured cortex compared to non-injured cortex, to determine overall cortical field potentials. Each section was then post-fixed, cryosectioned, and IHC of immature (NKCC1) and mature (KCC2) GABA cotransporter markers throughout brain development were analyzed. Additionally, we challenged injured or non-injured sham mice with repeated low dose pentylenetetrazol via intraperitoneal injection at pnd 60 and classified seizure threshold (dose and latency) and phenotypically scored seizure severity using the modified Racine scale. As analysis is currently in progress, we expect to see heightened random spike generation in mTBI versus sham injured mice throughout neural maturation. We also expect to see a delay of the GABA shift from expression of excitatory NKCC1 to inhibitory KCC2 chloride cotransporters after mTBI compared to un-injured shams, as has been reported in various other neurodevelopmental disorders. Importantly, we also expect to find that brain circuitry will remain impacted long-term through decreased threshold of seizure activity when chemically challenged. The results from this study will have significant impact on the field for we will for the first time evaluate how mTBI during early postnatal life alters circuit formation and excitatory/inhibitory balance through different stages of neural development. Furthermore, these results could explain for the first-time mechanisms responsible for the natural progression of post- traumatic epilepsies.

Disclosures: R.R. Corrigan: None. **T. Bedrosian:** None.

Poster

124. Brain Injury: Molecular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 124.19

Topic: C.10. Brain Injury and Trauma

Support: NIAAA Grant R21AA026356
NIH/NIGMS P20 GM109098

Title: The effects of 7,8-dihydroxyflavone on alcohol preference and anxiety-like behavior following a juvenile traumatic brain injury

Authors: *R. OLIVERIO, B. WHITE, R. VELAZQUEZ-CRUZ, J. T. IVEY, A. CLARKE, K. KARELINA, Z. M. WEIL;
Rockefeller Neurosci. Inst., West Virginia Univ., Morgantown, WV

Abstract: Traumatic brain injury (TBI) and alcohol misuse are bidirectionally related as alcohol misuse increases the risk of TBI *and* TBI increases the risk of alcohol misuse. Importantly, there is much to uncover about the latter component of this relationship. Previously, we reported that an early life mild TBI in females produced greater ethanol consumption compared to uninjured females. Interestingly, this effect was attenuated by prolonged housing in enriched environments (EE). The mechanism through which EE modulates alcohol preference following TBI remains unknown. As dysregulation of brain-derived neurotrophic factor (BDNF) is associated with both TBI and alcohol use disorder (AUD), and EE can promote BDNF release, we investigated the effect of environmental enrichment on the expression of *BDNF* mRNA and other plasticity-related genes after TBI. Five weeks of EE, begun immediately after injury, increased the gene expression of tropomyosin receptor kinase B (TrkB), doublecortin (DCX), and vascular endothelial growth factor (VEGF). To determine whether TrkB activation could recapitulate the effects of EE we administered the agonist 7,8-dihydroxyflavone (7,8-DHF) and assessed hippocampal neurogenesis. We additionally examined anxiety-like behaviors through the elevated plus maze and open-field test, as there is compelling comorbidity of anxiety-related disorders, such as posttraumatic stress disorder (PTSD) and TBI, as well as an association with BDNF dysregulation. Future studies will determine whether 7,8-DHF can prevent the TBI-induced increase in alcohol consumption. Uncovering the mechanism through which EE modulates the vulnerability to alcohol abuse following a TBI could lead to improved treatment methods which might better patient outcomes

Disclosures: R. Oliverio: None. **B. White:** None. **R. Velazquez-Cruz:** None. **J.T. Ivey:** None. **A. Clarke:** None. **K. Karelina:** None. **Z.M. Weil:** None.

Poster

124. Brain Injury: Molecular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 124.20

Topic: C.10. Brain Injury and Trauma

Support: Combat Casualty Care Research Program (CCCRP)

Title: Analyzing pulse oximetry in a concurrent traumatic brain injury and soman exposure mouse model.

Authors: *J. SAHARGUN, J. LEIGHTON, A. METHVIN, E. MILLER, E. JOHNSON;
United States Army Med. Res. Inst. of Chem. De, Gunpowder, MD

Abstract: Polytrauma treatment strategies for CNS management are currently poorly defined for austere military settings or mass casualty scenarios. Exposure to an acetylcholinesterase inhibitor

such as soman (GD) leads to decreased heart and breath rates and increased mortality. Similarly, traumatic brain injury (TBI) causes damage that can initiate a syndrome known as paroxysmal sympathetic hyperactivity (PSH), which is characterized by increased body temperature, systolic blood pressure, and respiration. However, there is insufficient research to determine best treatment strategies of concurrent TBI/GD exposures. This study created a TBI/GD polytrauma model using in-house-developed human acetylcholinesterase knock-in/serum carboxylesterase knockout (C57BL/6-Ces1ctm1.1LocAChEtm1.1Loc/J; a.k.a KIKO) mice to mimic delayed treatment and prolonged field care. First responders or combat medics are limited by available equipment, so pulse oximetry is an especially important treatment metric. Using a pulse oximeter, heart and breath rates were recorded following TBI, GD exposure or polytrauma. Immediately following TBI, heart and breath rates were not significantly altered, but there was evidence of increased breath rate characteristic of PSH peaking at 72 hours post-TBI. Moreover, there were significant decreases in both pulse metrics 40 minutes after GD exposure, and the degree of heart rate decrease was a reliable leading indicator of mortality. Following polytrauma, heart rate decline continued to indicate mortality as injury severity further influenced mortality. The synergistic effects revealed by heart rate changes confirm the importance of pulse oximetry as a field diagnostic. The views expressed in this poster are those of the author(s) and do not reflect the official policy of the Department of Army, Department of Defense, or the U.S. Government. The experimental protocol was approved by the Animal Care and Use Committee at the United States Army Medical Research Institute of Chemical Defense, and all procedures were conducted in accordance with the principles stated in the Guide for the Care and Use of Laboratory Animals and the Animal Welfare Act of 1966 (P.L. 89-544), as amended. These studies were funded by the Combat Casualty Care Research Program (CCCRP). J. Sahargun, J. Leighton and E. Miller were supported in whole or in part by an appointment to the Research Participation Program for the U.S. Army Medical Research and Development Command administered by the Oak Ridge Institute for Science Education (ORISE) through an agreement between the U.S. Department of Energy and U.S. Army Medical Research and Development Command.

Disclosures: **J. Sahargun:** None. **J. Leighton:** None. **A. Methvin:** None. **E. Miller:** None. **E. Johnson:** None.

Poster

124. Brain Injury: Molecular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 124.21

Topic: C.10. Brain Injury and Trauma

Support: Combat Casualty Care Research Program (CCCRP)

Title: Eeg evaluation of the compounding effects of traumatic brain injury on soman exposure in mice

Authors: *A. METHVIN, J. LEIGHTON, E. MILLER, J. SAHARGUN, E. JOHNSON;
US Army Med. Res. Inst. of Chem. Def. (USAMRICD), Gunpowder, MD

Abstract: There is an increasing potential for the concurrence of a head injury, already common in military settings, and exposure to chemical warfare nerve agents (CWNA) during military operations. Extensive research efforts documented the individual effects of exposure to various CWNAs such as soman (GD) or traumatic brain injury (TBI) on the brain; however, limited research exists that identified any synergistic effects of these two potentially severe injuries in conjunction. Both injuries initiate a neuroinflammatory response which can manifest pathologically as neuronal atrophy and loss, and more immediately cause altered synaptic activity, resulting in homeostatic dysregulation and altered behavior. In this study, the effects of GD exposure and mild to moderate TBI were evaluated, with a primary focus on EEG data. This study developed a TBI/CWNA exposure polytrauma model using in-house-developed transgenic mice (C57BL/6-Ces1ctm1.1LocAChEtm1.1Loc/J; human acetylcholinesterase knock-in/serum carboxylesterase knockout; KIKO). Male mice (15-20 weeks old) were exposed to GD and/or TBI and observed for 3 days to mimic prolonged field care conditions. Changes in EEG activity and body temperature were recorded using wireless Data Sciences International (DSI) telemetry transponders. Other metrics for physiology, behavior and neuropathology were also observed. Results indicated that a TBI exacerbated the effects of GD exposure, especially in seizure frequency and lethality for animals exhibiting CWNA exposure symptoms. These data suggest that the injuries are synergistic, though aggressive treatment of CWNA intoxication rather than of TBI may be of greater benefit in an instance of polytrauma. The views expressed in this poster are those of the author(s) and do not reflect the official policy of the Department of Army, Department of Defense, or the U.S. Government. The experimental protocol was approved by the Animal Care and Use Committee at the United States Army Medical Research Institute of Chemical Defense and all procedures were conducted in accordance with the principles stated in the Guide for the Care and Use of Laboratory Animals and the Animal Welfare Act of 1966 (P.L. 89-544), as amended. These studies were funded by the Combat Casualty Care Research Program (CCCRP). J. Sahargun, J. Leighton and E. Miller were supported in whole or in part by an appointment to the Research Participation Program for the U.S. Army Medical Research and Development Command administered by the Oak Ridge Institute for Science Education (ORISE) through an agreement between the U.S. Department of Energy and U.S. Army Medical Research and Development Command.

Disclosures: A. Methvin: None. **J. Leighton:** None. **E. Miller:** None. **J. Sahargun:** None. **E. Johnson:** None.

Poster

124. Brain Injury: Molecular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 124.22

Topic: C.10. Brain Injury and Trauma

Support: Combat Casualty Care Research Program (CCCRP)

Title: Activity deficits and anxiety are increased in a mouse polytrauma model compared to either traumatic brain injury or soman exposure alone.

Authors: *E. MILLER, J. LEIGHTON, A. METHVIN, J. SAHARGUN, E. JOHNSON; USA Med. Res. Inst. of Chem. Def., Gunpowder, MD

Abstract: The combination of traumatic brain injury (TBI) and exposure to chemical warfare nerve agent (CWNA) poses an increasing risk to military operations with no guidance on management in a prolonged field care environment. Both TBI and CWNAs such as soman (GD) are associated with neuropathy and behavioral deficits. These injuries are well characterized individually and have standard medical countermeasures. However, a GD/TBI polytrauma has not been examined before. This study created a novel GD/TBI polytrauma model using human acetylcholinesterase knock-in/serum carboxylesterase knockout (C57BL/6-Ces1ctm1.1LocAChEtm1.1Loc/J; KIKO) mice to characterize neurological and behavioral deficits and assess individual trauma medical countermeasures in a polytrauma scenario. Changes in innate behavior were tracked and quantified using an open field test (OFT) following a controlled cortical impact TBI, exposure to GD, or a combined polytrauma and treatment with corresponding standard medical countermeasures. Analysis of metrics such as distance traveled demonstrated that the severity of nerve agent exposure accounts for the majority of the behavioral deficits observed in the OFT. Similarly, a moderate TBI exacerbated behavioral deficits to a greater degree than a mild or sham TBI. In polytrauma, data suggest TBI plays less of a role in determining behavioral deficits than does GD exposure. In conclusion, we created a novel model of GD/TBI exposure that can be used to help inform treatments during mass casualty events, as well as for military units in prolonged field care settings. The views expressed in this poster are those of the author(s) and do not reflect the official policy of the Department of Army, Department of Defense, or the U.S. Government. The experimental protocol was approved by the Animal Care and Use Committee at the United States Army Medical Research Institute of Chemical Defense, and all procedures were conducted in accordance with the principles stated in the Guide for the Care and Use of Laboratory Animals and the Animal Welfare Act of 1966 (P.L. 89-544), as amended. These studies were funded by the Combat Casualty Care Research Program (CCCRP). E. Miller, J. Leighton and J. Sahargun were supported in whole or in part by an appointment to the Research Participation Program for the U.S. Army Medical Research and Development Command administered by the Oak Ridge Institute for Science Education (ORISE) through an agreement between the U.S. Department of Energy and U.S. Army Medical Research and Development Command.

Disclosures: E. Miller: None. **J. Leighton:** None. **A. Methvin:** None. **J. Sahargun:** None. **E. Johnson:** None.

Poster

124. Brain Injury: Molecular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 124.23

Topic: C.10. Brain Injury and Trauma

Support: Combat Casualty Care Research Program (CCCRP)

Title: Synergistic effects of traumatic brain injury and nerve agent polytrauma negatively impacts mortality, morbidity, and recovery in mice.

Authors: *J. LEIGHTON, A. METHVIN, E. MILLER, J. SAHARGUN, E. JOHNSON;
US Army Med. Res. Inst. of Chem. Def. (USAMRICD), Aberdeen Proving Ground, MD

Abstract: In a warfare setting, both traumatic brain injury (TBI) and nerve agent (CWNA) exposures have well-established pharmaceutical countermeasures. However, the effects of these injuries when combined, along with the effectiveness of their countermeasures in a polytrauma scenario, remain largely unknown. This study created a novel TBI/CWNA polytrauma model using a unique human acetylcholinesterase knock-in/serum carboxylesterase knockout (C57BL/6-Ces1ctm1.1LocAChEtm1.1Loc/J; a.k.a KIKO) mouse strain to investigate the consequences and treatment of TBI/CWNA polytrauma. Male mice received a TBI and standard countermeasures, then were exposed to the CWNA soman (GD) and standard countermeasures. Throughout and up to 72 hrs post-exposure, mice were monitored for physiological and behavioral changes including but not limited to EEG signals, burrowing behavior, and nesting behavior. Results of this study indicated that morbidity and mortality rates of TBI/CWNA polytrauma were higher than those of either injury on its own, despite the use of countermeasures. Further, TBI/CWNA polytrauma had a greater negative impact on return to normal behavior (i.e. nesting, burrowing) over a 72 hr period in comparison to either injury alone. Changes in mortality and behavior were clearly seen in animals that showed visible effects of CWNA poisoning. The results of this study suggest that TBI/CWNA exposures have a synergistic effect when combined, thus necessitating a more developed level of care than the current pharmaceutical countermeasures as well as different expectations for recovery time. In addition, the severity of CWNA exposure may inform treatment and recovery more than TBI severity in a polytrauma scenario.
 The experimental protocol was approved by the Animal Care and Use Committee at the United States Army Medical Research Institute of Chemical Defense, and all procedures were conducted in accordance with the principles stated in the Guide for the Care and Use of Laboratory Animals and the Animal Welfare Act of 1966 (P.L. 89-544), as amended. These studies were funded by the Combat Casualty Care Research Program (CCCRP). J.
Leighton, E. Miller, and J. Sahargun were supported in whole or in part by an appointment to the Research Participation Program for the U.S. Army Medical Research and Materiel Command administered by the Oak Ridge Institute for Science Education (ORISE) through an agreement between the U.S. Department of Energy and U.S. Army Medical Research and Development Command.

Disclosures: J. Leighton: None. **A. Methvin:** None. **E. Miller:** None. **J. Sahargun:** None. **E. Johnson:** None.

Poster

124. Brain Injury: Molecular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 124.24

Topic: C.10. Brain Injury and Trauma

Support: Intramural Research Program, NIA, NIH.

Title: Anti-inflammatory activity of a novel IMiD tetrafluorobornylphthalimide in mitigating traumatic brain injury in a mouse controlled cortical impact model

Authors: D. LECCA[1], W. LUO[1], D. TWEEDIE[1], D. KIM[2], B. J. HOFFER[3], N. H. GREIG[1], ***Y.-H. CHIANG**[4];
[2]NIH/NIA, [1]NIH/NIA, Baltimore, MD; [3]Dept. of Neurolog. Surgery, Case Western Reserve Univ. Sch. of Med., Cleveland, OH; [4]Taipei Med. Univ., Taipei Med. Univ., Taipei, Taiwan

Abstract: Tetrafluorobornylphthalimide (TFBP) and tetrafluoronorbornylphthalimide (TFNBP) were designed to retain the core phthalimide structure of the immunomodulatory imide drug (IMiD) class, which is linked to a bridged ring structure, in order to potentially preserve the beneficial anti-inflammatory properties but, importantly, hinder cereblon binding that underlies the adverse action of classical IMiDs. TFBP and TFNBP reduced markers of inflammation in mouse macrophage-like RAW cell cultures as well as in F344 8 week old rats challenged with lipopolysaccharide (LPS), lowering both plasma and brain levels of proinflammatory cytokines in the latter, following systemic drug administration. To evaluate whether anti-inflammatory actions were biologically meaningful, TFBP was administered to C57Bl6 8 week old mice following a controlled cortical impact (CCI) moderate severity traumatic brain injury (TBI). In comparison to vehicle treatment, the lesion size of TFBP-treated mice, together with the number of activated microglial cells adjacent to the CCI-induced lesion, were decreased on evaluation by immunohistochemistry at 2-weeks following TBI. Additionally, in behavioral assessments conducted at 1- and 2-weeks post injury, impairments in fine motor coordination and balance resulting from CCI TBI were more rapidly mitigated by TFBP, as compared to recovery in vehicle treated animals. All protocols were fully approved by the IACUC of NIA. Only male animals were used to avoid estrogen neuroprotection. Sample size was based on our previous work. The histochemical and behavioral measurements were made by blinded observers. In conclusion, TFBP and TFNBP represent a new class of IMiDs that lower proinflammatory cytokine generation, and provide a strategy to mitigate excessive neuroinflammation associated with moderate severity CCI TBI to, thereby, improve behavioral outcome measures.

Disclosures: D. Lecca: None. **W. Luo:** None. **D. Tweedie:** None. **D. Kim:** None. **B.J. Hoffer:** None. **N.H. Greig:** None. **Y. Chiang:** None.

Poster

124. Brain Injury: Molecular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 124.25

Topic: C.10. Brain Injury and Trauma

Support: R01NS110898

Title: Early life stress exacerbates neurodegeneration and worsens behavioral deficits following repeated closed head injury in the neonate rat

Authors: *J. HUH[1], Q. STEWART[2], C. MARTIN[2], R. RAGHUPATHI[2];
[1]Children's Hosp. of Philadelphia, Philadelphia, PA; [2]Drexel Univ. Col. of Med., Philadelphia, PA

Abstract: Abusive head trauma (AHT), characterized by repeated episodes of mild traumatic brain injury (TBI) is a leading cause of injury-associated mortality and morbidity in infants. Children raised in lower socio-economic environments are more likely to be subjected to AHT. To effectively model AHT, we hypothesized that early life stress (ELS) prior to and after repeated mild TBI in the neonate rat may potentially exacerbate brain atrophy and neurodegeneration along with cognitive and psychosocial behaviors in adolescence. Male and female rat pups (n=25) were subjected to ELS by maternal separation for 180 minutes per day from post-natal days 2 until weaning on day 21; control pups remained with the dam during the pre-weaning period (n=25). On postnatal days 11-13, pups were anesthetized with isoflurane and subjected to mild closed head injury once per day (n=12 ELS and 13 control) or just anesthetized without injury (sham-injury, n=13 ELS and 12 control). At 3-4 weeks after surgery/injury (adolescence), the rats were evaluated for spatial learning, anxiety-like behavior and social behavior and subsequently euthanized for histological analyses. Both control and ELS brain-injured animals exhibited deficits in spatial learning compared to their sham-injured counterparts with a greater deficit in ELS animals. Brain injury or ELS did affect behavior in the elevated plus maze but the combination of ELS and TBI led to increases in open arm time and entries suggestive of impaired response to stress. ELS alone reduced social recognition memory compared to control rats which was exacerbated by repeated TBI. No overt changes were observed in brains of ELS animals, whereas repeated mild TBI led to white matter atrophy, neurodegeneration, microglial and astroglial reactivity in both hemispheres. In ELS animals that were subjected to repeated mild TBI neurodegeneration, but not glial reactivity, was exacerbated. These data show that ELS is a risk factor for worsened long-term behavioral outcomes and neurodegeneration after abusive head trauma.

Disclosures: **J. Huh:** None. **Q. Stewart:** None. **C. Martin:** None. **R. Raghupathi:** None.

Poster

124. Brain Injury: Molecular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 124.26

Topic: C.10. Brain Injury and Trauma

Support: NIH Grant NS084921

Title: The Utilization of PLA_2rich Snake Venom to treat the effects of long and short-term Surgical Brain Injury

Authors: *Z. TRAVIS[1,2], P. SHERCHAN[1], W. KELLN[2], W. HAYES[2], J. ZHANG[1];
[1]Ctr. for Neurosci. Res., [2]Earth and Biol. Sci., Loma Linda Univ., Loma Linda, CA

Abstract: Due to the delicate architecture of the brain, inadvertent injury occurs, no matter how minimally invasive surgical procedures are. The phenomenon where brain tissue is injured and inflammatory cascades are triggered causing neuroinflammation and edema formation has been termed Surgical Brain Injury (SBI). SBI currently comprises one of the least studied traumatic brain injury (TBI) pathophysiologies, yet effects tens of thousands of neurosurgical patients worldwide annually. Both short and long-term neurological deficits from SBI not only impact the patient, but also their family, and the community. Inflammatory preconditioning is a mechanism in which exposure to small doses of inflammatory stimuli prepares the body against future massive insult by the activation of endogenous protective mechanisms. In recent years, due to the scheduled nature of neurosurgical procedures, inflammatory preconditioning has become an area of interest in SBI treatment and in prelimary studies resulted in positive outcomes. Phospholipase A_2 to 5-LOX cascade, an important inflammatory signalling pathway, has been explored in TBI models and was suspected to be a key player in SBI. *Pseudechis papuanus* venom contains 90.2% secretory PLA_2 in dry mass. The remaining 9.8% of the venom consists of 3FTXs, SVMPs, CRISPs, and LAAOs. Because of the protein composition, the venom causes neurotoxicity, hemolysis pulmonary inflammation, and edema. We experimentally investigated whether purified *P. papuanus* PLA_2 venom preconditioning (VPC) reduces SBI-induced neuroinflammation via activating the PLA_2/5-LOX cascade and attenuates intraoperative haemorrhage through a similar cascade using a partial frontal lobe resection SBI rat model. We injected sublethal doses of venom subcutaneously three consecutive days prior to SBI. We observed that VPC significantly reduced edema and improved neurological function at 24 h, 72 h, and 28 days after SBI. The VPC regime also significantly reduced intraoperative bleeding, while the sublethal dose caused no skin inflammation at the injection site and no other toxic effects. Our findings also confirmed the mechanistic nature of SBI and the role of PLA2, as injection of PLA_2 and 5-LOX inhibitors (manolide and zileuton) nullified the protective benefit of VPC. These findings suggest that VPC reduces edema formation and intraoperative hemorrhage, and improves neurological outcomes after SBI by activating the PLA_2/5-LOX cascade, Purified PLA_2 VPC may represent a beneficial therapy to reduce post-operative complications from brain surgeries and illustrates the need to further investigate novel venom therapeutics.

Disclosures: Z. Travis: None. **P. Sherchan:** None. **W. Kelln:** None. **W. Hayes:** None. **J. Zhang:** None.

Poster

124. Brain Injury: Molecular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 124.27

Topic: C.10. Brain Injury and Trauma

Support: National Institutes of Health [R01-NS117757 (D.K.C.)]

Title: The effects of neuronal lipid constituents on susceptibility to plasma membrane damage in traumatic brain injury

Authors: *K. NICHOLAS[1,2,3], A. BELLO[2,3], K. D. BROWNE[2,3], D. K. CULLEN[1,2,3,4]; [1]Neurosci., Perelman Sch. of Medicine, Univ. of Pennsylvania, Philadelphia, PA; [2]Neurosurg., Ctr. for Brain Injury & Repair, Univ. of Pennsylvania, Philadelphia, PA; [3]Ctr. for Neurotrauma, Neurodegeneration, & Restoration, Corporal Michael J. Crescenz Veterans Affairs Med. Ctr., Philadelphia, PA; [4]Bioengineering, Sch. of Engin. and Applied Sciences, Univ. of Pennsylvania, Philadelphia, PA

Abstract: Traumatic Brain Injury (TBI) afflicts over 2 million per year in the U.S. alone and may result in prolonged neurological deficits. TBI is caused by mechanical forces acting on the brain that may cause physical damage at the tissue, cellular, and/or sub-cellular level. A subtle form of structural damage is characterized by the immediate formation of micro- or nano-sized tears in the plasma membrane of neurons, termed “mechanoporation”. By fundamentally altering permeability across the plasma membrane, these changes often result in disruptions in ionic homeostasis that can be devastating for neuronal function, while also exacerbating an inflammatory response and potentially resulting in cell death. Interestingly, mechanoporation does not occur within all neurons after TBI. Indeed, our recent preclinical work suggests that the lipid composition of the neuronal plasma membranes affects the extent of TBI-induced damage following lateral fluid percussion injury (LFPI) in rats. For instance, when a high-fat diet (HFD) was fed to rats, we found that both TBI-induced neuronal mechanoporation and the extent of neurodegeneration were significantly decreased compared to rats fed a fish oil diet (FOD). While these diets broadly affected the levels of multiple lipids, liquid chromatography mass spectrometry (LC/MS) revealed that the HFD increased neuronal docosapentaenoic acid (DPA) in the brain, while the FOD increased neuronal docosahexaenoic acid (DHA). While both are omega-3 (ω-3) fatty acids that differ by a single double bond, DPA is thought to decrease membrane fluidity and increase membrane stiffness compared to DHA while also inhibiting oxidative damage and inflammation. Building on these findings, we are currently contrasting the neuronal lipidomic profiles of acutely permeabilized versus non-permeabilized neurons following LFPI in rats. Here, we are employing fluorescence activated cell sorting (FACS) based on uptake of normally-cell impermeant fluorescent dyes, with lipodomics analyses performed using LC/MS. These data are contextualized based on lipidomic profiles across various neuroanatomical regions as well as following feeding with specific ω-3 fatty acid supplemented diets. We anticipate that these findings will support previous work showing that dietary lipid intake influences neuronal membrane composition, while also showing that specific lipid supplements may prophylactically enhance neuronal membrane resistance to physical injury

associated with TBI. These findings may aid in the development of dietary prophylactics to "pre-condition" the brain for resilience to TBI, thereby lessening the burden for at-risk populations.

Disclosures: K. Nicholas: None. **A. Bello:** None. **K.D. Browne:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); U.S. Provisional Patent App. 63/108,160 titled "Lipid prophylactic brain injury treatment". **D.K. Cullen:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); U.S. Provisional Patent App. 63/108,160 titled "Lipid prophylactic brain injury treatment".

Poster

125. Spinal Cord Injury: Mechanisms of Inflammation and Pain

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 125.01

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Craig H. Neilson Foundation #546401

Title: Expression of opioid receptors in the spinal ejaculation generator after chronic spinal cord injury in male rats.

Authors: *P. A. GREEN[1], A. M. ENDERS[1], E. V. BROWN[1], L. M. COOLEN[2];
[1]Biol. Sci., [2]Brain Hlth. Res. Inst., Kent State Univ., Kent, OH

Abstract: Spinal cord injury (SCI) in men is commonly associated with sexual dysfunction, including anejaculation, and chronic mid-thoracic contusion injury in male rats also impairs ejaculatory reflexes. Ejaculation is controlled by a spinal ejaculation generator (SEG) consisting of a population of lumbar spinothalamic (LSt) neurons. LSt cells control ejaculation through release of neuropeptides and axonal connections with spinal autonomic and motor neurons. In addition, LSt cells are interconnected, however the functional significance of these interconnections is unknown. One of the key neuropeptides expressed in LSt cells is the endogenous opioid peptide enkephalin, controlling ejaculation via actions on mu (MOR) and delta (DOR) opioid receptors. Still, it is unknown where in the SEG these mu and delta opioid receptors are expressed. Unpublished observations from our laboratory have demonstrated that intrathecal infusions of MOR or DOR agonists can facilitate ejaculation in SCI males with similar or even greater effects in SCI males compared to sham controls. The current study thus examined the expression of MOR and DOR within LSt cells and tested if SCI affects receptor expression. Male rats received mid-thoracic contusion (n=5) or sham (n=6) injury and spinal cords were collected and sectioned 4 weeks later. Galanin (LSt cell marker) or Chat (Preganglionic cell marker), MOR, and DOR mRNA were visualized in the lumbar spinal cord using fluorescent in-situ hybridization using RNAscope. Confocal images were collected of LSt cells, and Chat cells in central autonomic nucleus (CAN), sacral parasympathetic nucleus (SPN), and intermediolateral cell column (IML). Analysis using Fiji image analysis software showed

high expression of MOR in LSt neurons (76% of LSt cells) and lower expression of DOR (42% of LSt cells). 39% of LSt cells expressed both MOR and DOR. Preganglionic cells also expressed MOR (CAN: 53%, IML: 39%; SPN: 25%), DOR (CAN: 54%, IML: 33%; SPN: 27%). 31%, 19% and 9% of Chat cells express both in CAN, IML, SPN resp. SCI did not significantly affect receptor expression in any area or cell type. These results suggest that enkephalin released from LSt cells can influence ejaculation via actions on the LSt cell soma via expression of postsynaptic receptors, or axonal release of enkephalin via actions on presynaptic receptors expressed on LSt axons, and/or on postsynaptic receptors in autonomic Chat cells. Finally, lack of changes of opioid receptors after SCI further support development of opioid receptor agonists as a potential treatment for sexual dysfunction after SCI.

Disclosures: P.A. Green: None. **A.M. Enders:** None. **E.V. Brown:** None. **L.M. Coolen:** None.

Poster

125. Spinal Cord Injury: Mechanisms of Inflammation and Pain

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 125.02

Topic: C.11. Spinal Cord Injury and Plasticity

Support: DOD W81XWH-16-1-0386, SC150225 to LMC

Title: Spinal cord GluA receptor activation is required for ejaculatory reflexes in adult male rats

Authors: *T. ETTEY[1], N. P. RITCHEY[2], L. M. COOLEN[3];
[1]Sch. of Biomed. Sci., [2]Brain Hlth. Res. Inst., [3]Dept. of Biol. Sci., Kent State Univ., Kent, OH

Abstract: Ejaculation is a reflex controlled by the spinal ejaculation generator (SEG) in the lumbar spinal cord. The generator in male rats and humans consists of a population of neurons named lumbar spinothalamic (LSt) cells, that convert sensory inputs during sexual activity into a coordinated autonomic and motor output required for ejaculation. The sensory inputs partially originate from the dorsal penile nerve (DPN) and require glutamate receptor activation in LSt cells. We previously demonstrated that LSt neurons express GluN1 receptor, and that antagonism of GluN receptors ablates the ejaculatory reflex upon DPN stimulation. Here, we test the hypothesis that GluA receptor activation in LSt cells is also required for sensory induced ejaculatory reflexes in adult male rats. Fluorescent *in situ* hybridization was used to test the expression of different GluA receptor subfamilies in LSt cells. Spinal cord tissues of male rats (n=4) were hybridized using RNAscope™ probes specific for *galanin* as a marker for LSt cells together with *Gria 1*, *Gria 2*, *Gria 3* and *Gria 4* genes. These label the mRNA transcripts of GluA1, GluA2, GluA3 and GluA4 receptors respectively. Confocal microscopy and Fiji image-analyses showed that LSt cells co-expressed mRNA for GluA1 (100%), GluA2 (90%), GluA3 (60%) or GluA4 (100%). To test the effects of GluA receptor antagonism, adult male Sprague Dawley rats received a complete spinal transection at T6-T7, and a laminectomy at L3-4. 3 hours

later, rats received bilateral injections of saline or NBQX (*1mM, 1mg/2.97mL*) in L3-4, 1.5 mm ventral from dura. Different groups of rats received either 4 injections of 1 uL each (n=5 saline; n=7 NBQX) or of 0.5 uL each (n=4 saline; n=7 NBQX). Five and 10 minutes post-injection, DPN was stimulated and bulbocavernosus muscle EMG activity recorded and analyzed for numbers of bursts, events, and latency to first burst. BCM EMG analysis showed that all saline-treated rats displayed robust BCM bursting upon DPN stimulation at both time intervals. Moreover, NBQX blocked DPN-stimulation of BCM bursting at both volumes, albeit the lower volume blocked reflexes at 10, but not 5 minute time interval. These data demonstrate that LSt cells express GluA receptors and that activation of GluA receptors is essential for regulation of ejaculatory reflexes.

Disclosures: **T. Ettey:** None. **N.P. Ritchey:** None. **L.M. Coolen:** None.

Poster

125. Spinal Cord Injury: Mechanisms of Inflammation and Pain

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 125.03

Topic: C.11. Spinal Cord Injury and Plasticity

Support: DOD Award # W81XWH-16-1-0386, Log Number SC150225

Title: Contusion spinal cord injury decreases glutamatergic axon inputs to spinal ejaculation generator in male rats

Authors: *E. BROWN[1], N. P. RITCHEY, II[1], N. J. MUDRAK[1], T. ETTEY[1], K. K. SONI[3], L. M. COOLEN[2];
[2]Biol. Sci., [1]Kent State Univ., Kent, OH; [3]Univ. of Mississippi Med. Ctr., Jackson, MS

Abstract: For an overwhelming majority of men, spinal cord injury (SCI) leads to chronic sexual dysfunction. SCI men are often unable to ejaculate without invasive medical intervention. Previous work in our lab has identified a group of neurons in laminae VII and X of the L3 and L4 spinal cord which comprise the spinal ejaculation generator (SEG). Owing to their thalamic projections, these are called lumbar spinothalamic (LSt) neurons; but the SEG is complex, coordinating sensory input with sympathetic, parasympathetic and motor outputs. Specific lesions of LSt neurons abolish ejaculation, while otherwise preserving normal mating behaviors. Furthermore, we have shown that NMDAR signaling, and subsequent activation of map kinase cascades are critical for ejaculation to occur. We have developed a rat model of SCI induced anejaculation in which we deliver a midline contusion SCI to the T5/6 spinal cord which recapitulates the anejaculation seen in human patients, as well as NMDAR antagonism in rat. Here we used this model to ask if SCI induced anejaculation is the result of changes in glutamatergic innervation of the SEG. Using IHC against vesicular glutamate transporters 1 and 2, we found that glutamatergic innervation of LSt soma and dendrites are predominately mediated by VGLUT2. We next investigated the effect of SCI on glutamatergic innervation of

the SEG (n=8 SCI vs 8 sham). There was an SCI induced decrease in both VGLUT1 and VGLUT2 innervation of the SEG. This was first evident by 7 days post-SCI and worsened in a time dependent fashion until 28 days post-SCI, the most chronic time point studied here. We next asked which cells were the source of this glutamatergic input. We hypothesized that some of this innervation was due to LSt-LSt connections, but the neurotransmitters of the SEG were previously unknown. First, we confirmed the glutamatergic identity of a subset of LSt neurons by using RNAscope against VGLUT2. Next, we quantified VGLUT2/galanin puncta surrounding LSt neuron soma, indicative of glutamatergic LSt-LSt connections. We found that a small subset of LSt-LSt connections were glutamatergic, however, were not altered by SCI. Hence, the SCI-induced loss of glutamate is from non-LSt sources. Together these findings demonstrate that SCI induced anejaculation is associated with a loss of glutamatergic input to LSt cells, which originates from spinal cells other than LSt neurons.

Disclosures: E. Brown: None. **N.P. Ritchey:** None. **N.J. Mudrak:** None. **T. Ettey:** None. **K.K. Soni:** None. **L.M. Coolen:** None.

Poster

125. Spinal Cord Injury: Mechanisms of Inflammation and Pain

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 125.04

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Craig H. Neilsen Foundation 385450

Title: The effects of oral ketone esters on the NLRP3 inflammasome after SCI

Authors: *D. PARK[1], O. SEIRA[2], J. LIU[2], K. CLARKE[3], W. TETZLAFF[1,2];
[1]Univ. of British Columbia, Vancouver, BC, Canada; [2]Intl. Collaboration on Repair Discoveries (ICORD), Vancouver, BC, Canada; [3]Univ. of Oxford, Oxford, United Kingdom

Abstract: Previous studies have demonstrated that dietary interventions such as the use of a ketogenic diet (KD), a high fat, low carbohydrate diet, can improve the pathophysiology that occurs after spinal cord injury (SCI). KD increases the production of three ketone bodies, β-hydroxybutyrate (BHB), acetoacetate, and acetone. Of the three, BHB is the most abundant and has a wide range of effects that go from serving as an energy source to function as a signaling molecule. However, the administration of KD to SCI patients would be highly restrictive and inconvenient. Alternatively, circulating BHB levels can be increased by oral administration of ketone esters (KE, ΔG® a β-hydroxybutyrate diester). In this study, we investigated the potential beneficial effects of KE supplementation in reducing the inflammatory response after SCI. The NLRP3 inflammasome is a large, cytoplasmic multiprotein complex that is essential in providing an immune response. However, following SCI, NLRP3 is significantly upregulated and plays a key role in the activation and subsequent prolongation of cytokine upregulation. Therefore, the NLRP3 inflammasome may contribute to secondary degeneration after SCI. Sprague-Dawley

rats (males 250-300g) received a spinal cord hemi-contusion (150kDyn) at the C5-C6 level using the Infinite Horizon Impactor. Starting from 3 hours post-injury, the rats were treated with oral gavage of either KE or water (control) every 8 hours for the first 3 days, then every 12 hours for 7 days, and later every 24 hours for the final 14 days, while having free access to a standard diet (SD, FD5960, Bioserv). The rats were sacrificed at 1 day, 2 days, 7 days, and 14 days post-injury, and three 5mm long pieces of the spinal cords (rostral, C4-C5; epicenter, C5-C6; caudal, C6-C7) were harvested immediately after PBS perfusion. Temporal (1 DPI, 2 DPI, 7 DPI, and 14 DPI) and positional (Rostral, C4-C5; Epicenter, C5-C6; Caudal, C6-C7) expression of the NLRP3 inflammasome components were analyzed by western blot. Our data reveal that SCI, compared to sham operation, induced a significant increase of the NLRP3-associated components (NLRP3, NEK7, and phosphorylated NF-κB), with the peak of expression and activity observed at 7 DPI. Importantly, KE-treated cohorts had a transient, yet significant reduction in some upstream activators of the inflammasome, suggesting KE's potential modifying effect on the inflammatory response following SCI. Furthermore, in other cohorts with the same paradigm, we identified improvements in distal digit movements. Taken together, these findings demonstrate the potential neuroprotective benefits of KE supplementation initiated soon after SCI.

Disclosures: **D. Park:** None. **O. Seira:** None. **J. Liu:** None. **K. Clarke:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Founder, chairman, and CEO of TdeltaS Ltd.. **W. Tetzlaff:** None.

Poster

125. Spinal Cord Injury: Mechanisms of Inflammation and Pain

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 125.05

Topic: C.11. Spinal Cord Injury and Plasticity

Title: Myelin basic protein serves as a novel macrophage survival factor in spinal cord injury

Authors: *M. AYAZI, A. ROLFE, D. BOSCO, C. VIED, S. ZIVKOVIC, L. SUN, Y. REN; Florida State Univ., Tallahassee, FL

Abstract: Spinal cord injury (SCI) causes a significant inflammatory response resulting in rapid infiltration of immune cells into the lesion core. Bone marrow-derived macrophages (BMDMs) are one of the immune cells that infiltrate into the lesion epicenter and phagocytose myelin debris (MD). MD-activated BMDMs remain in the injury site chronically, thus, focusing our study on determining the factor(s) responsible for BMDM's persistence in the epicenter of an injured spinal cord (SC). We hypothesized that this is due to MD as there is ongoing demyelination following SCI. We used a thoracic contusion SCI mouse model for our studies. We stained SC sections for a BMDM marker, F4/80, and astrocyte marker, GFAP, at 2 and 12 weeks post-injury (wpi). We detected similar distribution of BMDMs in the epicenter of the injured SC at both time points, surrounded by a glial scar. To determine if BMDMs in the

epicenter undergo apoptosis, we stained the injured SC sections for F4/80 and cleaved caspase-3, a marker for apoptotic cells. We observed that BMDMs do not undergo significant apoptosis at 1, 2, 4, or 12 wpi. To test whether MD supports the survival of BMDMs, we isolated primary BMDMs from C57BL/6J mice and treated them with MD without macrophage colony-stimulating factor (M-CSF), a cytokine required for BMDM survival. We used Sytox green to label dead BMDMs and observed that there are more live cells in MD-treated BMDMs compared to the untreated ($n=3$, $p\text{-value}<0.05$, t-test). To determine whether MD supports the survival of BMDMs by suppressing apoptosis, we measured relative caspase 3/7 activity in MD-treated BMDMs. Caspase 3/7 activity was significantly reduced in MD-treated BMDMs, indicative of apoptosis suppression ($n=3$, $p\text{-value}<0.05$, t-test). Next, we aimed to determine whether myelin basic protein (MBP) is responsible for MD-induced survival in BMDMs. We incubated BMDMs with MBP and observed that apoptotic activity was significantly reduced in BMDMs 24hrs after MBP treatment ($n=3$, $p\text{-value}<0.05$, t-test). Our results suggest that BMDMs do not undergo apoptosis in the injured SC. MD increases BMDMs' survival by apoptosis suppression and identifies MBP as a novel BMDM survival factor. Our study offers a new therapeutic target in treating SCI and other demyelinating diseases such as multiple sclerosis.

Disclosures: **M. Ayazi:** None. **A. Rolfe:** None. **D. Bosco:** None. **C. Vied:** None. **S. Zivkovic:** None. **L. Sun:** None. **Y. Ren:** None.

Poster

125. Spinal Cord Injury: Mechanisms of Inflammation and Pain

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 125.06

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NSF DMS- 2054014

Title: Insights into the mechanisms and factor initiating pathologic consequences in endothelial cells after spinal cord injury

Authors: *G. HAMMEL, M. AYAZI, S. ZIVKOVIC, Y. REN;
Florida State Univ., Tallahassee, FL

Abstract: Dysfunction of the endothelium lining of blood vessels is a hallmark characteristic of various types of neuronal injury and neuroinflammatory disorders such as spinal cord injury (SCI) and is typically characterized by endothelial cell (EC) activation, loss of endothelium integrity of the blood-spinal cord-barrier (BSCB), and enhanced inflammation. However, the entire spectrum of pathologic consequences that arise from EC dysfunction and the mediators of these consequences lack a complete understanding. In the context of SCI, our group has provided evidence that ECs engulf and process debris generated from damaged myelin sheaths called myelin debris (MD). We have previously shown that MD laden EC (Mye-EC) have various functionality changes including increased proliferation, microvessel dilation, upregulation of

genes associated with inflammation and fibrosis, and a downregulation of genes associated with endothelial BSCB cell-to-cell junctions. In this study, we aim to explore the role of MD as a crucial SCI lesion related factor that directly participates in the induction of BSCB disruption in the acute injured spinal cord. In order to assess the consequences of MD on the permeability of the BSCB we utilized bEnd.3 cells, a mouse brain endothelial cell line, to first monitor changes in key BSCB junctional proteins in Mye-ECs. We showed a significant decrease in VE-cadherin protein levels in bEnd.3 ECs treated with MD (unpaired t test; p= 0.0019, n=3). We further showed, utilizing immunocytochemistry staining, a significant disruption in another key junctional protein (ZO-2) in Mye-ECs (unpaired t test; p=0.0169, n=3). We also assessed the permeability of Mye-ECs using various assays capable of quantifying endothelial barrier integrity including transendothelial FITC-dextran permeability analysis and transendothelial electrical resistance measurements (TEER). We find that Mye-ECs have a significantly decreased barrier integrity with a significantly higher FITC-dextran permeability (unpaired t test; p=0.0328, n=4), and significantly lower TEER readings (paired t test; p=0.0471, n=4). These results suggest that MD can act as a pathological mediator in ECs after SCI, especially in the context of the breakdown of the BSCB. Therefore, targeting MD uptake by ECs may represent a novel therapeutic approach for SCI.

Disclosures: **G. Hammel:** None. **M. Ayazi:** None. **S. Zivkovic:** None. **Y. Ren:** None.

Poster

125. Spinal Cord Injury: Mechanisms of Inflammation and Pain

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 125.07

Topic: C.11. Spinal Cord Injury and Plasticity

Title: Myelin basic protein induces the migration of bone marrow-derived macrophages into the lesion of an injured spinal cord

Authors: *S. ZIVKOVIC[1], Z. CHENG[1], J. QIN[2], D. BOSCO[1], Y. LI[1], D. SUN[2], W. YOUNG[2], Y. REN[1];
[1]Biomed. Sci., Florida State Univ., Tallahassee, FL; [2]W. M. Keck Ctr. for Collaborative Neurosci., Rutgers, Piscataway, NJ

Abstract: Spinal cord injury (SCI) is a global problem, with 250K-500K people suffering from SCI yearly. Following the physical impact of SCI, secondary injury begins causing infiltration of immune cells and chronic inflammation. The bone marrow-derived macrophages (BMDMs) are one of the immune cells infiltrating the injured spinal cord and are migrating noticeably towards the lesion core 1-week post-injury. We hypothesized that myelin debris (MD) is responsible for BMDM infiltration into the lesion core. Our *in vitro* studies used primary bone marrow-derived cells freshly isolated from C57BL/6J mice and cultured for 7 days in media with macrophage colony-stimulating factor, allowing differentiation of monocytes into mature BMDMs. MD in our *in vitro* studies was isolated from mouse brains using ultracentrifugation and sucrose

gradient to enrich for myelin for a final concentration of 1 mg/ml upon treatment of BMDMs. The migration of BMDMs was investigated using NP chemotaxis chamber. Contusive SCI was induced using NYU impactor with a 5g rod dropped 6.25mm from the cord's surface using C3Fe.SWV-MBP^{shi}/J mice (MBP^{shi}) mice, a mouse line lacking myelin and MBP in the central nervous system. All experiments are N=3. Our *in vitro* studies show that MD causes the migration of BMDMs. Specifically, 20 μg/ml myelin basic protein (MBP) for 30 mins resulted in migration of BMDMs. Next, we confirmed that MBP was a major attractant for BMDMs *in vivo*. Compared to littermate control, we show fewer BMDMs infiltrated into the lesion core following SCI in MBP^{shi} mice 5 days post-injury. MBP (20 μg/ml) treatment of BMDMs for 30 mins revealed enhancement in the expression of ERK1/2 via Western blot and blocking the phosphorylation of ERK1/2 with PD98059 (50 μM) resulted in reduced BMDM migration. Treating BMDMs with a G-coupled protein receptor (GPCR) inhibitor, Suramin (15 μM), decreased the MBP-induced migration of BMDMs. Our results indicate that MBP attracts BMDMs by the GPCR-mediated ERK1/2 phosphorylation pathway. Our study offers a novel factor that may contribute to macrophage recruitment to the areas of demyelinated axons, providing a new novel therapeutic target for SCI treatment. Our study can apply to SCI and other demyelinating diseases that generate MD, such as stroke and multiple sclerosis.

Disclosures: S. Zivkovic: None. **Z. Cheng:** None. **J. Qin:** None. **D. Bosco:** None. **Y. Li:** None. **D. Sun:** None. **W. Young:** None. **Y. Ren:** None.

Poster

125. Spinal Cord Injury: Mechanisms of Inflammation and Pain

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 125.08

Topic: C.11. Spinal Cord Injury and Plasticity

Support: #WFL-US-15/21

Title: The effects of an adult rat spinal cord contusion milieu on the phenotype of transplanted Schwann cells

Authors: *G. SCESA[1], W. BOGUE[1], M. OUDEGA[1,2,3,4];
[1]Biologics Lab., Shirley Ryan Abilitylab, Chicago, IL; [2]Dept. of Physical Therapy and Human Movement Sci., [3]Dept. of Neurosci., Northwestern Univ., Chicago, IL; [4]Edward Hines Jr VA Hosp., Hines, IL

Abstract: Traumatic contusive spinal cord injury (SCI) typically causes immediate nervous tissue loss and functional deficits. In time, a cytotoxic milieu develops in the contusion site that impedes endogenous repair and function recovery. In pre-clinical studies, using animal models of SCI, transplants of Schwann cells (SCs) were shown to elicit repair of the damaged nervous tissue, which, albeit not always, accompanied by motor and sensory function improvements. SCs are thought to support tissue repair in the damaged spinal cord mostly due to secreted molecules,

including growth factors and cytokines that exert paracrine effects. The use of SCs for spinal cord repair is attractive because they can be relatively easily obtained from a SCI patient and thus enable autologous transplantation strategies. However, the overall repair effect of SC transplants in pre-clinical and clinical studies has been limited. One possible explanation for the limited repair effects of SCs in the injured spinal cord is that the cytotoxic milieu in the injury site in which they are transplanted changes their secretome profile, and so their therapeutic effects. At present, our knowledge about the response of SCs to the injury milieu in the damaged spinal cord is limited. We investigated how the injury milieu affects SCs phenotype using in vitro culture model systems and an adult rat model of contusive SCI. Our studies tested the premise that the cytotoxic injury milieu in the contused spinal cord causes a phenotypical change in SCs resulting in a decrease in their efficacy to repair damaged nervous tissue. We used the in vitro culture system to analyze the effect of exudates collected from the contusion injury site at different times after injury on SCs phenotype, which was comprehensively characterized using mass spectrometry, next-generation sequencing, and fluorometric assays. We used the in vivo model of contusive SCI to assess the effects of the injury milieu on the phenotype of SCs that were transplanted and then retrieved from the contusion using a similar approach as in the in vitro study.

Disclosures: G. Scesa: None. **W. Bogue:** None. **M. Oudega:** None.

Poster

125. Spinal Cord Injury: Mechanisms of Inflammation and Pain

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 125.09

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Daniel and Ada Rice Foundation

Title: Extended characterization of the intraspinal immune response in mice following contusive spinal cord injury

Authors: *N. J. WROBEL, B. T. DAVID, R. G. FESSLER;
Neurosurg., Rush Univ. Med. Ctr., Chicago, IL

Abstract: Traumatic spinal cord injury is rapidly followed by a robust, local immune response within the spinal cord, consisting of activation of central nervous system resident immune cells and infiltration by peripheral immune cells. This local immune response persists chronically and is widely recognized to hold considerable sway over the progression of secondary tissue damage. As the majority of spinal cord injury sufferers live with chronic injuries, studies examining chronic spinal cord inflammation are warranted, yet they are much fewer in number than studies of acute and subacute inflammation. We present an extensive, long-term characterization of the local post-injury immune response in adult (10-12-week-old) female wild type (C57BL/6) mice, following a moderate (50 kdyn) spinal cord contusion at T9. One group of mice will receive a T9

laminectomy and spinal cord contusion (n=6/timepoint), while the control group will receive T9 laminectomy only (n=6/timepoint). Multiple terminal assessment timepoints are included, ranging from 1 to 180 days post-injury. The relative levels of certain T cell subsets (helper T cells, cytotoxic T cells, regulatory T cells), as well as macrophages and microglia, are monitored via flow cytometry. By applying standard measures of locomotor (open-field task) and sensory (tail flick) function throughout the course of the investigations, we are able to identify any correlations between the progression of the local immune response and behavioral recovery. At 180 days post-injury, we observe elevated levels of all measured cell types in injured animals, relative to sham controls, most notably, a 5-fold increase in the number of observed regulatory T cells.

Disclosures: **N.J. Wrobel:** None. **B.T. David:** None. **R.G. Fessler:** None.

Poster

125. Spinal Cord Injury: Mechanisms of Inflammation and Pain

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 125.10

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Craig H. Neilsen Foundation
TIRR Foundation

Title: Neutrophil Extracellular Traps in Acute Spinal Cord Injury

Authors: *S. REID[1,2], M. LEAL[2], M. KIRCHHOFF[2], S. LEE[2], D. MCCREEDY[1,2];
[1]Inst. for Neurosci., [2]Biol., Texas A&M Univ., College Station, TX

Abstract: Neutrophils are the first peripheral immune cell to infiltrate the spinal cord in large numbers following spinal cord injury (SCI); however, their role in secondary tissue damage and locomotor recovery is poorly understood. Neutrophil extracellular traps (NETs) are a neutrophil effector function wherein chromatin is decondensed, decorated with granule proteins, and expelled from the cell as a mechanism to trap and destroy pathogens. However, NETs have also been shown to be damaging to host tissues under sterile inflammation conditions. The contribution of NETs to tissue damage and functional recovery following spinal cord injury (SCI) remains underexplored. To determine if NET formation occurs acutely in a murine model of SCI, we performed ELISAs for complexes of DNA with NET associated markers citrullinated histone 3 (CitH3) myeloperoxidase (MPO), and neutrophil elastase (NE)in spinal cord samples at various acute time points after SCI. We found that CitH3/DNA levels rapidly increased over the first 12 hours and peaked within the first 24 hours after injury with MPO/DNA and NE/DNA trending in a similar fashion. We verified NET formation in SCI via flow cytometry using neutrophils isolated from blood and spinal cord samples. At 24 hours post-SCI, we observed a nearly 7-fold increase in CitH3+/Ly6G+ cells in the injured spinal cord relative to the blood, confirming that NET formation occurs in the spinal cord post-SCI. Colocalization of NET

markers (CitH3, MPO, and NE) with neutrophil markers (Ly6G) in tissue sections further confirmed NET formation in vivo following SCI. Treatment with DNase I, a method used to reduce NET levels in many studies, did not significantly improve locomotor recovery in any of our studies. Collectively, our data demonstrate the first evidence of NETs in the injured murine spinal cord.

Disclosures: S. Reid: None. **M. Leal:** None. **M. Kirchhoff:** None. **S. Lee:** None. **D. McCreedy:** None.

Poster

125. Spinal Cord Injury: Mechanisms of Inflammation and Pain

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 125.11

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH R56 Grant (1R56NS117935-01A1)

Title: Inflammation after spinal cord injury: an analysis of local cytokine regulation

Authors: *D. J. HELLENBRAND, R. MISHRA, T. MARTI, M. TRUDRUNG, A. HANNA, M. J. BAER;
Univ. of Wisconsin, Madison, WI

Abstract: Objective: The initial trauma after spinal cord injury (SCI) results in ischemia, oxidative damage, edema, and glutamate excitotoxicity. This initial process sets off a secondary injury cascade leading to extensive infiltration of immune cells. Throughout the inflammatory response, these immune cells are guided to the lesion by chemokines and cytokines, which are released by microglia, astrocytes, and peripheral macrophages. Overall, this inflammatory response overreacts and exacerbates autoreactive mechanisms causing further neural destruction. Therefore, in order to develop treatments targeting secondary damage, delineation of the precise timeline of the immune response is imperative. We have previously shown that there is much discrepancy in the previous literature regarding cytokine upregulation/downregulation following SCI. There is also some previous literature showing that females regain a higher amount of function than males with similar SCI. We have three primary objectives to address from this work: 1. Delineate the precise timeline of local cytokine upregulation after SCI 2. Determine some of the local cytokines that significantly change based on the severity of SCI 3. Analyze differences in inflammation after SCI between male and female rats. Design/Methods: Sprague Dawley male and female rats underwent a T10 and T11 laminectomy. After the laminectomy, a MASCIS Weight Drop machine (Model II) was used to drop a 10-g weight to inflict a SCI, from a height of either 12.5mm (mild SCI), 25mm (moderate SCI), or 50mm (severe SCI). Then 7 mm of spinal cord was harvested and homogenized at varying times from 3 hours to 14 days post-injury. Cytokine levels in the tissue homogenates were measured using a 27 Plex-Immunology Multiplex Assay (Eve Technologies). All samples were diluted to 5 mg protein / ml solution

before being sent to Eve technologies for analyses and run in duplicate. Results: Our results show that several pro-inflammatory cytokines, including TNFα, IL-1β, and IL-6, returned to baseline much earlier (less than 24 hours post-injury) than most of the previous reports. Several anti-inflammatory cytokines, including IL-4, IL-13, and IL-10, were all significantly down regulated by 7 days post-injury. More severe injuries resulted in a significant increase of IL-1β and IL-6 in the first 24 hours post-injury and a significant decrease in IL-10 and VEGF. After a mild SCI, IL-6, TIMP-1, and MCP-1 peak at different times in male and female rats. However as the severity of injury increased, the differences in post-injury cytokine levels decreased between male and females.

Disclosures: D.J. Hellenbrand: None. **R. Mishra:** None. **T. Marti:** None. **M. Trudrung:** None. **A. Hanna:** None. **M.J. Baer:** None.

Poster

125. Spinal Cord Injury: Mechanisms of Inflammation and Pain

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 125.12

Topic: C.11. Spinal Cord Injury and Plasticity

Support: IN227020, IN209621, IN215522, IA200622 from PAPIIT-DGAPA-UNAM, Mexico City, Mexico
UNAM grant 1130-202-002 to C.A.
Grant CF-214971 from CONACYT, Mexico City, Mexico.

Title: Neurotrophic effects of GH and GnRH after a spinal cord injury include local anti-inflammatory actions and functional recovery

Authors: *C. G. MARTÍNEZ-MORENO[1], D. CALDERÓN-VALLEJO[2], M. DÍAZ-GALINDO[2], I. HERNÁNDEZ-JASSO[2], J. D. OLIVARES-HERNÁNDEZ[1], J. ÁVILA-MENDOZA[1], D. EPARDO[1], J. E. BALDERAS-MÁRQUEZ[1], V. A. URBAN-SOSA[1], R. BALTAZAR-LARA[1], M. E. CARRANZA[1], M. LUNA[1], C. ARÁMBURO[1], J. L. QUINTANAR[2];
[1]Neurobiología Celular y Mol., Inst. de Neurobiología, UNAM, Queretaro, Mexico;
[2]Farmacología y Fisiología, Univ. Autónoma de Aguascalientes, Aguascalientes, Mexico

Abstract: Spinal cord injury (SCI) represents an important public health problem that severely reduces quality of life and performing capacities of the affected person. There is evidence demonstrating that both Growth Hormone (GH) and Gonadotropin-releasing Hormone (GnRH) have roles in neuroprotection and neuroregeneration. However, the cellular and molecular mechanisms underlying these actions, including gene expression, signaling pathways, and cell interactions remain largely unknown. Under conditions of neural injury, both GH and GnRH have the potential to induce a synergic protective and/or regenerative effect, by modulating the expression of neurotrophins and growth factors that regulate axogenesis, synaptogenesis and

neuroinflammation. Here we analyzed the physiological, cellular, and molecular mechanisms that mediate the effects of GH and GnRH upon the regeneration/protection processes in the nervous system under damage and determine if they can exert an additive/synergistic action. Our experimental design included a SCI in T10 followed by 3 weeks of hormonal treatments in the next groups: 1) Sham/control; 2) SCI; 3) SCI + GH; 4) SCI + GnRH; and 5) SCI + GH + GnRH. For molecular and histological studies, the spinal cord was collected in 3 parts: injury site (T10-T11), proximal section (T8-9) and distal section (T12-13). Gene expression analyses for synaptogenic markers (Ngn1, Nxn1, Sintaxin-1, SNAP25, SPY), proinflammatory mediators (IL6, IL1b, iNOS) and neurotrophic factors (BDNF, NGF, NT3, IGF1, GH) were performed by qPCR. Hot plate latency (sensitivity) and cinematic studies were used to determine functional recovery. We found that GH and/or GnRH induced a strong anti-inflammatory effect in the spinal cord, particularly in the injury site and distal section; IL6, IL1b and iNOS expression was significantly reduced. Reactive gliosis was increased after the SCI and it was significantly limited by GH and/or GnRH since Iba1, CD86, CD206 and vimentin significantly reduced their expression. Interestingly, GnRH exerted a stronger recovery of both sensitivity and motor functions, whereas GH and the combinatory treatment only improved sensitivity. In summary, we found that both GH and GnRH, individually or combined exert neurotrophic effects that reduce local inflammation and promote functional recovery in the SCI model.

Disclosures: C.G. Martínez-Moreno: None. **D. Calderón-Vallejo:** None. **M. Díaz-Galindo:** None. **I. Hernández-Jasso:** None. **J.D. Olivares-Hernández:** None. **J. Ávila-Mendoza:** None. **D. Epardo:** None. **J.E. Balderas-Márquez:** None. **V.A. Urban-Sosa:** None. **R. Baltazar-Lara:** None. **M.E. Carranza:** None. **M. Luna:** None. **C. Arámburo:** None. **J.L. Quintanar:** None.

Poster

125. Spinal Cord Injury: Mechanisms of Inflammation and Pain

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 125.13

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NINDS-R21 Grant

Title: Decreased TrkB-mediated responses in primary sensory neurons following spinal cord injury

Authors: *K. JANG, S. M. GARRAWAY;
Emory Univ., Emory Univ., Atlanta, GA

Abstract: Brain-derived neurotrophic factor (BDNF) and its receptor TrkB have been shown to promote pronociceptive effects, although their contribution to neuropathic pain (NP) after spinal cord injury (SCI) remains unknown. We previously reported that BDNF and TrkB levels are decreased in the injured spinal cord even when mechanical hypersensitivity is evident. However,

in a current study, we found that pharmacogenetic inhibition of TrkB immediately after SCI delayed the development of mechanical hypersensitivity and improved locomotor recovery. These results suggest that not spinal but peripheral TrkB signaling is a potential contributor to NP after SCI. In this study we examined TrkB signaling in small diameter dorsal root ganglion (DRG) neurons, using adult TrkBF616A mice which allow reversible inhibition of TrkB signaling by administration of a cell-permeable kinase inhibitor, 1NM-PP1. Mice received a contusion SCI at the thoracic (T) 10 level, and were immediately treated with vehicle of 1NM-PP1 in drinking water. T4-T12 DRGs were collected for dissociation from 1NM-PP1 or vehicle-treated uninjured mice, and at acute (5-7 days) and chronic (21-28 days) time points after SCI. Whole-cell patch clamp recordings were made from the cultured neurons, and responses to 3 μM capsaicin (to identify nociceptors) and the small molecule TrkB agonist 7, 8-dihydroxyflavone (DHF; 50-500 μM) were assessed. Capsaicin induced an inward current in >90% of recorded cells. In uninjured mice, DHF induced an inward current that was significantly reduced in 1NM-PP1-treated mice compared to vehicle treatment ($p<.001$; ANOVA). Interestingly, at both acute and chronic time points after SCI, DHF-induced current was reduced compared to uninjured mice, and the current was further decreased by 1NM-PP1 treatment. Importantly, these findings suggest that nociceptors are less sensitive to TrkB manipulations after SCI, an effect that is comparable to previous results observed in the spinal cord (Garraway et al. *JNeurophys 94:3, 2005*). Although these results fail to identify primary nociceptors as critical to TrkB signaling in pain after SCI, future studies will provide additional insight into peripheral TrkB signaling and the mechanisms by which it promotes maladaptive plasticity and pain after SCI.

Disclosures: K. Jang: None. **S.M. Garraway:** None.

Poster

125. Spinal Cord Injury: Mechanisms of Inflammation and Pain

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 125.14

Topic: C.11. Spinal Cord Injury and Plasticity

Support: National Institutes of Health NS104422 to JWG

Title: Whether norepinephrine treatment after spinal cord injury induces hemorrhage depends upon time, duration, and route of administration

Authors: *T. JOHNSTON[1], G. A. GIDDINGS[1], H. L. BORLAND[1], R. S. ELEJALDE[1], C. R. WEST[2], J. W. GRAU[1];
[1]Psychological & Brain Sci., Texas A&M Univ., College Station, TX; [2]Dept. of Cell. and Physiological Sci., Univ. of British Columbia, Vancouver, BC, Canada

Abstract: Our prior work examined how pain after spinal cord injury (SCI) undermines locomotor recovery, and provided evidence that pain increases the area of hemorrhage. We hypothesized that pain may be having this effect because it drives an acute rise in systolic blood

pressure. The current studies explore this issue by pharmacologically inducing hypertension with norepinephrine (NE). In all experiments, male Sprague-Dawley rats received a contusion injury at the T10-T11 spinal level. Baseline BBB and/or tail blood pressure (BP) were assessed prior to treatment. In experiment 1, rats received a subcutaneous (SQ) injection of NE or vehicle 30 min or 24 hrs post-SCI to assess the window of time in which the spinal cord is most vulnerable to hypertension. In experiment 2, rats received SQ injections of NE or vehicle at the beginning of treatment and then again 1.5 hr later to examine the effects of maintained hypertension. In experiment 3, rats received an intravenous (IV) injection of NE or vehicle 24-hrs post-SCI to assess the effects of route of administration as compared to previous studies. BP and/or BBB scores were assessed 0, 1, 2, and 3 hours after treatment. After 3 hours, a 1-cm region of tissue encompassing the injury site was collected and assessed for hemorrhage using spectrophotometry. NE produced an increase in BP and hemorrhage with the magnitude of these effects varying with time post-SCI. Maintained hypertension significantly undermined locomotor recovery, but treatment was not associated with an increase in hemorrhage. Further analysis is being conducted examining the effects of IV administration and the mechanisms by which norepinephrine is exerting it's detrimental effects.

Disclosures: T. Johnston: None. **G.A. Giddings:** None. **H.L. Borland:** None. **R.S. Elejalde:** None. **C.R. West:** None. **J.W. Grau:** None.

Poster

125. Spinal Cord Injury: Mechanisms of Inflammation and Pain

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 125.15

Topic: C.11. Spinal Cord Injury and Plasticity

Support: CIHR

Title: Cx3cr1 is a critical mediator of neurodegeneration in degenerative cervical myelopathy

Authors: *J. HONG[1], W. YU[2], S. K. KARADIMAS[3], M. G. FEHLINGS[4];
[2]Genet., [1]Krembil Res. Inst., Toronto, ON, Canada; [3]Genet. and Develop., Krembil Discovery Tower, Toronto, ON, Canada; [4]Neurosurg., Univ. of Toronto, Toronto, ON, Canada

Abstract: The molecular cascades involved in the induction and maintenance of neuroinflammation resulting from chronic compression of the cervical spinal cord in the setting of degenerative cervical myelopathy (DCM) have yet to be defined. Here, we determined the role of the fractalkine receptor, CX3CR1, during the neuroinflammatory response in a novel mouse model of DCM and demonstrated the relevance of this mechanism with human DCM tissue. Using CX3CR1 knockout mice and a neutralizing antibody of CX3CR1 in wild-type mice, we examined protein, neurobehavioural and immunohistochemical readouts. The animal data were then complemented with immunohistochemical results from human post-mortem spinal cord tissue from individuals with DCM. Humans and mice with DCM exhibited an up-regulation of

CX3CR1 as well as markers of activated microglia/macrophages in the cervical cord. Knockout and neutralization of CX3CR1 hindered microglia/macrophage activation and accumulation at the site of spinal cord compression. DCM mice exhibited decreased body speed and increased stance phase duration, which mirrors human DCM gait deficits. Strikingly, both CX3CR1 deficiency and CX3CR1 neutralization alleviated these gait deficits in DCM mice. Collectively, these data provide strong evidence that CX3CR1 plays a critical role in the secondary injury of neural structures in the setting of DCM. Further, targeting of CX3CR1 represents a promising therapeutic strategy to enhance neurological outcomes in DCM.

Disclosures: J. Hong: None. **W. Yu:** None. **S.K. Karadimas:** None. **M.G. Fehlings:** None.

Poster

125. Spinal Cord Injury: Mechanisms of Inflammation and Pain

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 125.16

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH NS104422 to JWG

Title: Deleterious effects of pain input after spinal cord injury can be transferred between animals via blood serum

Authors: *S. R. PARTIPILO[1], J. A. DAVIS[2], K. E. HUDSON[1], E. D. GILES[3], J. W. GRAU[1]; [1]Texas A&M Univ., College Station, TX; [2]Univ. of California, San Francisco, San Francisco, CA; [3]Univ. of Michigan, Ann Arbor, MI

Abstract: Spinal cord injury (SCI) involves both the primary insult to the spinal cord and the progressive secondary damage that occurs after the initial injury. Our laboratory has found that nociceptive stimulation applied caudal to the primary lesion can worsen this secondary damage by fueling hemorrhage and inflammation. This promotes cell death, which ultimately expands the size of the lesion, and impairs long-term locomotor recovery (Grau et al., 2017, *J Neurotrauma*, 1873). Further, a complete spinal cord transection rostral to the injury blocks these effects, which suggests the involvement of brain-dependent mechanisms (Reynolds et al., 2019, *Front Syst Neurotrauma*). The present experiment provides further evidence that this pain-induced exacerbation in secondary injury is not a strictly local process. In the preliminary phase of this experiment, eight “donor” rats received a spinal cord contusion injury at T12. The next day, four of the rats received pain input in the form of electrical stimulation to the tail (shock) and the other four rats received an equal period of restraint (no shock). All animals were then sacrificed, and their blood was collected, spun into serum, and pooled by condition. Next, 16 “recipient” rats received a contusion injury at T12. The following day, these rats were given a 0.3mL intravenous transfusion of shock serum or no shock serum. Western blotting revealed that rats that had received blood serum from shocked animals had increased hemorrhage and pro-inflammatory cytokines IL-1β, IL-18, and TNF-α at the lesion site. These rats also showed a

decline in acute locomotor performance. A multiplex immunoassay found that the blood serum from the donor rats that received shock had a significant increase in IL-6 as well as an increase in IL-4, IL-5, TNF- α, and KC/GRO. Interestingly, an uptick in IL-6, IL-10, IL-4, KC/GRO, and TNF- α was also seen in the blood serum of the animals that received a transfusion of shock serum. An ongoing experiment is examining the role of the brain in these effects. For this experiment, half of the recipient animals will receive a T2 transection in addition to the T12 contusion. Shock or no shock serum will then be administered. If a transection blocks the effects of the shock serum, this suggests that the brain interacts with factors in the blood to fuel secondary injury. If these effects are not diminished, this suggests that the brain is necessary to create blood serum that has the capacity to be neurotoxic, but once this has taken place, secondary injury processes can fuel additional tissue loss in a brain-independent manner.

Disclosures: S.R. Partipilo: None. **J.A. Davis:** None. **K.E. Hudson:** None. **E.D. Giles:** None. **J.W. Grau:** None.

Poster

125. Spinal Cord Injury: Mechanisms of Inflammation and Pain

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 125.17

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Mission Connect, a project of the TIRR Foundation

Title: Acute effects of spinal cord injury on sublesional bone marrow

Authors: *J. BRYAN, L. DUPLESSIS, L. WEISE, M. HOOK;
Neurosci. and Exptl. Therapeut., Texas A&M Hlth. Sci. Ctr., Bryan, TX

Abstract: At least 80% of people living with spinal cord injury (SCI) are diagnosed with osteoporosis, with loss of approximately 40% of bone volume, particularly in the long bones of the legs, in the first 2 years post injury. This rapid loss leaves bone more vulnerable to fracture and people with SCI are 104 times more likely than able-bodied people to have a fracture by the age of 50. Further, in approximately 50% of cases, post-fracture complications occur including, but not limited to, increased pulmonary and urinary tract infections, pressure ulcers, and venous thromboembolism. Despite the high prevalence of osteoporosis after SCI and the devastating effects on quality of life, however, very few studies have looked at changes in the bone marrow to better understand the mechanisms driving this dramatic bone loss. We hypothesize that loss of sympathetic nerve signaling to sublesional bone after SCI may fuel critical changes in the marrow. To address this, we have begun to assess bone marrow extracted from male rats after a moderate T11-12 spinal contusion injury, as well as rats that received a chemical sympathectomy via 6-OHDA denervation. Bone marrow from the femur and tibia were collected 28 days after SCI. First, the extracted cells were plated and cultured to assess changes in osteoclast and osteoblast proliferation. Consistent with previous studies, we found that osteoclastogenesis is

elevated 28 days after SCI and 6-OHDA chemical sympathectomy, but osteoblast proliferation does not significantly change. Increased osteoclast activity, without commensurate increases in osteoblast activity would result in bone loss. We then used ELISAs to assess the effects of sympathetic denervation on the proinflammatory tone of the bone marrow, hypothesizing that loss of sympathetic signaling would drive HPSC proliferation after SCI and, in turn, increase proinflammatory cytokine release and osteoclastogenesis. Supporting an effect of sympathetic denervation, 6-OHDA treatment increased IL-1β, IL-18 and IL-10 expression, relative to SCI and sham-injured rats 28 days after injury. At 28 days, however, SCI did not significantly increase cytokine expression, relative to sham controls. Further analyses of the marrow environment are ongoing, focusing on earlier changes that would parallel the disruption of sympathetic signaling to sublesional bones after SCI. Given the robust and negative effects of osteoporosis on recovery and quality of life after SCI, it is critical that we determine the proximate cause of bone loss in our rat SCI model and develop novel interventions to protect bone after injury.

Disclosures: **J. Bryan:** None. **L. Duplessis:** None. **L. Weise:** None. **M. Hook:** None.

Poster

125. Spinal Cord Injury: Mechanisms of Inflammation and Pain

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 125.18

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH Grant 2RF1 NS094527

Title: Impairment of autophagy after spinal cord injury potentiates neuroinflammation and motor function deficit in mice

Authors: *Y. LI, Z. LEI, R. M. RITZEL, J. HE, H. LI, H. M. CHOI, M. M. LIPINSKI, J. WU; Univ. of Maryland Sch. of Med., Baltimore, MD

Abstract: Autophagy is a catabolic process that serves an important role in cellular homeostasis and protection against insults. We previously reported that defects in autophagy contribute to neuronal cell damage in traumatic spinal cord injury (SCI). Recent data from other inflammatory models implicate autophagy in immune response regulation, with inhibited flux associated with pro-inflammatory phenotypes. In the present study, we examined the effects of genetically or pharmacologically manipulating autophagy on posttraumatic neuroinflammation and motor function after SCI in mice. Young adult male C57BL/6, CX3CR1-GFP, autophagy hypomorph *Becn1*$^{+/-}$ mice, and their wildtype (WT) littermates were subjected to moderate thoracic spinal cord contusion. Flow cytometry demonstrated dysregulation of autophagic function in both microglia and infiltrating myeloid cells at 3 days (d) post-injury. Transgenic CX3CR1-GFP mice revealed increased autophagosome formation and inhibition of autophagic flux in activated microglia/macrophages. NanoString analysis using the neuroinflammation panel demonstrated

increased expression of proinflammatory genes and decreased expression of genes related to neuroprotection in *Becn1*$^{+/-}$ mice as compared to WT controls at 3d post-SCI. These findings were further validated by qPCR, wherein we observed significantly higher expression of proinflammatory cytokines. Western blot analysis confirmed higher protein expression of the microglia/macrophage marker IBA-1, inflammasome marker NLRP3, and innate immune response markers cGAS and STING in *Becn1*$^{+/-}$ mice at 3d SCI. Flow cytometry demonstrated that autophagy deficit did not affect microglial and myeloid counts at 3d post-injury but led to increased production of proinflammatory cytokines. Finally, locomotor function showed significantly worse impairments in *Becn1*$^{+/-}$ mice up to 6 weeks(w) after SCI, which was accompanied by worsening tissue damage. Conversely, treatment with an autophagy inducer trehalose, reduced protein levels of p62, an adaptor protein targeting cargo to autophagosomes as well as NLRP3, STING, and IBA-1 at 3d SCI. Continuous treatment with trehalose for up to 6w after SCI led to improved motor function recovery and reduced tissue damage as compared to control group. Our data indicate that inhibition of autophagy after SCI potentiates pro-inflammatory activation in microglia and is associated with worse functional outcomes. Conversely, increasing autophagy with trehalose, decreased inflammation and improved outcomes. These findings highlight the importance of autophagy in spinal cord microglia and its role in secondary injury after SCI.

Disclosures: **Y. Li:** None. **Z. Lei:** None. **R.M. Ritzel:** None. **J. He:** None. **H. Li:** None. **H.M. Choi:** None. **M.M. Lipinski:** None. **J. Wu:** None.

Poster

125. Spinal Cord Injury: Mechanisms of Inflammation and Pain

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 125.19

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Comisión Sectorial de Investigación Científica (CSIC-UDELAR), Uruguay
FOCEM (MERCOSUR Structural Convergence Fund), COF 03/1111
PEDECIBA, Uruguay

Title: Role of the immunoreceptor CD200R1 in neuroinflammation induced by spinal cord injury and LPS challenge

Authors: *B. PANNUNZIO[1,2], A. CAWEN[1], F. EVANS[1,3], H. PELUFFO[1,3,4], N. LAGO[1,5]; [1]Neuroinflam. and Gene Therapy Lab., Inst. Pasteur De Montevideo, Montevideo, Uruguay; [2]Dept. de Histología y Embriología, Fac. de Medicina, Univ. de la República, Montevideo, Uruguay; [3]Dept. de Histología y Embriología, Facultad de Medicina, Univ. de la República, Montevideo, Uruguay; [4]Unitat de Bioquímica i Biología Molecular, Dept. de Biomedicina, Fac. de Medicina i Ciències de la Salut, Univ. de Barcelona, Barcelona, Spain; [5]Dept. de Biologia Cel·lular, Fisiologia i Immunologia, Inst. de Neurociències, CIBERNED, Univ. Autònoma de Barcelona, Bellaterra, Spain

Abstract: The CD200 - CD200R1 interaction has been identified as a critical regulator of the immune response in several pathologies associated with the nervous system. Recently, we showed that CD200R1 plays an important role in defining the severity of the outcome after spinal cord injury (SCI) and sciatic nerve injury. Although blocking CD200R1 with an antibody after SCI induced an increased inflammatory milieu and decreased functional recovery, after sciatic nerve injury it induced both a reduction in cell infiltration and in functional recovery. In the current study we have analyzed the role of CD200R1 in local and systemic inflammation after SCI (DAMP) and LPS (PAMP) induced inflammatory challenge. First, we performed a T11 spinal cord contusion injury in mice lacking CD200R1 (KO) and wildtype mice (WT). We evaluated myeloid cells infiltration into the spinal cord at different time points. We did not find differences in the number of macrophages and microglia. However, at 3 days post injury there was a significant lower number of neutrophils in KO than in WT mice. Long term study did not show differences in the locomotor function observed by the BMS score nor in the histopathological parameters evaluated. Nevertheless, KO mice showed a higher weight loss in comparison to WT mice, suggesting systemic alterations. Under naïve conditions, blood counts showed a tendency to have lower number of white blood cells in KO animals in comparison with WT mice, in particular neutrophils and lymphocytes. Accordingly, spleen weight showed a significant lower weight in KO mice compared to WT under naïve conditions and after SCI in both sexes, being more marked in female mice. Moreover, while there was no difference in TNFα expression under naïve conditions in the spleen and spinal cord between WT and KO mice, an increase was observed 24 hours after SCI in the spleen of KO mice. We then used a second model of acute neuroinflammation triggered by Lipopolysaccharide (LPS) administration, which induces a systemic immune challenge, to evaluate whether KO mice showed an exacerbation of the inflammation. Although we did not find a difference in microglia reactivity in the cerebral cortex, we found a more severe sickness behaviour in KO mice and also reduced spleen size. This was correlated with lower blood levels of IL-27 and IL-10 acutely after LPS injection (while other cytokines such as IL1b and TNFa did not change) and a higher neutrophil blood count in KO mice when compared to WT mice. Altogether, we have observed that CD200R1-KO mice do not present increased inflammation under homeostatic conditions but display an enhanced systemic inflammatory and behavioral response to different inflammatory stimuli.

Disclosures: B. Pannunzio: None. **A. Cawen:** None. **F. Evans:** None. **H. Peluffo:** None. **N. Lago:** None.

Poster

125. Spinal Cord Injury: Mechanisms of Inflammation and Pain

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 125.20

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Wings for Life WFL-US-12/20

Title: The functional role and therapeutic potential of heme binding proteins after cervical SCI

Authors: J. PAGE[1], J. ROSAS[2], B. APERI[3], *A. KRONER-MILSCH[4];
[1]Neurosurg., [2]Neurosci. Labs, [4]Med. Col. of Wisconsin, [3]Med. Col. of Wisconsin, Milwaukee, WI

Abstract: Parenchymal hemorrhage is often observed in SCI as a result of sheared blood vessels. In spinal cord injury (SCI) patients, this is associated with worsened functional outcome. Blood and its breakdown products from lysed red blood cells, like hemoglobin, heme and iron, have pro-inflammatory and cytotoxic properties. Rapid binding and detoxification of these products is therefore critical for tissue protection and prevention of secondary damage. In the vasculature, free hemoglobin and heme are sequestered by specialized acute phase proteins, haptoglobin (Hp) and hemopexin (Hx), until complexes can be cleared by macrophages through receptor mediated endocytosis. Despite lower concentration of Hp and Hx in CNS tissue, their absence results in increased tissue and functional damage after CNS hemorrhage. Binding and neutralization of heme can also be achieved by additional heme binding proteins like alpha-1 anti-trypsin (A1AT) and alpha-1 microglobulin (A1M). These proteins have anti-inflammatory and radical scavenging properties and have been shown to improve outcome in models of intraventricular hemorrhage. Our data indicate that A1M mRNA was upregulated in the first week after SCI, before returning to baseline. A1AT, in contrast, showed later upregulation after thoracic but not cervical SCI. Expression of A1M and A1AT was primarily detectable on astrocytes after SCI To evaluate the effectiveness of A1M and A1AT in reducing cell cytotoxicity in a heme saturated cytotoxic environment in vitro, bone marrow derived macrophages (BMDM) were treated with hemin in the absence or presence of either A1M or A1AT. Our results indicate that A1AT slightly reduced cytotoxicity and ROS production. To evaluate the functional impact of A1M and A1AT in vivo, we are utilizing AAV mediated overexpression and pharmacological treatment for SCI, followed by behavioral assessment. The results of this project may provide therapeutic approaches to control hemorrhage associated secondary tissue damage and promote functional outcome after SCI.

Disclosures: **J. Page:** None. **J. Rosas:** None. **B. Aperi:** None. **A. Kroner-Milsch:** None.

Poster

125. Spinal Cord Injury: Mechanisms of Inflammation and Pain

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

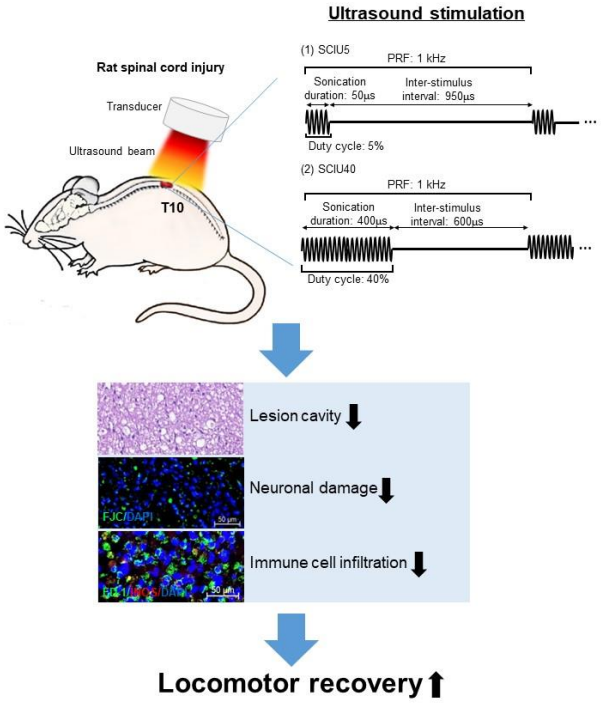
Program #/Poster #: 125.21

Topic: C.11. Spinal Cord Injury and Plasticity

Title: Ultrasound stimulation improves inflammatory resolution, neuroprotection, and functional recovery after spinal cord injury

Authors: *K.-T. KIM;
Neurosurg., Sch. of Medicine, Kyungpook Natl. Univ., Daegu, Korea, Republic of

Abstract: Rationale: Spinal cord injury (SCI) is a traumatic event associated with limited functional recovery. In this study, the effects of non-invasive ultrasound (US) treatment on behavior and inflammatory responses were evaluated in a rat model of SCI. **Methods:** Adult female Sprague-Dawley rats were subjected to spinal cord contusion injury at thoracic level T10 using an Infinite Horizon spinal cord injury impactor with 140 Kdyn. Two different US parameters (SCIU5: 5% duty cycle and SCIU40: 40% duty cycle) with an acoustic frequency of 1 MHz, pulse repetition frequency (PRF) of 1 kHz, and acoustic intensity of 0.8 W/cm^2 were applied to the rat model of SCI. The effects of US treatment on behavioral responses [A1] after SCI were quantified using the Basso, Beattie, and Bresnahan (BBB) scale and the ladder rung test. To detect tissue and neuronal responses to US sonication, H&E and Fluoro-Jade C (FJC) staining were performed. Immunofluorescence was used to detect the inflammatory markers inducible nitric oxide synthase (iNOS) and tumor necrosis factor alpha (TNF-α) secreted by the macrophage/microglia (detected by ED-1). **Results:** In the rat model of SCI, motor function was more effectively restored and the lesion cavity area was smaller in the SCIU5 group that in the sham control group. In addition, the SCIU5 protocol elicited an anti-inflammatory response at the site of injury via degenerative FJC-labeled neurons, macrophage activation, and the infiltration of microglia. As a result, the lesion area decreased and tissue density increased. The SCIU40 protocol improved motor function but did not induce an anti-inflammatory response at the site of damage. **Conclusions:** The SCIU5 protocol effectively accelerated the rate of improvement in exercise performance in the rat model of SCI and reduced inflammation. Accordingly, appropriate US stimulation could be a promising treatment modality for SCI with beneficial anti-inflammatory effects. [A1]Alternatively: locomotion or behavioral recovery.



Disclosures: K. Kim: None.

Poster

126. Spinal Cord Injury: Stimulation, Training, and Recovery

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 126.01

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Tim Reynolds Foundation
RERC #90RE5021-01-00

Title: Activity-based recovery training with neuromodulation: effect on lower extremity muscle activation

Authors: *A. BHEEMREDDY[1], K. MOMENI[3], M. RAVI[1], M. ANJARIA[1], F. ZHANG[1], R. PILKAR[2], G. F. FORREST[1];
[1]Ctr. for Spinal Stimulation, [2]Ctr. for Mobility and Rehabil. Engin. Res., Kessler Fndn., West Orange, NJ; [3]Koneksa Hlth., New York, NY

Abstract: Individuals with an incomplete chronic spinal cord injury (SCI) have significant impairment to voluntary movement of the lower extremity, limiting their overall ability to walk and to stand, therefore negatively impacting their quality of life. Spinal cord transcutaneous stimulation (scTS) with activity-based recovery training (ABRT- stand training and stepping) as well as exoskeleton training, has been shown to positively affect lower extremity muscle electromyogram (EMG) activity during gait. The underlying changes in the lower extremity motor pools and activation of lower extremity EMG after longitudinal ABRT with neuromodulation have not been reported. We hypothesize that targeted scTS will immediately affect inter and intra-limb lower extremity firing patterns during gait, and that post-training, there will also be an effect on inter and intra-limb lower extremity firing patterns without stimulation. For this study, spatial-temporal physiological mapping sessions determined individualized targeted stimulation using established site locations, stimulation frequency, waveform, and amplitude for neuromodulation parameters during training. Cathodes were placed at cervical, thoracic, lumbar, and sacral spinal sites; bilateral anterior superior iliac crests were identified as anodes. Non-ambulatory participants with incomplete SCI were recruited. Data was collected at baseline, during, and after 60 sessions of scTS with ABRT. Dependent variables included intra-limb burst duration, intra-limb EMG amplitude, and measures for intra-limb muscle co-contraction: co-inhibition (CO), co-excitation (CE), and co-activation (CA). Muscle activation of the lower limbs and trunk were collected using surface EMG electrodes (Motion Lab Systems Inc., Baton Rouge, LA). All participants' results included neuromodulation specific to the lumbar spinal cord in chronic human SCI. Integrated systematic neuromodulation at multiple sites including the lumbosacral spinal sites now has shown the ability to improve motor and gait control/function, both devastating consequences after severe SCI.

Disclosures: A. Bheemreddy: None. **K. Momeni:** None. **M. Ravi:** None. **M. Anjaria:** None. **F. Zhang:** None. **R. Pilkar:** None. **G.F. Forrest:** None.

Poster

126. Spinal Cord Injury: Stimulation, Training, and Recovery

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 126.02

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Tim Reynolds Foundation
NIDILRR (RERC #90RE5021 01 00)

Title: Effect of different anode placements and stimulation waveforms on Spinal Cord Transcutaneous Stimulation induced EMG responses after SCI

Authors: *M. RAVI[1], K. MOMENI[2], M. BAYRAM[1], F. ZHANG[1], A. BHEEMREDDY[1], M. ANJARIA[1], G. FORREST[1];
[1]Reynolds Ctr. for Spinal Stimulation, Kessler Fndn., West Orange, NJ; [2]Koneksa, New York, NY

Abstract: Spinal Cord Transcutaneous Stimulation (scTS) and Epidural Stimulation (scES) have been shown to modulate spinal sensorimotor networks for individuals with Spinal Cord Injury (SCI). Furthermore, both techniques, in combination with activity-based training have been shown to enable some sensorimotor functions such as standing, stepping and voluntary movement in individuals with SCI. Computational modeling studies have shown that both scTS and scES recruit similar neural structures. However, due to the non-invasive nature of scTS, it can be challenging to target specific motor pools for muscles or muscle groups necessary for specific tasks. In this study, we examine the differences in the induced Electromyography (EMG) responses for different anode placements (Bilateral ASIS, Clavicle and Umbilicus) and for different stimulation waveforms (Monophasic, Biphasic and Rectified). We were able to recruit individuals with SCI (both complete and incomplete) and applied scTS at select spinal levels between cervical and coccyx as cathodes. Carrier-wave frequency was set at 5 kHz for Monophasic and Biphasic waveforms (No carrier frequency for Rectified waveform). EMG was recorded at key lower limb and upper limb muscles. Systematic modulations of amplitude and frequency were performed at various spinal levels and the EMG responses to the various conditions (different anode placements, stimulation waveforms) were analyzed. The responses were analyzed by latency - Early Responses (<15ms after stimulation pulse) and Late Responses (>15ms). Results of the analyses show that certain anode placements work better than others for targeting specific motor pools as the resulting electric field is different for each anode configuration. Therefore, determining optimal anode placement and stimulation waveform could help us target specific motor pools after SCI.

Disclosures: M. Ravi: None. **K. Momeni:** None. **M. Bayram:** None. **F. Zhang:** None. **A. Bheemreddy:** None. **M. Anjaria:** None. **G. Forrest:** None.

Poster

126. Spinal Cord Injury: Stimulation, Training, and Recovery

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 126.03

Topic: C.11. Spinal Cord Injury and Plasticity

Title: Spinal cord transcutaneous stimulation modulates sensorimotor cortical activity and corticospinal excitability in able-bodied participants: a case study

Authors: *N. BRIHMAT[1], M. B. BAYRAM[1], K. MOMENI[1], M. RAVI[1], A. BHEEMREDDY[1], M. ANJARIA[1], S. H. SALEH[2], G. F. FORREST[1];
[1]Reynolds Ctr. for Spinal Stimulation, [2]Ctr. for Mobility and Rehabil. Engin. Res., Kessler Fndn., West Orange, NJ

Abstract: Spinal cord transcutaneous stimulation (scTS) is a non-invasive method with immediate and long-term positive impact on recovery and quality of life after spinal cord injury (SCI). Indeed, continuous increases in arm voluntary control and grip, with improvements in sensory function and trunk stability were observed after repeated sessions of scTS combined

with task-specific motor training in individuals with complete and incomplete SCI (Zhang et al, 2020; 2021). Brain involvement and modulation during scTS remain unclear. Using fNIRS and TMS respectively, we aim to study sensorimotor cortex (SMC) activity and corticospinal excitability (CSE) modulation in response to scTS, in comparison to sham scTS, in able-bodied (AB) participants. Preliminary data were obtained from 1 AB (male, 34 yo., right-handed). During both scTS and sham scTS sessions, separated by 2 weeks, stimulation was applied using biphasic pulses at 30 Hz (5 kHz carrier frequency) for 15 min (BioStim-5, Cosyma Inc.). For scTS, the targeted spinal site (C7/T1) and the stimulation intensity (SI, 55 mA) were identified during a mapping session, where sets of parameters were tested regarding participant' motor output and scTS tolerability. For sham scTS, the SI was set at 55 mA and gradually decreased down to 0 in less than 30 s. Real-time SMC activity was assessed using fNIRS technology (8*8 optodes, NIRSport2, NIRx Medical Technologies, LLC) during a motor task-block design (with/wo. stimulation). Before (Pre) and immediately after (Post) each session, we assessed CSE with measures of active motor threshold (AMT) and active motor evoked potential (aMEP) (performed during slight voluntary contraction of the targeted opponens pollicis (OP) muscle); intracortical inhibition with a measure of the cortical silent period ratio (cSP ratio); and OP maximal voluntary contraction (MVC). fNIRS and TMS data were analyzed using nirsLAB and TMS Analysis toolbox, respectively. As compared to sham scTS, scTS appears to increase and extend the task-related SMC activity, increase Pre to Post CSE (ΔAMT = -2%, ΔaMEP = +71%), associated with decrease of intracortical inhibition (ΔcSP ratio = -35%) and increase of OP MVC (ΔMVC = +40%) in the participant tested. These preliminary and new evidence suggest that scTS is able to induce specific changes in spinal and cortical activity and excitability in non-injured individuals, changes that may mediate the neuromodulatory processes responsible for potentiating the effects of motor training observed in SCI (Barss, 2022).

Disclosures: N. Brihmat: None. **M.B. Bayram:** None. **K. Momeni:** None. **M. Ravi:** None. **A. Bheemreddy:** None. **M. Anjaria:** None. **S.H. Saleh:** None. **G.F. Forrest:** None.

Poster

126. Spinal Cord Injury: Stimulation, Training, and Recovery

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 126.04

Topic: C.11. Spinal Cord Injury and Plasticity

Title: Retrospective comparison of different Transcranial Magnetic Stimulation hotspot hunting procedures

Authors: *M. B. BAYRAM[1,2], N. BRIHMAT[1,3], M. RAVI[1], A. BHEEMREDDY[1], M. ANJARIA[1], G. H. YUE[1,3], J. ZHONG[4], G. F. FORREST[1,3];
[1]Kessler Fndn., West Orange, NJ; [2]Acibadem Mehmet Ali Aydinlar Univ., Istanbul, Turkey; [3]Physical Med. & Rehabil., Rutgers, the State Univ. of New Jersey, Newark, NJ; [4]Weill Cornell Med. Col., Burke Med. Res. Inst., White Plains, NY

Abstract: INTRODUCTION: Transcranial Magnetic Stimulation (TMS) is a non-invasive exploratory and neuromodulatory technique, widely investigated for its therapeutical effects, notably in individuals with spinal cord injury (SCI). To target the chosen muscle, the TMS operator needs to find the so-called "hotspot" (HS) location on the scalp, preferably using a neuronavigation system. Although essential to the efficacy of the application, there is no standard algorithm for the hotspot hunting procedure. This retrospective study evaluated 1) the effect of hunting procedure of the HS location 2) the time saved by using an optimized approach.
METHODS: With a study protocol approved by the local IRB, preliminary analysis included 4 TMS sessions for 2 individuals (1 motor complete SCI and 1 able-bodied). Data collection followed the Rossini-Rothwell method; hotspot hunting needed 6 positive motor evoked potential (MEP) response out of 10 stimuli, where a positive site is considered when a criterion-based MEP amplitude (≥50 μV for resting motor threshold (MT) and 100 μV for active MT) is achieved in 6 out 10 stimulations. The TMS intensity gradually decreased until the lowest intensity was achieved for the site. Using the neuronavigation system, the TMS coil is moved around the site within a 1 cm radius until the site at the lowest intensity is found. The latter site is called the HS. If at least 6 out of 10 stimuli were positive, lowering the stimulator output to the same location was tried, then hunting around that location with different spots within a 1 cm radius was the next step in the algorithm.
Various TMS hotspot hunting procedures (3 out of 5, 4 out of 7, 5 out of 10, where the first number shows the positive response out of the total number of stimulations on the same location) were simulated using the same criterion cited above, to investigate a change of hotspot location and the time saved when using a lower number of stimulations.
RESULTS: Preliminary analysis showed that out of the 4 TMS sessions for one SCI session and one able-bodied session could have yielded the same hotspot location with all the simulated procedures. Simulation parameters showed the time saved for 3 out of 5 procedure replacing 6 out of 10 would be ~25 minutes on a typical 1-hour session.
CONCLUSION: Hunting procedures change the timing for the study protocol thus save time for both the participant and clinical/research team while stimulating less. More analysis would need to be done to verify the preliminary results.

Disclosures: M.B. Bayram: None. **N. Brihmat:** None. **M. Ravi:** None. **A. Bheemreddy:** None. **M. Anjaria:** None. **G.H. Yue:** None. **J. Zhong:** None. **G.F. Forrest:** None.

Poster

126. Spinal Cord Injury: Stimulation, Training, and Recovery

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 126.05

Topic: C.11. Spinal Cord Injury and Plasticity

Title: Effect of single and multi-site spinal stimulation for voluntary movement for motor complete SCI

Authors: *R. PILKAR[1], M. B. BAYRAM[2], M. RAVI[3], M. ANJARIA[3], G. F. FORREST[4]; [1]Ctr. for Mobility and Rehabil. Engin. Res., [2]Reynolds Ctr. for Spinal Stimulation, [3]Ctr. for Spinal Stimulation, [4]Kessler Fndn., West Orange, NJ

Abstract: Non-invasive spinal cord transcutaneous stimulation (scTS) for neuromodulating the spinal circuitry above and below a spinal lesion can improve motor control after spinal cord injury (SCI). Multimodal studies have demonstrated that scTS may enable self-assisted standing as well as facilitate overall walking and coordination in motor-complete SCI, through increased muscle activations in the lower extremities by activating locomotor networks. We have previously reported that scTS and targeted activity-based training can improve upper extremity and trunk function for individuals with motor-complete SCI. We have further shown that targeted scTS using two cohorts for cathodes can effectively neuromodulate the spinal neuronal circuitries in augmentation of voluntary-induced muscle contraction of lower extremities in a gravity-neutral position. The purpose of the current study is to extend our recent work to use more targeted cohorts and stimulation parameters to initiate and maintain volitional control during a specific and targeted lower-extremity motor task (i.e., knee extension), during tonic scTS, for motor-complete SCI. Neurophysiological mapping sessions determined targeted stimulation cohorts and parameters for voluntary initiation of motor task. The participant was in a lateral-recumbent position, legs supported in gravity-neutral position to freely move in the sagittal plane on timed cues. Bilateral surface electromyography (sEMG) recorded from lower extremity muscles at 10kHz (Motion Lab Sys) were band-pass filtered (20-350Hz) and processed using our custom-developed algorithm (EMD-notch) to provide artifact-free sEMGs. Cumulative integrated EMG values were calculated and time-normalized for comparisons. Several thoracic and lumbosacral spinal site cohorts for cathodes determined increased voluntary movement compared to our previous work. No muscle activity was observed either without voluntary intent during scTS or with voluntary intent in the absence of scTS. Previous research has shown that spinal sensorimotor networks are activated for individuals with SCI when scTS is delivered to the corresponding spinal segments (e.g. scTS in the lumbosacral regions induces self-assisted standing). Our research notes that individualized targeted spatial-temporal scTS cohorts and parameters are critical to maximizing the neuromodulatory effects. The current study demonstrates the effectiveness of targeting relevant spatial-temporal spinal networks for increased excitability to facilitate voluntary recovery for motor-complete SCI.

Disclosures: R. Pilkar: A. Employment/Salary (full or part-time):; Actigraph LLC. **M.B. Bayram:** None. **M. Ravi:** None. **M. Anjaria:** None. **G.F. Forrest:** None.

Poster

126. Spinal Cord Injury: Stimulation, Training, and Recovery

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 126.06

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIDILRR (RERC #90RE5021-01-00)
NIDILRR (ARRT #90ARHF0002)
the Tim Reynolds Foundation

Title: Assessing the Pre-Post Changes in Spinal Excitability Following Spinal Cord Transcutaneous Stimulation Combined with Activity-based Training in Individuals with Tetraplegia

Authors: *F. ZHANG, M. RAVI, A. BHEEMREDDY, J. CARNAHAN, M. ANJARIA, G. F. FORREST;
Kessler Fndn., West Orange, NJ

Abstract: Approximately 60% of individuals following spinal cord injury (SCI), an annual incidence of 54 cases per one million people in the United States, suffer from tetraplegia. For them, recovery of upper extremity (UE, arms and hands) function is ranked as the top priority. Current SCI rehabilitation therapies focus on promoting activity-dependent neuroplasticity by performing functional and activity-based training (ABT) at high intensity and high repetition. Growing evidence has demonstrated that the non-invasive spinal cord transcutaneous stimulation (scTS) can activate the spinal network and facilitate the weak or silent descending drive for restoration of motor and sensor function after SCI. The goal of this study is to quantitatively assess the pre-post changes in spinal excitability following the intervention of scTS combined with ABT in people with tetraplegia. Two individuals with chronic, neurological complete tetraplegia (American Spinal Injury Association Impairment Scale [AIS] A) completed this study. Each subject received a short-term intervention of cervical scTS combined with ABT for 60 minutes/session and 2~3 sessions/week. UE ABT was administered by physical therapists, with scTS concomitantly applied. Sub-motor-threshold, tonic scTS (rectangular pulses with 1ms duration, filled with a carrier frequency of 5kHz) was delivered at the cervical and thoracic spinal segments over the dorsal skin. Spinal excitability was evaluated at pre- and post-intervention by recording scTs-evoked potentials (EP) when participants remained in a supine position. The intensity of stimulation (1-ms pulse width and an inter-stimuli interval of 5s) was gradually increased to obtain the recruitment curve (RC) of responses for UE muscles simultaneously. Two excitability measures were extracted from the sigmoid-shaped RC: 1) excitation threshold which indicates the excitability to the initial recruitment of motoneurons, and 2) the maximum slope of RC which indicates the excitability relative to the increasing stimulation intensity. At post-intervention, both participants exhibited higher amplitudes of scTS-induced EP measured from UE motor pools, lower excitation threshold, and greater maximum slope in RC, suggesting an increased level of spinal network excitability modulated by scTS+ABT. The research findings will provide preliminary data for a larger clinical trial to understand the mechanisms underlying functional and neurological recovery.

Disclosures: F. Zhang: None. **M. Ravi:** None. **A. Bheemreddy:** None. **J. Carnahan:** None. **M. Anjaria:** None. **G.F. Forrest:** None.

Poster

126. Spinal Cord Injury: Stimulation, Training, and Recovery

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 126.07

Topic: C.11. Spinal Cord Injury and Plasticity

Support: RERC #90RE5021-01-00
Tim Reynolds Foundation

Title: Improved Gait symmetry with transcutaneous spinal cord stimulation in subjects with spinal cord injury

Authors: *M. ANJARIA[1], K. MOMENI[3], M. RAVI[1], A. BHEEMREDDY[1], F. ZHANG[1], R. PILKAR[2], G. F. FORREST[1];
[2]Ctr. for Mobility and Rehabil. Engin. Res., [1]Kessler Fndn., West Orange, NJ; [3]Koneksa Hlth., New york City, NY

Abstract: A previous study by our group showed preliminary results showcasing the usage of optimal and individualized spinal cord transcutaneous stimulation(scTS) parameters during overground gait training to facilitate more consistent gait kinematics profiles for one participant with an incomplete spinal cord injury (SCI). The goal of this study was to use the targeted scTS and training to improve spatial and temporal parameters to achieve a symmetrical gait profile. Spatial-temporal parameters and three-dimensional kinematics were evaluated for several chronic incomplete SCI participants who completed activity-based recovery training (ABRT) (stepping, stand training) and exoskeleton training with and without scTS. Multiple, targeted cohorts of scTS were delivered as part of the integrated systematic neuromodulation at the lumbosacral and thoracic spinal sites for cathodes and bilateral iliac crest for anodes. The stimulation waveforms consisted of a rectangular pulse (width of 1ms) with 5kHz carrier frequency. Individuals were tested before, at midpoint and after training. Full-body kinematics (Motion Analysis, California) were collected while participants walked overground with and without scTS. For scTS trials, when overground gait post training was compared to overground gait before training, the results showed an increase in range of motion (ROM) and a decrease in interlimb coefficient of variance for joint angles respective to targeted stimulation sites. These changes persisted with trials without stimulation, demonstrating the effectiveness of targeted scTS+ ABRT and exoskeleton training, and its sustenance post training, across the participant population. Our data indicates that stimulation with optimal and individualized parameters can lead to more effective, stable and symmetric gait patterns in participants with varied levels of SCI.

Disclosures: **M. Anjaria:** None. **K. Momeni:** None. **M. Ravi:** None. **A. Bheemreddy:** None. **F. Zhang:** None. **R. Pilkar:** None. **G.F. Forrest:** None.

Poster

126. Spinal Cord Injury: Stimulation, Training, and Recovery

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 126.08

Topic: C.11. Spinal Cord Injury and Plasticity

Support: The National Institutes of Health Roadmap Initiative, Office of Strategic Coordination – The Common Fund, Other Transactions, Stimulating Peripheral Activity to Relieve Conditions (SPARC) Program Award # OT2OD024898

Title: Impact of epidural stimulation on lower urinary tract function in rats with chronic incomplete spinal cord injuries

Authors: *N. WILKINS[1], D. MEDINA AGUINAGA[3], R. F. HOEY[2], F. KHALIFA[5], B. UGILIWENEZA[6], J. FELL[1], A. NAGLAH[5], A. EL-BAZ[5], S. J. HARKEMA[7], C. HUBSCHER[4]; [2]Anatom. Sci. and Neurobio., [1]Univ. of Louisville Sch. of Med., Louisville, KY; [3]anatomical sciences and neurobiology, [4]Dept Anatom. Sci. & Neuro, Univ. of Louisville Anatom. Sci. & Neurobio., Louisville, KY; [5]Univ. of Louisville J. B. Sch. of Engin., Louisville, KY; [6]Neurosurg., [7]KSCIRC, Univ. of Louisville, Louisville, KY

Abstract: Spinal cord injury (SCI) can have life-changing effects on lower urinary tract (LUT) function. Epidural stimulation of the lumbosacral spinal cord (scES) has demonstrated clinical effectiveness for improving both bladder compliance and reflex control of voiding. Our previous pre-clinical scES mapping studies at T13-L2, L3-4, and L5-S1 in spinally intact and T9-transected female rats further demonstrate efficacy of scES for modulating bladder storage and emptying. scES for maintaining continence or reflex voiding was applied at the same three spinal levels with two modifications: 1) female rats with clinically relevant T9 graded contusion injuries were tested; and 2) a novel miniature 15-electrode array was used to enhance stimulation specificity. The results obtained during bladder fill and void cycles conducted under urethane anesthesia indicate frequency and intensity dependent effects on void volume, inter-contractile interval (ICI), detrusor contraction, and external urethral sphincter (EUS) activation. Without stimulation, ICI was the shortest in animals with mild contusion injuries and increased in length with moderate and severe contusion injuries. Responsiveness of the LUT to scES differed based upon severity of injury, whereby contusion injuries displayed some responses similar to complete transected animals and some that were similar to spinally intact animals. Stimulation at T13 resulted in an increase in ICI in all injury severities, with the greatest change in response seen in moderately contused animals at low frequency stimulation. Stimulation at L3 resulted in a decrease in ICI in mild and severely injured animals with an increase in ICI in animals with a moderate contusion injury. Stimulation at L6 also yielded differential results with an increase in the ICI in mild and moderately contused animals yet a decrease in ICI in severely contused animals. The potential for selective activation of the LUT circuitry at multiple levels with the flexibility for adaptation to an individuals' needs adds to an accumulating body of evidence supporting scES as a singular intervention that can programmed to target multiple systems.

Disclosures: N. Wilkins: None. **D. Medina Aguinaga:** None. **R.F. Hoey:** None. **F. Khalifa:** None. **B. Ugiliweneza:** None. **J. Fell:** None. **A. Naglah:** None. **A. El-Baz:** None. **S.J. Harkema:** None. **C. Hubscher:** None.

Poster

126. Spinal Cord Injury: Stimulation, Training, and Recovery

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 126.09

Title: WITHDRAWN

Poster

126. Spinal Cord Injury: Stimulation, Training, and Recovery

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 126.10

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH Grant R01HL150581

Title: Spinal cord epidural stimulation and respiratory training in patients with chronic spinal cord injury.

Authors: *F. FATIMA[1], A. M. WILLHITE[1], I. SHEKHOVSTOV[1], B. DITTERLINE[2], C. A. ANGELI[3], E. REJC[2], S. J. HARKEMA[4], A. V. OVECHKIN[1];
[1]Kentucky Spinal Cord Injury Res. Ctr., Louisville, KY; [2]Neurolog. Surgery, [4]KSCIRC, [3]Univ. of Louisville, Louisville, KY

Abstract: Spinal cord epidural stimulation and respiratory training in patients with chronic spinal cord injury.Authors*F. FATIMA[1,3], A. WILLHITE[1,3], I. SHEKHOVSTOV [1,3], B. DITTERLINE[1,3], C. ANGELI[1,2,3], E. REJC[1,3], S. HARKEMA[1,2,3], A. OVECHKIN[1,3].[1]Kentucky Spinal Cord Injury Research Center, University of Louisville, Louisville, KY; [2]Frazier Rehab Institute, UofL Health, Louisville, KY, Departments of [3]Neurological Surgery, University of Louisville, Louisville, KY **Abstract*Introduction*:** Due to the compromised spinal respiratory motor activity, respiratory complications are listed as the leading causes of morbidity and mortality in individuals with chronic spinal cord injury (SCI). However, there is no effective rehabilitation strategy that has been established for these abnormalities. We demonstrated previously that application of lumbosacral spinal cord epidural stimulation (scES) specifically configured to target cardiovascular (CV-scES) and voluntary trunk motor (Vol-Trunk-scES) control(s) can positively affect both cardiovascular and respiratory functional outcome measures. We hypothesized that Respiratory Training (RT) combined with optimally configured scES for respiration (Resp-scES) is effective rehabilitative approach to restore respiratory motor function after injury.***Methods:*** Resp-scES optimization was based on pulmonary functional changes assessed from 13 individuals with motor-complete SCI above T1 with CV-scES (n=7) and Vol-Trunk-scES (n=6) configurations. Spirometry measures (Forced Vital Capacity /FVC/; Forced Expiratory Volume in 1 sec /FEV_1/; Maximum Inspiratory and Expiratory Pressure /PI_{max} and PE_{max}/ have been compared between the pre- and post-intervention timepoints. Following randomization, four participants have been assessed

after 40 sessions of RT alone, Resp-scES alone, and when the Resp-scES was combined with RT.***Results:*** Overall, respiratory functional values were increased in all participants with a pronounced increase in Resp-scES+RT group.***Conclusion:*** The results of this pilot study indicate that traditional rehabilitative approaches combined with neuromodulation in the form of scES can facilitate respiratory-cardiovascular remodeling in individuals with chronic SCI.

Disclosures: F. Fatima: None. **A.M. Willhite:** None. **I. Shekhovstov:** None. **B. Ditterline:** None. **C.A. Angeli:** None. **E. Rejc:** None. **S.J. Harkema:** None. **A.V. Ovechkin:** None.

Poster

126. Spinal Cord Injury: Stimulation, Training, and Recovery

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 126.11

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH SPARC award OT2OD024898
ES_BI-2017, Christopher and Dana Reeve Foundation
University of Louisville Foundation
Kessler Foundation
APL Internal Research and Development

Title: Development of automated spinal cord epidural stimulation to modulate cardiovascular function in people with spinal cord injury

Authors: *B. CHRISTIE[1], H. LEDBETTER[2], S. WANG[2], C. A. ANGELI[2], B. DITTERLINE[3], G. F. FORREST[5], E. C. JOHNSON[1], S. J. HARKEMA[4], F. V. TENORE[1];
[1]Johns Hopkins Univ. Applied Physics Lab., Laurel, MD; [3]Neurolog. Surgery, [4]KSCIRC, [2]Univ. of Louisville, Louisville, KY; [5]Kessler Fndn., West Orange, NJ

Abstract: Spinal cord injury (SCI) can not only restrict sensory and motor function, but it can also have a profound impact on the autonomic nervous system. This often manifests in orthostatic hypotension: dangerously low and unstable blood pressure when changing postures [Krassioukov et al. 2009]. Chronic orthostatic hypotension can result in reduced cognitive function, decreased quality of life, increased risk of stroke, and can be life threatening, yet there are few viable treatment options. A newer approach, spinal cord epidural stimulation (scES), can regulate systolic blood pressure (SBP) in people with SCI [Harkema et al. 2018]. Despite the vast potential of scES, stimulation paradigms are highly patient-specific. To make this treatment option available to a larger population, it is critical to develop a technique that does not require close supervision by experts. Our goal was to develop an algorithm that produces patient-specific stimulation paradigms that closely mimic paradigms developed by experts.
To date, we have performed an offline analysis using datasets collected from four people with cervical-level SCI that have epidural stimulators (16 electrode-array; Medtronic) implanted over spinal segments L1 to S1. In the lab, clinicians can regulate SBP by modulating various

stimulation parameters to keep the target SBP within 110-120 mmHg. Each dataset contained two hours of data, during which SBP and stimulation parameters were recorded.
For simplicity, and because of the offline nature of the computations, we focused the algorithm on the modulation of pulse amplitude (PA) only. We observed that increases in PA resulted in increases in SBP, and each dataset contained between 13-56 PA adjustments. To closely mimic the clinician's approach, we extracted the median PA change for each dataset. We then ran optimization analyses to determine how long to wait before increasing or decreasing PA in response to low and high SBP, respectively. We found differences between datasets, but typically waiting ~60 sec produced the lowest error (the difference between algorithmic PA and clinician-driven PA). Overall, the stimulation paradigm of the algorithm closely tracked that of the clinician: the mean Pearson correlation coefficient was 0.95.
Our preliminary results indicate that the use of algorithmic stimulation to regulate SBP may be a suitable approach for minimizing assistance required from clinicians. The development of a more generalizable approach for improving cardiovascular function has the potential to make scES more accessible. The next steps of this work are to make the algorithm robust to external perturbations, such as changes in posture.

Disclosures: **B. Christie:** None. **H. Ledbetter:** None. **S. Wang:** None. **C.A. Angeli:** None. **B. Ditterline:** None. **G.F. Forrest:** None. **E.C. Johnson:** None. **S.J. Harkema:** None. **F.V. Tenore:** None.

Poster

126. Spinal Cord Injury: Stimulation, Training, and Recovery

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 126.12

Topic: C.11. Spinal Cord Injury and Plasticity

Support: New York State Spinal Cord Injury Research Board under Grant C31290GG
Christopher and Dana Reeve Foundation
Kessler Foundation
Leona M. & Harry B. Helmsley Charitable Trust
UofL Health - University of Louisville Hospital
Medtronic Plc

Title: Upright reactive postural responses promoted by epidural stimulation in individuals with motor complete SCI are enhanced when upper limbs are not used for self-balance assistance

Authors: *E. REJC[1], C. D. BOWERSOCK[1], T. PISOLKAR[1], X. AI[2], C. ZHU[2], C. A. ANGELI[1], S. AGRAWAL[2], S. J. HARKEMA[1];
[1]Kentucky Spinal Cord Injury Res. Ctr., Univ. of Louisville, Louisville, KY; [2]Columbia Univ., New York, NY

Abstract: Objective. Individuals with severe spinal cord injury (SCI) regularly implement self-balance assistance while standing and walking overground with spinal cord epidural stimulation (scES), placing their hands on assistive devices such as walker or standing frame. In this study, we assessed the effect of self-balance assistance on upright postural responses to trunk perturbations in five individuals with motor complete SCI receiving scES. Methods. Lateral, front, and back perturbations were delivered by a robotic upright stand trainer (RobUST) while participants were standing (i) with their hands on fixed handlebars for self-balance assistance (hands-on), or (ii) with their hands off the handlebars (free-hands). Trunk displacement, ground reaction forces, and bilateral EMG activity of the vastus lateralis (VL), medial hamstring (MH), tibialis anterior (TA), and medial gastrocnemius (MG) were collected and analyzed. Results: Standing with free-hands resulted in postural responses that were collectively more appropriate and robust than with hands-on. Lateral perturbations with free-hands resulted in greater percent change from baseline in ipsilateral loading and contralateral unloading (10% and 24% greater, respectively; $p<.001$) compared to hands-on. Similarly, with free-hands, a greater percent change from baseline in horizontal forces was observed for front (16%; $p=.04$) and back (7%; $p=.09$) perturbations. During lateral perturbations with free-hands, an increase in baseline EMG amplitude was more frequent and larger for ipsilateral VL and MG (33%, 27% $p<.01$) compared to hands-on, and a decrease in baseline EMG amplitude was more frequent and larger for contralateral VL, MH and TA (25%, 16%, 10%; $p<.03$). Also, activation of contralateral muscles was more frequent during lateral hands-on perturbations. During front perturbations, larger increase in baseline EMG amplitude was observed with free-hands for bilateral VL and MH (35%, 27% $p<.01$). No muscle response trends comparing free-hands and hands-on were observed during back perturbations. Further, similar lower limb muscle synergies were observed with free-hands and hands-on. However, the contribution of these synergies was substantially perturbation direction-dependent with free-hands, whereas it was independent of perturbation direction with hands-on. Conclusion: Upright postural responses to trunk perturbations were enhanced while standing with free-hands. Upright postural control with free-hands enabled by RobUST and scES has the potential to improve future activity-based training paradigms and assessments of upright postural control in individuals with paralysis.

Disclosures: E. Rejc: None. **C.D. Bowersock:** None. **T. Pisolkar:** None. **X. Ai:** None. **C. Zhu:** None. **C.A. Angeli:** None. **S. Agrawal:** None. **S.J. Harkema:** None.

Poster

126. Spinal Cord Injury: Stimulation, Training, and Recovery

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 126.13

Topic: C.11. Spinal Cord Injury and Plasticity

Support: DoD Grant SC190100

Title: Case report of bladder and bowel responses to lumbosacral epidural stimulation in a female Yucatan minipig

Authors: *D. MEDINA AGUIÑAGA[1], C. KNIBBE[2], R. U. AHMED[3], M. MORGAN[4], S. E. DAVISON[4], D. R. HOWLAND[5], M. BOAKYE[6], M. CHOPRA[7], K. JOSHI[3], C. H. HUBSCHER[1];
[1]Univ. of Louisville Anatom. Sci. & Neurobio., Louisville, KY; [2]Univ. of Louisville, Union, KY; [3]Kentucky Spinal Cord Injury Res. Ctr., [5]Kentucky Spinal Cord Injury Res. Center, Depts of Neurolog. Surgery, Anat, [6]Neurosurg., [4]Univ. of Louisville, Louisville, KY; [7]Univ. of Louisville Kentucky Area Hlth. Educ, Louisville, KY

Abstract: Lower urinary tract (LUT) and bowel dysfunctions are ranked as major concerns of the spinal cord injury (SCI) population. Toileting management includes a combination of catheterization and pharmacological approaches for voiding as well as laxatives and digital stimulation for defecation. Promising results from individuals receiving spinal cord epidural stimulation (scES) for motor control or cardiovascular regulation have off-target improvements in urinary and colorectal functions. Pre-clinical (rat) and clinical scES experiments specifically targeting the lumbosacral circuitries for bladder/bowel have shown improvements in urinary and defecatory related functions. Larger animal models offer additional advantages for studies having translational potential. Yucatan minipigs have been considered ideal for preclinical model systems in spinal cord injury research and more recently, for the study of the LUT and colorectal functions. In the current pre-clinical study, the lumbo-sacral spinal cord was mapped with scES at different frequencies and intensities to explore the optimal spinal cord segments and stimulation parameters to trigger specific bladder and bowel responses. Using a 16-electrode array (Medtronic), different scES combinations, in terms of intensity (0.5, 1, 1.5, 2 and 2.5V) and frequency (5 or 10Hz), as well as different electrode configurations were applied from L1 to S1 level in acute anesthetized terminal preparation using a urinary bladder pressure sensor and intrarectal pressure sensors at 15, 10 and 5cms in one non-injured female Yucatan minipig. Unilateral electrode configurations evokes weak responses in both urinary bladder and rectum contractions. Bilateral 10Hz stimulation using all the stimulation pads triggers noticeable contractile responses on the urinary bladder at L3 level and in colon at L6-S1. Significant voltage dependent movements were noticed in the abdominal wall, pelvic area, and hind limbs. The appearance of collateral muscle activation was avoided by using just two pads as cathodes and two as anodes with a pair of inactive pads in between. This configuration allows to increase the frequency to 20Hz and the voltage up to 2.5 Volts without any undesirable movement. Colon contractions up to 35mmHg were observed with 20Hz-2.5V stimulation at S1 level. Meanwhile the urinary bladder had contractions up to 10mmHg in amplitude with stimulation at the L3 level with the same parameters. Neuromodulation with scES at mid-lumbar and upper sacral spinal levels selectively targets the nuclei involved with urinary bladder and rectal activation triggering noticeable and relevant contractile responses in both organs.

Disclosures: D. Medina Aguiñaga: None. **C. Knibbe:** None. **R.U. Ahmed:** None. **M. Morgan:** None. **S.E. Davison:** None. **D.R. Howland:** None. **M. Boakye:** None. **M. Chopra:** None. **K. Joshi:** None. **C.H. Hubscher:** None.

Poster

126. Spinal Cord Injury: Stimulation, Training, and Recovery

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 126.14

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NICHD Award #2R01HD080205
NIH Roadmap Initiative - Office of Strategic Coordination, Other Transactions, SPARC Program Award # OT2OD024898
Christopher and Dana Reeve Foundation
Leona M. & Harry B. Helmsley Charitable Trust
University of Louisville Hospital
Medtronic Inc.

Title: Regulation of cardiovascular responses to bladder distension with spinal epidural stimulation in individuals with chronic spinal cord injury

Authors: *C. HUBSCHER[1], A. HERRITY[2], J. WYLES[2], S. WANG[2], S. HARKEMA[2]; [1]Anatom. Sci. & Neurobio., [2]Kentucky Spinal Cord Injury Res. Ctr., Univ. of Louisville, Louisville, KY

Abstract: Bladder distention has been identified as a primary trigger of autonomic dysreflexia (AD) in individuals with spinal cord injury (SCI) at cervical and upper thoracic levels (majority of population), with systolic blood pressure (SBP) rising more than 20 mmHg and remaining elevated with intolerable symptoms (pounding headache and/or chills, for example).The current study examined control of blood pressure during bladder filling with neuromodulation in six SCI individuals previously implanted with a spinal cord epidural stimulation (scES) electrode array. Application of scES with a neurostimulator attached to a 16-electrode array for maintenance of low bladder and normative blood pressure was first examined in a controlled lab setting during filling cystometry by interactively identifying optimal stimulation parameters (cathode/anode configuration, stimulation frequency and voltage). Intersystem training efficacy was then tested in the lab for six-hour periods during natural bladder filling. A total of six research participants with C4-T2 levels of SCI were mapped (5 males/1 female; average age 29 years; average time since injury 6 years). Non-void contractions with or without episodes of incontinence occurred at low fill volumes at baseline (pre-scES) with sharp rises in SBP with one or more of the following symptoms: chills, tingling, headache, flushing, perspiration. Effective scES programs consisted of multiple cohorts targeting the detrusor to maintain a low bladder pressure below 10 cmH_2O during filling and maintaining normative SBP (110-120 mmHg). During natural filling using the scES program optimized during prior mapping, participants experienced reductions of SBP with fewer episodes of incontinence. The ability to maintain low filling pressure and prevent AD allows for increased storage, which translates to greater capacity and reduced frequency of catheterizations, thus improving bladder management, overall health, and quality of life. A major advantage of scES is the versatility of the multi-electrode array and the ability to activate multiple spinal cord regions and associated functions with a single electrode placement and device using numerous cohorts simultaneously.

Disclosures: C. Hubscher: None. **A. Herrity:** None. **J. Wyles:** None. **S. Wang:** None. **S. Harkema:** None.

Poster

126. Spinal Cord Injury: Stimulation, Training, and Recovery

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 126.15

Topic: C.11. Spinal Cord Injury and Plasticity

Support: 2016PG-MED001, Leona M. & Harry B. Helmsley Charitable Trust
ES_BI-2017, Christopher and Dana Reeve Foundation
University of Louisville Hospital
Medtronic Plc

Title: Immediate effect of lumbosacral spinal cord epidural stimulation on cerebral blood flow regulation during orthostatic stress in individuals with chronic spinal cord injury

Authors: S. WANG[1,2], J. M. WECHT[3,4], B. LEGG DITTERLINE[1,2], G. F. FORREST[5,6], O. BLOOM[7,8], A. V. OVECHKIN[1,2], S. J. HARKEMA[1,2,9], J. D. GUEST[10];
[1]Kentucky Spinal Cord Injury Res. Ctr., [2]Dept. of Neurolog. Surgery, Univ. of Louisville, Louisville, KY; [3]Spinal Cord Injury Res., James J Peters VA Med. Ctr., Bronx, NY; [4]Icahn Sch. of Med. at Mount Sinai, New York, NY; [5]Kessler Fndn., West Orange, NJ; [6]Physical Med. & Rehabil., Rutgers New Jersey Med. School, Rutgers, the State Univ. of New Jersey, Newark, NJ; [7]Mol. Medicine; Physical Med. and Rehabil., The Feinstein Inst. For Med. Res., Manhasset, NY; [8]Zucker Sch. of Med. at Hofstra Northwell, Hempstead, NY; [9]Frazier Rehab Inst., Louisville, KY; [10]Neurolog. Surgery/Miami Project to Cure Paralysis, Univ. of Miami Miller Sch. of Med., Miami, FL

Abstract: Introduction: Orthostatic hypotension (OH), defined as a substantial drop in arterial blood pressure (BP) when assuming an upright position, commonly occurs after spinal cord injury (SCI). OH can cause cerebral hypo-perfusion and is difficult to manage. Controlled tilt is able to provoke OH and is limited by clinical symptoms of reduced cerebral bloof flow. We previously showed that lumbosacral spinal cord epidural stimulation (scES), optimized for cardiovascular function (CV-scES), specifically optimized to stablize BP, mitigates OH in individuals with chronic SCI. This study evaluated the immediate effects of CV-scES on cerebral blood flow velocity (CBFv). **Methods:** Ten individuals with chronic cervical SCI and OH or chronic low BP had a 16-electrode array implanted over the lumbosacral spinal segments. Personalized stimulation parameters were identified to maintain systolic BP between 110-120 mmHg. Orthostatic tolerance was tested with a 70° head-up tilt maneuver lasting up to 30 minutes, with and without CV-scES. Beat-to-beat CBFv at the middle cerebral artery and BP at the finger were monitored simultaneously. Stability measure of BP and CBFv (magnitude and rate of deviation from normative systolic BP, or from supine systolic CBFv), and cerebrovascular pulsatility index [(systolic minus diastolic) devided by mean CBFv] were calculated. Dynamic buffering of BP oscillations by cerebro-autoregulation was evaluated by using phase synchronization index derived from wavelet decomposition analysis. **Results:** Compared to tilt without stimulation, CV-scES increased tilt time (10±3 vs. 30±0 minutes),

reduced the fall in systolic BP (-45±9 vs. -4±17 mmHg), mean BP (-28±4 vs. -2±4 mmHg) and mean CBFv (-16±2 vs. -8±1 cm/s) and improved autoregulation of CBFv across participants, manifesting in two distinct patterns: (Group 1) increased stability of systolic CBFv without change in pulsatility index, and (Group 2) reduced pulsatility index without change in systolic CBFv stability. Dynamic buffering of BP oscillations within the sympathetically mediated ultra-low-frequency range (0.025-0.03 Hz) during heat-up tilt was more impaired in Group 1 compared to Group 2, which was improved by acute CV-scES. **Conclusions:** The maintenance of BP that rapidly follows CV-scES initiation during orthostatic stress is associated with improved cerebral blood flow regulation and prolonged orthostatic tolerance in individuals with chronic cervical SCI.

Disclosures: S. Wang: None. **J.M. Wecht:** None. **B. Legg Ditterline:** None. **G.F. Forrest:** None. **O. Bloom:** None. **A.V. Ovechkin:** None. **S.J. Harkema:** None. **J.D. Guest:** None.

Poster

126. Spinal Cord Injury: Stimulation, Training, and Recovery

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 126.16

Topic: C.11. Spinal Cord Injury and Plasticity

Support: ES_BI-2017, Christopher and Dana Reeve Foundation

Title: Sitting postural improvements promoted by spinal cord epidural stimulation following cervical motor complete spinal cord injury

Authors: *K. JOSHI[1], C. A. ANGELI[1,3], S. J. HARKEMA[2,3], E. REJC[2];
[1]Kentucky Spinal Cord Injury Res. Center; Bioengineering, [2]Kentucky Spinal Cord Injury Res. Center; Dept. of Neurolog. Surgery, Univ. of Louisville, Louisville, KY; [3]Frazier Rehab Inst., Louisville, KY

Abstract: Past evidence suggests that spinal cord epidural stimulation (scES) in individuals with spinal cord injury (SCI) lead to improvement in trunk stability during tall-sit (Gill et al., 2020). Improved trunk control along with better sitting posture was also observed as a result of transcutaneous electrical stimulation (Rath et al., 2018).
Seven individuals with chronic motor complete cervical SCI (Age: 36.8 ± 10.8 yrs; time post-injury: 15.4 ± 11.3 yrs) who had an scES unit implanted were asked to perform a 5-minute tall-sit in two conditions: without stimulation and with optimal trunk-specific scES. They were instructed to complete the activity without their hands or trunk being supported, but were allowed to put their hands down if needed. Trainers were also present to provide trunk support when necessary. Full-body kinematics including 3D locations of markers at five different spine levels (Sacrum, L1, T10, T3/T4, and C3/C4) was acquired and later post-processed. Vertical inclination of the lowest spine segment (Sacrum to L1) and the uppermost spine segment (T3/T4 to C3/C4) were calculated. Duration of trunk assistance, by trainers or placing hands on the mat,

along with frequency of independence changes were also noted.
Results obtained from spine marker sagittal plane data were compared for without and with scES. The mean lower spine inclination without scES was -10.26° with a range of -17.20° to 1.07° and the mean upper spine inclination was 56.58° with a range of 39.35° to 65.53°. With scES, the mean lower inclination decreased to -9.25° with a range of -16.42° to 1.22°. Mean upper inclination also decreased to 54.42° with a range of 34.22° to 60.36°. Fraction of duration of trunk independence increased from 81.5% to 85.57% when scES was applied. Without scES, the distribution of level of assistance was 62.76% hands down only, 0.05% trunk only, and 32.53% trunk assisted with hands on mat. This distribution skewed towards only hands down assistance for 96.74% of the total assistance duration when scES was applied as trunk assistance was required only for 3.26%. Frequency of independence changes per individual also decreased from 12.14 to 0.43.
These results suggest that individuals with SCI were able to gain immediate improvements in posture in the presence of scES whilst only needing lower levels of trunk assistance. The trunk-specific scES targets large muscle groups in the lower abdomen that are responsible for trunk extension, which could have led to better lower spine posture. These results provide evidence for a potential intervention to improve seated posture in individuals with motor complete cervical spinal cord injury.

Disclosures: K. Joshi: None. **C.A. Angeli:** None. **S.J. Harkema:** None. **E. Rejc:** None.

Poster

126. Spinal Cord Injury: Stimulation, Training, and Recovery

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 126.17

Topic: C.11. Spinal Cord Injury and Plasticity

Support: R01 NS048425
R01 NS091031

Title: Changes in C fiber function following a small spinal lesion affecting dexterity in primates

Authors: *K. M. FISHER, M. KLUKINOV, C. PACHARINSAK, M. CROWLEY, B. FRANCO, M. ZHANG, D. YEOMANS, C. DARIAN-SMITH;
Stanford Univ., Stanford Univ., Stanford, CA

Abstract: Chronic pain is common following spinal cord injury and notoriously intractable. Dorsal rhizotomy has long been a treatment option, but its effectiveness is mixed, and patients often report initial pain relief, followed by hypersensitivity and pain resurgence in the months/years after surgical intervention. To determine the etiology of this form of neuropathic pain, we have begun to investigate C fiber function in macaque monkeys, both before and after focal dorsal root/dorsal column lesions (DRL/DCL) that affect only the thumb, index and middle fingers of one hand. Two measures of C fiber function were obtained at different timepoints over

the first year post-injury. First, we used laser pulse selective stimulation of C fiber thermonociceptors in glabrous skin of the digits in 3 DRL/DCL animals to determine changes in sensitivity over the first 3-6 mo post-injury. Withdrawal reflexes were elicited with 2s pulses from a diode infrared laser (980nm wavelength). During testing sessions, monkeys were lightly anesthetized with IV propofol. Second, in a larger group of animals (n=10; controls, DRL/DCL animals: 1 wk, 4-5 mo, 6 mo & 1 yr post-lesion), we looked at immunolabeling for calcitonin gene-related peptide (CGRP) in the dorsal horn of the spinal cord. CGRP is expressed in C fiber central terminals and is typically abundant in layers I and II. Surprisingly, we observed no change to C fiber thresholds in the affected digits during the first 9 days post-lesion. However, by 2 wk post surgery, C fiber thresholds were significantly higher in the affected digits, and this increase persisted for at least 6 mo. Correspondingly, CGRP intensity was unaltered at the 1 wk timepoint, but a significantly lower density of CGRP staining was observed on the lesioned side of the cord in monkeys sampled 4-5 mo-1 yr post-injury. These results suggest that following a focal DRL/DCL, when we know C fibers are lost, there is a period of 1-2 weeks before diminished C fiber nociception or terminal density is detectable. Once impairment was measurable in our animals, there was no evidence of C-fiber recovery within the 1 yr time period studied. Whether this deficit is permanent, or precedes C fiber regeneration and sensitization after 1 year, remains unclear.

Disclosures: K.M. Fisher: None. **M. Klukinov:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Pending grant R01 NS131176-01, testing intranasal oxytocin in post-traumatic headache, DOD (CDMRP) grant 13113162, impact of estrogen on analgesia effect of oxytocin. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); NewBio. **C. Pacharinsak:** None. **M. Crowley:** None. **B. Franco:** None. **M. Zhang:** None. **D. Yeomans:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Pending grant R01 NS131176-01, testing intranasal oxytocin in post-traumatic headache, DOD (CDMRP) grant 13113162, impact of estrogen on analgesia effect of oxytocin. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Material transfer of lidocaine patches from Scilex Pharma. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Stock ownership: Tonix Pharmaceuticals, SiteOne, NewBio, Cytonics; Patents: numerous, Royalties for US Patent 8,198,240. F. Consulting Fees (e.g., advisory boards); Tonix Pharmaceuticals. **C. Darian-Smith:** None.

Poster

126. Spinal Cord Injury: Stimulation, Training, and Recovery

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 126.18

Topic: C.11. Spinal Cord Injury and Plasticity

Support: MCW Project 3309719
MCW Project FP18576

Title: Sensory cortical-locomotor pathway restores walking after spinal cord injury

Authors: *C. DOLICK[1], D. GRAHAM[1], A. KRONER-MILSCH[1], C. M. OLSEN[2], S. GOSGNACH[3], K. SATKUNENDRARAJAH[1];
[1]Neurosurg., [2]Neurosci. Res. Ctr., Med. Col. of Wisconsin, Milwaukee, WI; [3]Physiol., Univ. of Alberta, Edmonton, AB, Canada

Abstract: Spinal cord injury (SCI) often results in significant locomotor impairments. There is a dire need for approaches that promote functional restoration below the level of injury since current treatment options are limited. To date, motor cortex stimulation has produced minimal improvements in functional recovery after SCI, likely because contusion injuries entirely disrupt the main corticospinal pathways. We have previously shown that the primary somatosensory cortex (SI) has direct neural control over the lumbar locomotor central pattern generator through cervical excitatory interneurons (SI locomotor pathway) independent of the motor cortex. Here we demonstrate the input-output architecture of the cervical projecting SI pyramidal neurons, and that part of this SI-locomotor circuitry is preserved after thoracic SCI. By implementing in vivo calcium imaging, we identify SI neurons that are involved in locomotor initiation and maintenance of movement. Finally, we use optogenetics, and an intersectional viral approach, to selectively stimulate the SI pyramidal neurons that project to the cervical spinal cord (SI-cervical pyramidal neurons) after SCI and demonstrate their activation promotes significant locomotor recovery without adverse effects on movement, such as loss of balance or pain. Importantly, we demonstrate that the recovered locomotor function after SCI is attributed to the neuromodulation of this pathway. In conclusion, neuromodulation of the novel SI locomotor pathway enhances movement, and emerges as a promising therapeutic approach for promoting locomotor recovery after SCI.

Disclosures: C. Dolick: None. **D. Graham:** None. **A. Kroner-Milsch:** None. **C.M. Olsen:** None. **S. Gosgnach:** None. **K. Satkunendrarajah:** None.

Poster

126. Spinal Cord Injury: Stimulation, Training, and Recovery

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 126.19

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Office of the Assistant Secretary of Defense for Health Affairs, Spinal Cord Injury Research Program (W81XWH-18-1-0807) to JWG
Project grant R01NS122888

Title: Pentobarbital anesthesia after spinal cord injury (SCI) blocks hemorrhage induced by stress

Authors: *J. DAVIS[1], R. BAINE[2], M. M. TARBET[2], T. JOHNSTON[2], G. GIDDINGS[2], H. BOURLAND[2], G. N. FAUSS[2], S. R. PARTIPILO[2], J. W. GRAU[2];
[1]Neurolog. Surgery, Univ. of California, San Francisco, San Francisco, CA; [2]Texas A&M Univ., College Station, TX

Abstract: Recent work suggests that brain systems may fuel tissue loss after spinal cord injury (SCI). Evidence for this comes from studies examining the effect of engaging pain (nociceptive) pathways in rats that have undergone a lower thoracic contusion injury. Noxious stimulation a day after injury fosters hemorrhage, expands the area of secondary tissue loss, and undermines long-term recovery. Cutting communication with the brain by means of a surgical transection, or by slowly infusing a local anesthetic (lidocaine) rostral to injury, blocks these effects. Further, inhibiting brain activity prior to noxious stimulation, using a general anesthetic, also has a protective effect.
The present study explores whether placing animals in a state akin to a medically-induced coma soon after a contusion injury has a protective effect. Rats in Experiment 1 received a lower thoracic injury and were maintained in an anesthetic state for 12 hrs with pentobarbital. Tissue was then collected and assessed for hemorrhage. Controls were treated the same, but received vehicle. Because hemorrhage has been linked to a rise in blood pressure, half of the animals were placed in restraining tubes and underwent blood pressure testing during the recovery period. Animals in Experiment 2 were treated the same except that tissue was collected 12 hrs after the cessation of pentobarbital treatment. In both experiments, pentobarbital anesthesia lowered blood pressure. Vehicle treated animals that underwent restraint and blood pressure testing exhibited greater hemorrhage. This stress-induced hemorrhage was blocked by pentobarbital anesthesia. The results imply that immobilization after SCI injury can promote tissue loss/hemorrhage. Inducing a state of anesthesia can block this effect. We are in the process of cross-validating these results in other models of stress after SCI.

Disclosures: J. Davis: None. **R. Baine:** None. **M.M. Tarbet:** None. **T. Johnston:** None. **G. Giddings:** None. **H. Bourland:** None. **G.N. Fauss:** None. **S.R. Partipilo:** None. **J.W. Grau:** None.

Poster

126. Spinal Cord Injury: Stimulation, Training, and Recovery

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 126.20

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Research Center Network for Realization of Regenerative Medicine by AMED Japan under grant nos. JP22bk0104114

Title: Microenvironmental modulation via human stem cell transplantation enhances functional recovery after chronic transection spinal cord injury

Authors: *S. HASHIMOTO[1,2], N. NAGOSHI[1], T. SHIBATA[1,2], M. SHINOZAKI[2], H. OKANO[2], M. NAKAMURA[1];
[1]Dept. of Orthopaedic Surgery, [2]Dept. of Physiol., Keio Univ. Sch. of Med., Tokyo, Japan

Abstract: INTRODUCTION
While rapid advances in regenerative medicine for spinal cord injury (SCI), most of this research targeted subjects of incomplete injury at early stages. Given the demographic background, the majority are in the chronic phase of severe damage, and therefore, the development of treatments for this situation is becoming fundamentally important. Here, we hypothesized that environmental modulation at chronic transected SCI contributed to functional recovery by using clinical-relevant hepatocyte growth factor (HGF)-releasing scaffold with human stem cell transplantation (TP).
METHODS
Collagen scaffold were established to release HGF for a few weeks in chronic complete SCI rat model. First, the scaffold containing HGF was implanted surgically into lesion epicenter 42 days after complete SCI (chronic phase) to confirm the effect of our scaffold on modifying spinal cord microenvironment around lesion. Protein quantifications, histological analyses, and single nuclei RNA expression analysis were conducted 7 days after scaffold implantation. To assess the effectiveness of combination therapy of HGF-releasing scaffold and TP, human stem cells were transplanted into the epicenter 49 days after SCI. Histological analyses, WGA trans-synaptic tracing were conducted 42 days after transplantation. Motor functional restoration were assessed by the Basso, Beattie and Bresnahan (BBB) score and motor evoked potentials (MEP). Urinary functions were also histologically evaluated by the thickness of bladder wall.
RESULTS
Tissue analysis 7 days after scaffold implantation showed sustained HGF release, promoted vascularization, anti-inflammatory effects (elevation of neuroprotective microglia/macrophage, reduction of TNF-α and TGF-β), neuroprotective effect (elevation of BDNF), and endogenous axonal regrowth, which involved the activation of microglia/macrophage, meningeal cell and astrocyte. Combination therapy of HGF-releasing scaffold and transplantation increased the graft cell viability, host neuronal elongation beyond the lesion, and also decreased scar tissues. The synaptic formation between host and graft neurons was observed by WGA trans-synaptic tracing and immunoelectron microscopy. In addition, locomotor and urinary functional recovery was confirmed by BBB score, MEP and bladder wall thickness.
CONCLUSION
We demonstrated that motor and urinary functional recovery was achieved after microenvironmental modulation with hNS/PCs-transplantation even in chronic transected injury. The present study emphasized possibility of human application by using combination of these three clinical-relevant materials.

Disclosures: S. Hashimoto: None. **N. Nagoshi:** None. **T. Shibata:** None. **M. Shinozaki:** None. **H. Okano:** None. **M. Nakamura:** None.

Poster

126. Spinal Cord Injury: Stimulation, Training, and Recovery

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 126.21

Topic: C.11. Spinal Cord Injury and Plasticity

Support: JP20bm0204001
JP19bm0204001
JP18bk0104017

Title: Relationship between the preliminary MRI and the effect of stem cell therapy in spinal cord-injured mice.

Authors: *M. SHINOZAKI[1], N. NAGOSHI[2], J. HATA[3], M. NAKAMURA[4], H. OKANO[2]; [1]Keio Univ. Sch. of Med., Dept. of Physiology, Keio Univ. Sch. of Med., Shinjuku-Ku, Tokyo, Japan; [2]Keio Univ. Sch. of Med., Keio Univ. Sch. of Med., Tokyo, Japan; [3]Keio Univ. Sch. of Medicine, Tokyo, Japan, Shinjuku-ku, Tokyo, Japan; [4]Keio Univ., Keio Univ., Tokyo, Japan

Abstract: After spinal cord injury (SCI), spontaneous recovery is limited, and the sequelae are serious. In recent years, various new treatments have been developed, and not a few clinical studies have also been launched. The effect of those treatments generally depends on the timing of treatment and the degree of injury. While complete and chronic phase-SCI is most resistant to therapies, some reports have reported that remarkable therapeutic effects are sometimes achieved with those severe states. This suggests that the condition and potential of the spinal cord is different, even if the severity of the symptom is the same. Imaging technique is useful to evaluate live spinal cord conditions, and MRI is especially superior, since it can visualize and quantify the fiber-structure of the spinal cord using the protocol of diffusion tensor tractgraphy (DTT). We used thoracic spinal cord injury model mice of different severity and performed live MRI in the chronic phase to quantify the number of fibers passing through the injured site. Then, human iPS-derived neural progenitor cells were transplanted, and motor function was observed over time. We investigated the relationship between the DTT data and pretreatment motor function, as well as the relationship between the DTT data and therapeutic effect. While the strong relationship was demonstrated between the fiber number and the pretreatment motor function, there was a negative correlation between the fiber number and the therapeutic effect of stem cell therapy. This suggests the potential of the injured spinal cord is more complex than we had expected.

Disclosures: **M. Shinozaki:** None. **N. Nagoshi:** None. **J. Hata:** None. **M. Nakamura:** F. Consulting Fees (e.g., advisory boards); advisory boards of K pharma inc. **H. Okano:** F. Consulting Fees (e.g., advisory boards); advisory boards of K pharma inc., advisory boards of San Bio.

Poster

126. Spinal Cord Injury: Stimulation, Training, and Recovery

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 126.22

Topic: C.11. Spinal Cord Injury and Plasticity

Support: R01HL153102
Craig H. Neilsen Pilot Grant
SPARC OT2 OD023854

Title: Automated adaptive thresholding enables diaphragm EMG burst analysis in awake, freely behaving animals

Authors: *A. R. MICKLE[1], E. A. DALE[2];
[1]Neurosci., [2]Physiol., Univ. of Florida, Gainesville, FL

Abstract: Epidural stimulation has shown promise for recovery of somatosensory function after spinal cord injury. Previous work from our lab indicates 4 days of closed-loop epidural stimulation (CLES; stimulation triggered from diaphragm EMG) facilitates the spinal motor evoked response of the diaphragm in C2-hemisected rats (Malone et al, 2022). However, the impact of CLES on breathing *per se* is unknown. While diaphragm EMG analysis methods exist, many of these algorithms are intended for anesthetized animals and may not be ideal for awake animals. Here, we describe a novel algorithm which utilizes an adaptive threshold to identify respiratory events. The algorithm determines the root mean square (RMS) value with a 50 ms time step and calculates the derivative, smoothing via a third-order Savitzky-Golay filter with a 101 ms time bin. The threshold value is set using the ratio between baseline (RMS at rising zeros of the derivative) and event peaks (RMS value at falling zeros). Event starts are defined as the time of the closest local max of the derivative to threshold crossing, while event ends are the nearest rising zero of the derivative. For each event, the algorithm calculates length, RMS75, duty cycle, stimulation frequency, breathing rate, modulus, and max peak and further classifies the event behavior (i.e., eupnic breath, sigh, or sniffing). To test the algorithm, adult, female, Sprague-Dawley rats were implanted with electrodes at C4 and bilaterally on the diaphragm. A subset of rats underwent a C2-hemisection (n = 4). The hemisected rats and an uninjured group (n = 3) underwent closed-loop epidural stimulation, receiving 10-15 hours of stimulation per day for 4 days. A third group of sham rats (n = 2) had no stimulation. All EMG data were analyzed with identical algorithm parameters. The algorithm identified an average of 44,000 ± 3000 breaths and 107 ± 13 sighs per recording. There were no significant differences in max peak, modulus, or RMS75 between hemisected and sham rats, or across the 4 nights of stimulation. However, injured rats had significantly shorter breath length than uninjured rats (0.396 ± 0.011 vs 0.466 ± 0.012, p = 0.007) with an associated increase in breathing frequency (102 ± 4.2 vs 93 ± 4.5). This work represents the first functional analysis of CLES in awake, freely behaving rats. Rats may be compensating for injury via a decrease in breath length and concomitant increase in breathing rate. Despite the CLES-induced increase in amplitude of evoked potentials, it does not lead to functional differences in breathing under eupnic conditions. Further study is necessary to determine if CLES leads to functional improvement during respiratory challenges.

Disclosures: A.R. Mickle: None. **E.A. Dale:** None.

Poster

127. Human Chronic Pain Including Post-Injury

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 127.01

Topic: D.02. Somatosensation – Pain

Title: Chronic pain participants using cannabinoids demonstrate significantly lower lateral (F7/F8) prefrontal asymmetry measured by EEG

Authors: I. CASMEDES[1], J. E. GAGLIARDI[2], K. GOFF[1], T. BROWN[3], K. N. COLPITTS[4], C. M. BOTELLO[5], K. P. SEYMOUR[2], *A. L. HARRIS BOZER[2];
[2]Tarleton State Univ., [1]Tarleton State Univ., Stephenville, TX; [3]Tarleton State Univ., Tarleton State Univ., Fort Worth, TX; [4]Tarleton State Univ., Tarleton State Univ., Temple, TX; [5]Univ. of Texas Rio Grande Valley, Univ. of Texas Rio Grande Valley, Edinburg, TX

Abstract: Chronic pain is the primary reason to seek medical attention worldwide. Cannabinoid use for chronic pain is increasing, and while there is a wealth of literature about cannabinoids in the brain and pain in the brain, there is a dearth of literature about neurophysiological and neuropsychological effects of cannabinoids and chronic pain together. We examined EEG data from participants with chronic pain using cannabinoids to explore if cannabinoids and chronic pain would generate summative effects on cortical activity. Forty-eight right-handed participants aged 18-30 reported current pain state and condition and cannabinoid use and were thus placed into four groups (pain/cannabinoids, pain/no cannabinoids, no pain/cannabinoids, and no pain/no cannabinoids). Resting state EEG data were recorded with iMotions software and a B-Alert 20-electrode system with 10-20 electrode placement (referenced to mastoids) after a 9-minute impedance check and benchmark test. Matlab and Cartool were used to filter (.05-50Hz) data, reject artifacts, and compute fast fourier transforms. Alpha band data (8-12 Hz) were extracted and medial (Fp3/Fp4) and lateral (Fp7/Fp8) prefrontal asymmetry (PFA) were computed using the log of right side alpha- log of left side alpha. Medial and lateral PFA were compared across groups using one-way ANOVAs using JASP software. There were no significant differences in medial PFA across groups. There was a significant difference across groups for lateral PFA, $p < .05$. Specifically, the pain/cannabinoids group demonstrated significantly lower PFA compared to the no pain/no cannabinoids group. These results are in line with previous studies that indicate a reduction in prefrontal alpha activity due to chronic pain and cannabinoids independently, and also demonstrate a summative effect for cannabinoids and pain together. Future research will be focused on examining the accompanying cognitive isomorphisms that result in changes in lateral prefrontal asymmetry.

Disclosures: I. Casmedes: None. **J.E. Gagliardi:** None. **K. Goff:** None. **T. Brown:** None. **K.N. Colpitts:** None. **C.M. Botello:** None. **K.P. Seymour:** None. **A.L. Harris Bozer:** None.

Poster

127. Human Chronic Pain Including Post-Injury

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 127.02

Topic: D.02. Somatosensation – Pain

Support: DK121724
DK110669
DK082370
DK082342
DK082315
DK082344
DK082325

Title: Brain connectivity changes associated with pain fluctuations in a 3-year longitudinal study of chronic pelvic pain: A MAPP Research Network Study

Authors: *N. J. MCLAIN, J. J. KUTCH;
Div. of Biokinesiology and Physical Therapy, USC, SOUTH PASADENA, CA

Abstract: Fluctuations in pain intensity for individuals with chronic pain conditions are a common but poorly understood phenomenon. Identifying the changes in brain activity that underlie these fluctuations is critical to understanding individual variability as well as progression in chronic pain. However, neural circuits underlying pain fluctuations in the chronic pain state have not yet been identified. To address this, we analyzed data from the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network study: we collected average self-reported pain (0-10 over the week prior to their visit) and subsequently resting-state functional magnetic resonance imaging (rs-fMRI) data in a population of 492 urologic chronic pelvic pain syndrome (UCPPS) patients. UCPPS is a chronic pain condition affecting both males and females with no identified neural correlates of pain fluctuations. 315 of the subjects were female and 177 were male. Mean age of all participants (mean±SD)= 44.2±15.5 years, age range=18.5-78.9 years, and data was collected across 6 sites. To most directly focus on state-independent (trait-like) brain network activity, connectivity features in 400 cortical nodes derived from the Schaefer atlas and 36 subcortical nodes adopted from the Brainnetome atlas were averaged across two 10-minute resting state scans, one with full and one with empty bladder. To assess the relationship between pain and functional connectivity, we then regressed the connectivity measures on the self-reported pain measures available from one baseline and three follow-up visits (6, 18, and 36 months) in each patient. p-values for the fixed effects of pain were FDR corrected ($q<0.05$). We found that the areas of connectivity most likely to vary as a person experienced more or less pelvic pain were medial sensorimotor regions, bilateral insula, cingulate, and ventromedial prefrontal cortex. Importantly, this relationship existed after controlling for site, age, and sex. These areas include nodes in the salience network, sensorimotor areas related to the painful body region (pelvis), and the prefrontal cortex which has been previously associated with patient control differences in UCPPS. These results suggest that functional connectivity changes in a common set of regions underlie the fluctuations in pain that UCPPS patients experience.

Disclosures: **N.J. McLain:** None. **J.J. Kutch:** None.

Poster

127. Human Chronic Pain Including Post-Injury

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 127.03

Topic: D.02. Somatosensation – Pain

Support: IBS Grant IBS-R015-D1
NRF Grant 2019R1C1C1004512
NRF Grant 2021M3E5D2A01022515
NRF Grant 2021M3A9E4080780
KIST Grant 2E30410-20-085
NRF Grant 2018H1A2A1059844

Title: Precision neuroimaging of chronic pain and personal narratives in fibromyalgia

Authors: ***J.-J. LEE**, C.-W. WOO;
Sungkyunkwan Univ., Sungkyunkwan Univ., Suwon-si, Gyeonggi-do, Korea, Republic of

Abstract: The experience of chronic pain is individually unique and multidimensional. However, it remains elusive how the human brain represents the idiographic experience of chronic pain. In this study, we used functional magnetic resonance imaging to investigate the brain representation of pain perception and self-narratives of individual patients with fibromyalgia. Two participants clinically diagnosed with fibromyalgia were recruited, who completed 11 (participant #1) and 9 (participant #2) out of 30 planned visits of Magnetic Resonance Imaging (MRI) scanning. For every visit, we collected functional MRI data from participants while they were continuously rating their subjective pain intensity, with or without performing a physical activity that exacerbated the ongoing pain before the scan. We also collected functional MRI data while participants were resting, answering questions designed to elicit personal narratives of pain, and listening to their recorded answers. Preliminary behavioral results showed that both participants reported an increase of pain intensity after the physical activity, though only the participant #2 showed statistically significant increase (participant #1, $t_{10} = 1.35$, $p = 0.21$; participant #2, $t_8 = 2.66$, $p = 0.029$). We further characterized personalized structural and functional brain architecture, and the relationships between the brain representations of pain and self-narratives. This study proposes a deeply-sampled and task-extensive imaging of individual patients as a new approach to understanding the neural mechanisms of chronic pain and to advancing the clinical utility of neuroimaging.

Disclosures: **J. Lee:** None. **C. Woo:** None.

Poster

127. Human Chronic Pain Including Post-Injury

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 127.04

Topic: D.02. Somatosensation – Pain

Support: NHMRC Grant APP1091302
NHMRC Grant APP1194937
CIHR Grant 358797

Title: Glial activation in motor cortex is related to sensory and motor function in individuals with low back pain maintained by nociplastic mechanisms

Authors: M. SHRAIN[1], H. MASSE ALARIE[2], M. FARRELL[3], M. L. LOGGIA[4], ***P. HODGES**[1];
[1]Univ. Queensland, Brisbane, Australia; [2]Laval Univ., Quebec City, QC, Canada; [3]Dept. of Med. Imaging & Radiation Sci., Clayton, Australia; [4]Radiology, Massachusetts Gen. Hosp. / Harvard Med. Sch., Charlestown, MA

Abstract: Neuroinflammation (i.e., glial cell activation) in the sensorimotor cortex (S1/M1) has recently been identified in chronic low back pain (LBP). It is plausible that the diverse functions of glia might contribute to sensorimotor changes commonly present in these individuals. LBP presentation is heterogenous and it is likely that this might be predominantly involved in individuals with pain maintained by nociplastic rather than nociceptive mechanisms. This study aimed to: (1) compare glial activation in S1/M1 between healthy individuals and two groups of individuals with chronic LBP with features consistent with ongoing nociceptive or nociplastic mechanisms; and (2) evaluate relationships between glial activation and measures of sensory and motor function. Simultaneous PET-fMRI using [^{18}F]-FEMPA was used to measure glial activation in functionally defined regions of S1/M1 in painfree individuals (n=8) and individuals with chronic LBP (n=9) who were sub-grouped according to clinical criteria into primary nociceptive (n=4) and nociplastic (n=5) pain mechanism groups. The somatotopic regions of M1 and S1 related to the low back were identified using fMRI during standardized motor tasks and thermal stimuli. In a separate session, sensorimotor measures included single and paired-pulse transcranial magnetic stimulation (TMS) and quantitative sensory testing (QST). Sleep, depression, disability, and pain questionnaires were administered. Glial activation was significantly greater in the lower back cortical representation of S1/M1 for individuals with LBP group who presented with clinical features consistent with primary nociplastic pain than both nociceptive LBP and painfree groups. The nociplastic LBP group had lower corticospinal excitability (measured with recruitment curve). Glial activation in S1/M1 was positively correlated with greater sensitivity to hot (r=0.52) and cold (r=0.55) pain thresholds, positively correlated with poor sleep, depression, functional disability and BMI and weakly negatively correlated with intra-cortical facilitation (r=-0.41). This study provides evidence for neuroinflammation in S1/M1 of the brain that is greater in individuals with clinical features that suggest predominant nociplastic pain mechanisms. Glial activation was associated with sensitivity to noxious inputs and and clinical features that are common in nociplastic pain.

Although this cannot be interpreted as causal, the data provide foundation to speculate on possible mechanisms.

Disclosures: M. Shrain: None. **H. Masse Alarie:** None. **M. Farrell:** None. **M.L. Loggia:** None. **P. Hodges:** None.

Poster

127. Human Chronic Pain Including Post-Injury

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 127.05

Topic: D.02. Somatosensation – Pain

Support: Quebec Pain Research Network
Quebec Bio-Imaging Network
Arthritis Society
Fonds de Recherche du Québec - Santé

Title: Identifying Chronic Low Back Pain patients Using Machine Learning on Graph Theory measures from functional brain MRI: preliminary results

Authors: *M. VAFAEI[1], M. SEAN[1], P. TÉTREAULT[1,2];
[1]Anesthesiol. and nuclear medicine and radiobiology, Univ. de Sherbrooke, Sherbrooke, QC, Canada; [2]Med. imaging axis, Ctr. de recherche du CHUS, Sherbrooke, QC, Canada

Abstract: Chronic low back pain (CLBP) is one of the most prominent types of musculoskeletal pain in the world. In recent years, the use of brain neuroimaging such as functional Magnetic Resonance Imaging (fMRI) appears to be a promising approach to define biomarkers that could characterize patients suffering from chronic pain conditions or identify treatment response propensity. To search for such biomarkers, we are investigating the brain properties of 52 subjects, 27 suffering from CLBP and 25 healthy controls (HC) (age and sex matched). All participants are followed for 4 months, with visits at 0, 2, and 4 months. In each visit, our team collected structural and functional MRI, together with a battery of questionnaires pertaining to their pain, anxiety, depression, past traumatic events, and more.
In this study, we specifically used resting-state functional MRI images to model brain gray matter (GM) fMRI Blood Oxygen Level Dependent (BOLD) signal as a graph. Then, by using graph theory approaches, we computed and extracted local and global features. We used degree count as local properties from ~ 3000 nodes (number of GM voxels at 8 mm^3 resolution) which is a feature that quantifies the number of connections made by each brain region to the rest of the brain. Then we applied a support vector machine (SVM) to identify more complex brain functional patterns to stratify CLBP patients from HC. However, even when using data driven feature selection approaches (filter or wrapper type selection), classification was unstable due to the big gap in the number of features and number of subjects. Our second approach was to compute 10 global features from each subject's graph. Using this approach, our primary results

from the SVM optimized by leave one out cross-validation and polynomial kernel showed a 72% stratification accuracy. To evaluate our method, we used Wilcoxon rank-sum test with $p < 0.05$ and compared our model with a random classifier that doesn't learn. The result shows that our current accuracy is statistically significant. One hypothesis-driven approach currently under investigation is to use hippocampal nodes only, considering the role this region has in CLBP. Another approach will be to use the fMRI data from the second and third visits to test and optimize our method. Finally, we will evaluate the reproducibility of our optimized stratification method by using an open source CLBP and healthy participants dataset that can be found on the OpenPain.org repository.

Disclosures: M. Vafaei: None. **M. Sean:** None. **P. Tétreault:** None.

Poster

127. Human Chronic Pain Including Post-Injury

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 127.06

Topic: D.02. Somatosensation – Pain

Title: Development of a novel fMRI task for the assessment of chronic lower back pain in vivo

Authors: *T. A. MCGAUGHEY[1], J. E. SUFFRIDGE[1], V. S. FINOMORE, Jr.[2];
[1]Neurosci., West Virginia Univ., Morgantown, WV; [2]West Virginia University- Rockefeller Neurosci., Morgantown, WV

Abstract: Chronic lower back pain (CLBP) is one of the leading causes of disability in the United States. Traditional assessment measures rely primarily on subjective pain ratings. However, we have developed a novel functional magnetic resonance imaging (fMRI) task to aid in the objective measure of the population of interest. First, novel pain inducing cues were developed that included both biological sexes, various ethnicities, and individuals from across the life spectrum. These cues were then validated with chronic pain patients' subjective ratings in a pilot task outside of the MRI. During the pilot investigation CLBP patients rated the painfulness of assorted images on a scale of one to ten, with ten being the most pain-inducing. The images were then stratified and sorted into neutral and active cues. Then, twenty-five CLBP patients underwent two fMRI sessions before and after a series of chronic pain treatments. While in the scanner the participants viewed the previously validated cues in a block design paradigm. Each block contained either ten neutral or active images starting with the neutral block first and alternating from there to in theory produce a box car function in brain regions of interest. An initial baseline fixation was followed by image presentation for two seconds, equivalent to one repetition time, followed by a one and a half second interval during which the participant is asked to rate the painfulness of the image on a scale of one to four with four being the most painful. If the participant responds before the allotted time is up, then another fixation is presented for the remained of the time. In addition to a brief five hundred millisecond fixation between the response block and the next image. Thus, keeping the timing of the task time locked

to each brain scan. In addition to further subjective ratings, blood oxygen level dependent signal was derived from a T2* fMRI to provide an objective correlation to the participant's cue derived pain response. The fMRIs were processed via standard methods via AFNI and FSL. The proposed task showed a significant difference in subjective ratings between the neutral and active pain blocks. In addition, there were significant activations in brain areas associated with chronic pain states, identified in the literature, like the hippocampus, cingulate cortex, and prefrontal cortex. These results show that we were able to successfully activate areas of interest associated with chronic pain, and therefore this task can be used as a chronic pain assessment. This is further validated by the decrease in activation in the areas of interest and changes in subjective ratings after pain treatments over three weeks.

Disclosures: T.A. McGaughey: None. **J.E. Suffridge:** None. **V.S. Finomore:** A. Employment/Salary (full or part-time):; West Virginia University.

Poster

127. Human Chronic Pain Including Post-Injury

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 127.07

Topic: D.02. Somatosensation – Pain

Support: CIHR

Title: Hypothalamic Structural Changes in Trigeminal Neuralgia

Authors: *A. NOORANI[1,3,2], P. HUNG[2], S. HANYCZ[4], M. HODAIE[1];
[1]Neurosurgery, Toronto Western Hosp., [2]Univ. of Toronto, Toronto, ON, Canada; [3]Krembil Res. Inst., Toronto, ON, Canada; [4]Fac. of Med., Univ. of Ottawa, Ottawa, ON, Canada

Abstract: Introduction: Pain and stress are two different processes with significant physiological overlaps. Chronic pain patients commonly experience increased anxiety and depression. In this study, we aim to investigate the hypothalamic changes in chronic pain using trigeminal neuralgia (TN) as our model. Here, we investigated the hypothalamic subregions in TN patients compared to healthy controls (HC) and we hypothesize that the hypothalamic subregion volumes are statistically different compared to healthy controls.
Methods: 3 Tesla T1-weighted anatomical MRIs were retrospectively identified from 61 patients with classical TN (age: 61.4+-14.0 s.d. years, 36 females and 25 males) and their respective age- and sex-matched healthy controls from the Cam-CAN database. The FreeSurfer 7.2 was leveraged to automatically extract gray matter volume from the hypothalamus and its associate subunits bilaterally in each subject. To account for individual variability in brain size, gray matter volumes were corrected for estimated total subcortical gray matter volume. Welch's t-tests were subsequently performed to compare corrected gray matter volume between TN patients and healthy controls across 12 regions of interest (6 bilaterally: anterior-inferior subunit, anterior-superior subunit, posterior subunit, inferior tubular subunit, superior tubular subunit, and

whole hypothalamus). These tests were further performed within sex subgroups to assess for possible sex differences in the hypothalamus and hypothalamic subunit gray matter volumes. Statistical analyses were performed in Python with statistical significance set at $p < 0.05$ after Bonferroni correction.
Results: Gray matter volumes of bilateral anterior superior and posterior subunits were markedly smaller in classical TN patients compared to healthy controls ($p < 0.01$). This is associated with a significant bilaterally smaller whole hypothalamus gray matter volume ($p< 0.001$). Sex subgroup analysis further revealed that the significantly smaller gray matter volume in classical TN patients was driven by females ($p < 0.05$), but not males. Additionally, sex-independent abnormalities in gray matter volume were observed in contralateral tubular superior subunit ($p < 0.05$) and ipsilateral tubular inferior subunit ($p < 0.05$) in TN patients compared to controls.
Conclusions: Our study reports for the first-time hypothalamic subunit changes in chronic pain patients. Additionally, this study is yet another demonstration of significant sex differences in chronic pain-induced abnormalities in the brain.

Disclosures: A. Noorani: None. **P. Hung:** None. **S. Hanycz:** None. **M. Hodaie:** None.

Poster

127. Human Chronic Pain Including Post-Injury

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 127.08

Topic: D.02. Somatosensation – Pain

Support: Fonds de recherche du Québec - santé
Natural Sciences and Engineering Research Council

Title: Structural MRI brain properties and behavioral evaluation of a non-fully invasive model of chronic low back pain: challenges and opportunities

Authors: *M.-A. FORTIER[1], S. DUMONT[1], M.-A. DANSEREAU[2], G. RICHARD[3], P. TÉTREAULT[1,3];
[1]Departments of Anesthesiol. and nuclear medecine and radiobiology, [2]Dept. of pharmacology and physiology, Fac. of Med. and Hlth. Sci. Univ. de Sherbrooke, Sherbrooke, QC, Canada; [3]Med. Imaging Axis, Ctr. de recherche du CHUS, Sherbrooke, QC, Canada

Abstract: Finding alternative therapies for the treatment of chronic pain (CP) has become imperative to minimize opioid uses. Many promising drugs do not reach the market because of invalid preclinical trials. It is therefore essential to set up representative preclinical models of CP conditions with appropriate tests capable of confirming the drugs' analgesic potential. Also, given the role of the brain in the development and maintenance of CP, brain plasticity could reveal mechanisms of pain relief. This can be done with non-invasive Magnetic Resonance Imaging (MRI) analysis of brain structure coupled with histological analysis to identify cellular and molecular changes underlying MRI variations.

We present a preclinical model of chronic low back pain (CLBP) that reflects a clinical population experiencing mild to severe pain rather than an all or nothing response typically seen in preclinical models. A unilateral or bilateral 3% carrageenan injection in the muscle and paravertebral fascia at L4/L5 level in Sprague-Dawley rats was performed. Their behaviors were observed every week for 42 days. Behavioral tests evaluated maximal force capacity, thermal hyperalgesia, mechanical allodynia, exploratory and motor ability, anxiety, and non-evoked pain-induced postural changes. When the difference between the score at day 42 and day 0 was evaluated at the groups level, no statistical differences were seen between the pain groups and control or sham (pain animals n=21, control/sham n=20). However, when evaluated individually, several animals presented behavioral profiles compatible with sensory and/or comorbid impairments. For example, in the grip strength test for maximal force capacity, we observed from 0% up to 172% decrease in score difference to the mean score of control and sham groups. Brain structural MRI was performed using a T2* scan (0.15 mm isotropic voxels) before carrageenan injection and 42 days after (all pain animals n=6, control/sham n=6). Using Voxel-based morphometry (VBM), a paired t-test determined which regions of the brain underwent notable changes in gray matter density with the development of chronic pain. Differences were observed in the right superior basal ganglia, left posterior retro-splenial cortex and right superior periaqueductal gray. These results suggest that brain changes may appear before pain chronification can be observed behaviorally. Furthermore, histological analyses of brain tissues are underway.
We hope that such studies will help in the development of valid preclinical models of chronic pain where the evaluation of new treatment approaches should have more chances to succeed when transferred in clinical settings.

Disclosures: **M. Fortier:** None. **S. Dumont:** None. **M. Dansereau:** None. **G. Richard:** None. **P. Tétreault:** None.

Poster

127. Human Chronic Pain Including Post-Injury

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 127.09

Topic: D.02. Somatosensation – Pain

Support: KIOM Grant KSN2211010
KIOM Grant KSN2021240

Title: The links between altered brain function to abdominal pressure stimuli and clinical symptoms in functional dyspepsia

Authors: *J. KIM[1], S.-J. KO[3], S. EUN[4], J.-H. JANG[1], J.-W. PARK[3], K. PARK[5], J.-H. LEE[2]; [1]KM Sci. Res. Div., [2]Korea Inst. of Oriental Med., Deajeon, Korea, Republic of; [3]Dept. of Gastroenterology, Col. of Korean Medicine, Kyung Hee Univ., Seoul, Korea, Republic of; [4]Ctr.

for Neurosci. Imaging Research, Inst. for Basic Sci. (IBS),, Suwon, Korea, Republic of; [5]Kyunghee Univ., Kyunghee Univ., Yongin, Korea, Republic of

Abstract: While the neural correlates of experimental gastrointestinal pain using gastric balloon distension in functional dyspepsia (FD) patients have investigated, the neural mechanism underlying the processing pain or discomfort is less understood. In this study, we used fMRI to investigate the modulation of brain function during pressure-induced discomfort in patients with FD and age/sex matched healthy controls (HC). We delivered an individually calibrated pressure stimuli on upper abdominal area to elicit moderated discomfort intensity of 60/100. BOLD fMRI data from 48 FD patients and 23 HC were collected for brain responses to block-designed pressure stimuli, resting-state and discomfort state connectivity under continuous pressure stimuli. Patients with FD were randomized to be treated either real or sham acupuncture for 4 weeks. Compared to HC, patients exhibited reduced brain responses in anterior/mid insular cortex (a core region of salience network) to pressure stimuli. The less brain responses of insular cortex in patients were correlated with clinical symptoms of GIS (Gastrointestinal symptom, r=-0.32, p=0.032) and CESD (Center for Epidemiological Studies-Depression Scale, r=-0.33, p=0.027). PPI analyses using a seed of anterior/mid insular cortex showed greater anterior/mid insular cortex connectivity to medial prefrontal cortex (MPFC) and dorsal anterior cingulate cortex (dACC) during pressure stimuli in FD, compared to HC. The increased insular cortex connectivity to MPFC and dACC were also correlated with clinical symptoms (NDI, r=0.285, p=0.05). A seed of temporo-parietal junction (TPJ) was defined to investigate salience connectivity. TPJ connectivity at rest was not significantly different between FC and HC, while TPJ connectivity to MPFC and PCC were increased by the continuous pressure stimuli in FD, but not in HC. Following acupuncture, clinical symptoms were improved in both real and sham acupuncture groups without significant difference between groups. For fMRI data, PPI insular cortex connectivity to MPFC and pgACC were associated with improvement of clinical symptoms of NDI and CESD in real acupuncture group. Moreover, decreased TPJ connectivity to mPFC during cDISF was associated with improvement of NDI following real acupuncture. Our results with pressure-induced discomfort stimuli, FD patients exhibited diminished brain activation and elevated functional connectivity in visceral sensation and autonomic processing area (anterior/mid insular cortex). Functional connectivity between salience and default mode network regions may serve as a key neural circuitry supporting acupuncture.

Disclosures: J. Kim: None. **S. Ko:** None. **S. Eun:** None. **J. Jang:** None. **J. Park:** None. **K. Park:** None. **J. Lee:** None.

Poster

127. Human Chronic Pain Including Post-Injury

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 127.10

Topic: D.02. Somatosensation – Pain

Support: NCCIH R61-AT009306, R33-AT009306
NCRR P41RR14075, CRC 1 UL1 RR025758
MGH R90DA023427
NIH S10RR023401, S10RR019307, S10RR019254, S10RR023043
KIOM

Title: Brain activity in nociceptive processing areas is modulated by the patient-clinician relationship: a longitudinal hyperscan fMRI study

Authors: *A. GRAHL[1,2], A. ANZOLIN[1,2], M. BARTON-ZUCKERMAN[1,2], J. LEE[1,2], K. ISENBURG[2,3], D.-M. ELLINGSEN[2,4,5], C. JUNG[6,2], J. GERBER[2], J. KELLEY[7,8], I. KIRSCH[7], T. KAPTCHUK[7], V. NAPADOW[1,2,9];
[1]Dept. of Physical Med. and Rehabil., Spaulding Rehabil. Hospital, Harvard Med. Sch., Boston, MA; [2]Dept. of Radiology, Martinos Ctr. for Biomed. Imaging, Massachusetts Gen. Hosp., Boston, MA; [3]Dept. of Psychological and Brain Sci., Boston Univ., Boston, MA; [4]Sch. of Hlth. Sci., Kristiania Univ. Col., Oslo, Norway; [5]Dept. of Physics and Computat. Radiology, Div. of Radiology and Nuclear Med., Oslo Univ. Hosp., Oslo, Norway; [6]KM Fundamental Res. Div., Korea Inst. of Oriental Med. (KIOM), Daejeon, Korea, Republic of; [7]Program in Placebo Studies & Therapeut. Encounter (PiPS), Harvard Med. Sch., Boston, MA; [8]Endicott Col., Beverly, MA; [9]Dept. of Radiology, Logan Univ., Chesterfield, MO

Abstract: The quality of a clinical encounter is fundamental to fostering patient trust and building a collaborative relationship. Our recent functional MRI hyperscanning study found that patient-clinician brain concordance in the temporoparietal junction (TPJ) was associated with analgesia in fibromyalgia patients (Ellingsen et al., 2020). Furthermore, we have found that a warm and empathic (*Augmented*) clinician interaction compared to a neutral, business-like (*Limited*) encounter can improve clinical outcomes, though the underlying mechanisms are unknown. This longitudinal study investigates the influence of different clinical interaction styles, linking patient's neural activity with measures of therapeutic alliance. Twenty women with fibromyalgia (mean age±SD=40.50±12.60) were randomly assigned to an *Augmented* (N=9) or *Limited* (N=11) patient-clinician dyadic interaction style (trained acupuncturists). Each dyad underwent synchronized real-time dual-brain fMRI with a live video connection between two scanners and an evoked cuff pressure pain/treatment paradigm (TR/TE=1250/33ms; SMS MB acc. factor 5; voxel size 2mm^3; 2x358 volumes) before and after 6 acupuncture treatments (i.e. biweekly over 3 weeks). The quality of the patient-clinician relationship and clinical outcomes were assessed via self-report questionnaires. Patients rated Therapeutic Alliance (THA) and clinicians' Warmth (WM) higher for the *Augmented* (THA=43.02 ± 2.39; WM=4.00±0.0) vs. *Limited* group (THA=21.48±12.51; WM=2.38±1.10; $t_{THA}(18)=5.10$, $p<0.001$; $t_{WM}(18)=4.49$; $p<0.001$). Pain catastrophizing was significantly reduced after the intervention in the *Augmented*, Δ_A=-8.11±5.30, but not the *Limited* group, Δ_L=1.27±5.57 (time by group interaction: $F(1,18)=14.66$; $p=0.001$). For both groups, the intervention decreased clinical pain (no difference in mean pain relief over 6 treatments: $p=0.502$, Δ_A=-1.04±0.52, Δ_L=-1.33±1.17) and reduced patients' fMRI response to evoked pressure pain in nociceptive processing areas (i.e. S2, posterior insula, SPL). However, post-therapy increase in anterior insula response during pain anticipation was associated with better therapeutic alliance ratings. This suggests that a more beneficial and empathic clinical relationship during therapy was linked with greater salience processing in the brain, potentially due to greater patient-clinician engagement to the pain

treatment context. In summary, this study highlights the importance of the patient-clinician interaction for clinical outcomes in chronic pain patients treated by non-pharmacological therapies and points to brain mechanisms that may underlie these effects.

Disclosures: A. Grahl: None. **A. Anzolin:** None. **M. Barton-Zuckerman:** None. **J. Lee:** None. **K. Isenburg:** None. **D. Ellingsen:** None. **C. Jung:** None. **J. Gerber:** None. **J. Kelley:** None. **I. Kirsch:** None. **T. Kaptchuk:** None. **V. Napadow:** None.

Poster

127. Human Chronic Pain Including Post-Injury

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 127.11

Topic: D.02. Somatosensation – Pain

Support: NCCIH K99/R00-AT008238
NCCIH R01-AT009693
Robert Coghill, PhD

Title: Mindfulness meditation-induced pain relief is associated with reduced generalized and stimulus-type-specific signatures of negative affect

Authors: *G. RIEGNER[1], J. G. DEAN[1], Y. JUNG[2], G. POSEY[3], M. CEKO[4], T. D. WAGER[5], F. ZEIDAN[6];
[1]Anesthesiol., UCSD, La Jolla, CA; [2]Univ. of California, Davis, Sacramento, CA; [3]Wake Forest Sch. of Med., Winston-Salem, NC; [4]Inst. of Cognitive Sci., Boulder, CO; [5]Psychological and Brain Sci., Dartmouth Col., Hanover, NH; [6]Anesthesiol., Univ. of California San Diego, La Jolla, CA

Abstract: Pain is constructed from the integration of nociceptive and higher-order affective processes shared across a spectrum of negatively valenced stimuli. Recent studies show that mindfulness meditation (MM) reduces pain through multiple, unique neural mechanisms. Yet, it is unclear if MM analgesia modulates brain representations of stimulus-specific and/or generalized negative affect. To disambiguate the targets of MM, we tested five distinct multivariate fMRI predictive signatures sensitive and specific to noxious thermal, mechanical, auditory, and visual stimuli, and general negative affect, respectively.
Across two clinical trials using blood-oxygen level dependent and perfusion-fMRI, respectively, 77 healthy volunteers (mean age = 29, 38 females) were randomized to a four session, 20-minute MM (N=38) or book-listening (N=39) regimen. After the interventions, volunteers rested during fMRI and noxious thermal stimulation (ten, 12-sec plateaus of 49°C; right calf). In the 2nd half of the scan, the MM group were instructed to “meditate” and the controls to “continue resting.” Visual analog pain ratings (0= “not unpleasant” to 10= “most unpleasant imaginable”) were collected after each run.
Stimulus-type-specific and general negative affect brain responses were calculated for each of

the five models against observed input images using the dot product. Signature responses during MM were compared to rest and the control group using 2 (group) X 2 (pre- vs post-manipulation) mixed ANOVAs. Significant interactions (Bonferroni corrected; $p < .01$) were investigated with paired samples t-tests. To determine if MM analgesia significantly correlates with affect signature responses, within-subject *r* values between predicted and observed ratings were tested.
The group X manipulation interaction ($p < .001$, $n^p_2 = .43$) was driven by significant pain reductions in the MM group (-41%) but not the controls (+20%). MM significantly reduced thermal-specific negative affect (interaction $p < .001$, $n^p_2 = .15$; MM $p < .001$) and generalized negative affect brain responses (interaction $p < 0.01$, $n^p_2 = .08$, MM $p < .001$). The controls did not modulate any negative affect signatures (*ps* > .29). Importantly, MM-based pain relief was associated with lower thermal ($r = .32$, $p < .01$) and common ($r = .31$, $p < .01$) negative affect signature responses, but not other signatures (*ps* > .05).
This is the first study to show that MM reduces stimulus-type-specific and generalized representations of negative affect, two systems that intersect to optimize pain-relief. These findings suggest that MM attenuates pain through multiple mechanisms supporting the affective regulation of nociception.

Disclosures: **G. Riegner:** None. **J.G. Dean:** None. **Y. Jung:** None. **G. Posey:** None. **M. Ceko:** None. **T.D. Wager:** None. **F. Zeidan:** None.

Poster

127. Human Chronic Pain Including Post-Injury

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 127.12

Topic: D.02. Somatosensation – Pain

Support: NIH Grant 1R61AT009306-01
KIOM Grant KSN2021240

Title: Temporoparietal junction (TPJ) brain-to-brain connectivity during patient-clinician interaction affects pain analgesia: an EEG hyperscanning study

Authors: *A. ANZOLIN[1], A. GRAHL[1], M. BARTON-ZUCKERMAN[1], K. M. ISENBURG[3], J. TOPPI[4], D.-M. ELLINGSEN[5], L. ASTOLFI[4], J. LEE[1], T. J. KAPTCHUK[2], V. NAPADOW[1]; [1]Spaulding Rehabil. Hosp., [2]Beth Israel Deaconess Med. Ctr., Harvard Med. Sch., Boston, MA; [3]Boston Univ., Boston, MA; [4]Sapienza, Univ. of Rome, Rome, Italy; [5]Dept. of Physics and Computat. Radiology, Univ. of Oslo, Oslo, Norway

Abstract: Therapeutic alliance between chronic pain patients and clinicians can significantly impact the perception and experience of pain. Previous studies suggest that the quality of the clinical encounter is a major contributor to treatment efficacy. To elucidate the brain mechanisms underlying these processes, objective measures simultaneously acquired from two interacting

brains (i.e. hyperscanning) are needed. Our team applied fMRI hyperscanning to demonstrate that patient-clinician brain concordance in the temporoparietal junction (TPJ) was up-regulated following a clinical interaction and correlated with analgesia in fibromyalgia patients (Ellingsen et al., 2020). Here, we applied EEG hyperscanning to evaluate patient-clinician brain connectivity in a more ecologically valid setting to further explore the role of TPJ during pain treatment. EEG was recorded (28 dyads, 64 channels) from chronic low back pain patients and acupuncturists during trials of cuff-evoked pain paired either with electroacupuncture treatment or no treatment. Using a linear-inverse approach, we reconstructed the electrical activity from 17 ROIs, defined in our previous fMRI study. Brain-to-Brain connectivity was estimated using Partial Directed Coherence (α=0.05, FDR corr.). We found that TPJ was a dominant node in the patient-clinician brain network (Theta band). Patients' TPJ inter-degree (total number of brain-to-brain links involving TPJ) was higher during treatment compared to no-treatment trials ($p<0.01$). TPJ inter-degree during treatment also correlated with patient-rated analgesia for evoked pain. Further, we found increased brain-to-brain connectivity in clinicians' TPJ when evoked pain in patients was observed, but not treated. The key role of the TPJ in the patient-clinician interaction during pain treatment, suggested by our fMRI study, has been corroborated by these EEG results. Future studies will investigate how TPJ inter-brain connectivity predicts the quality of the patient-clinician interaction and clinical outcomes following a longitudinal course of therapy.

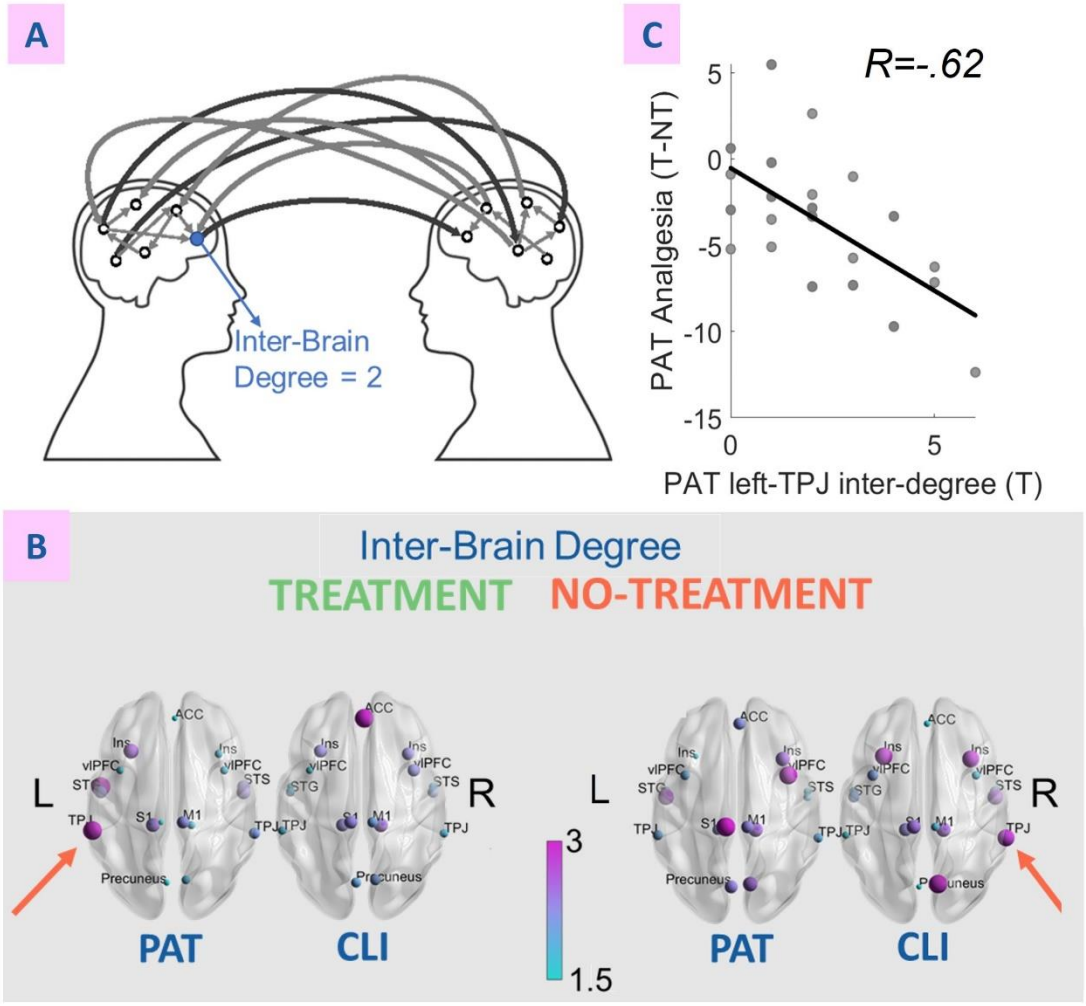


Figure1 *– **(A)** Illustration of a multiple-brain statistical connectivity map including inter- and intra-connections as well as an example of inter-brain degree (number of significant links connecting the patients' and the acupuncturists' brains).* ***(B)*** *Statistical inter-brain degree maps in Theta band. The diameter and the color of the spheres representing different brain regions are proportional to their inter-brain degree. The inter-brain degree of each node is modulated by the presence of the pain treatment.* ***(C)*** *Evoked pain analgesia associated with electro-acupuncture treatment correlates with the inter-brain degree of patients' TPJ (**r =-0.62**).*

Disclosures: **A. Anzolin:** None. **A. Grahl:** None. **M. Barton-Zuckerman:** None. **K.M. Isenburg:** None. **J. Toppi:** None. **D. Ellingsen:** None. **L. Astolfi:** None. **J. Lee:** None. **T.J. Kaptchuk:** None. **V. Napadow:** None.

Poster

127. Human Chronic Pain Including Post-Injury

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 127.13

Topic: D.02. Somatosensation – Pain

Support: MSIT 2019R1C1C1006980
Yonsei University College of Medicine (6-2019-0100)
NIH grant R01MH113929
NIH grant R21MH126271
NIH grant R56AG069086
NIH grant R21NS123813
Kaye Family Research Endowment

Title: Network Effects of Brain Lesions Causing Central Post-stroke Pain

Authors: *N. KIM[1,3], J. J. TAYLOR[4], Y. KIM[2], D. BORSOOK[5], J. JOUTSA[6], J. LI[5], C. QUESADA[7], R. PEYRON[8], M. FOX[9];
[1]Yonsei Univ., Yonsei Univ. Col. of Med., Seoul, Korea, Republic of; [2]Yonsei Univ. Col. of Med., SEoul, Korea, Republic of; [3]Yongin Severance Hosp., Yongin-si, Korea, Republic of; [4]3Center for Brain Circuit Therapeutics, Brigham and Women's Hosp., Boston, MA; [5]Harvard Med. Sch., Boston, MA; [6]Univ. of Turku, Turku, Finland; [7]Lyon Neurosciences Res. Ctr., Lyon, France; [8]Hosp. Nord, Hosp. Nord, Saint-Etienne Cedex 2, France; [9]Ctr. for Brain Circuit Therapeutics, Brigham and Women's Hosp., Boston, MA

Abstract: Objective: To test whether lesions causing central post-stroke pain (CPSP) are associated with a specific connectivity profile, whether these connections are associated with metabolic changes, and whether this network aligns with neuromodulation targets for pain. **Methods:** Two independent lesion datasets were utilized: 1) subcortical lesions from published case reports and, 2) thalamic lesions with metabolic imaging using 18F- fluorodeoxyglucose PET-CT. Functional connectivity between each lesion location and the rest of the brain was assessed using a normative connectome (n = 1000) and connections specific to CPSP were identified. Metabolic changes specific to CPSP were also identified and related to differences in lesion connectivity. Therapeutic relevance of the network was explored by testing for alignment with existing brain stimulation data and by prospectively targeting the network with repetitive transcranial magnetic stimulation (rTMS) in 7 patients with CPSP. **Results:** Lesion locations causing CPSP showed a specific pattern of brain connectivity that was consistent across two independent lesion datasets (spatial $r = 0.82$, $p < 0.0001$). Connectivity differences were correlated with post-lesion metabolism ($r = -0.48$, $p < 0.001$). The topography of this lesion-based pain network aligned with variability in pain improvement across 12 prior neuromodulation targets and across 32 patients who received rTMS to primary motor cortex ($p < 0.05$). Prospectively targeting this network with rTMS improved CPSP in 6/7 patients. **Interpretation:** Lesions causing pain are connected to a specific brain network that shows metabolic abnormalities and promise as a neuromodulation target.

Disclosures: **N. Kim:** None. **J.J. Taylor:** None. **Y. Kim:** None. **D. Borsook:** None. **J. Joutsa:** None. **J. Li:** None. **C. Quesada:** None. **R. Peyron:** None. **M. Fox:** None.

Poster

127. Human Chronic Pain Including Post-Injury

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 127.14

Topic: D.02. Somatosensation – Pain

Support: R01-AR064367
R01-AT007550
R61/R33-AT009306
P01-AT009965
P41-RR14075
S10-RR021110
S10-RR023043

Title: Posterior Cingulate Cortex Connectivity Underlies Reduced Pain Catastrophizing Following Cognitive Behavioral Therapy in Fibromyalgia

Authors: *J. LEE[1,2], A. LAZARIDOU[3], M. PASCHALI[3], D.-M. ELLINGSEN[4], A. GRAHL[1,2], M. L. LOGGIA[2,5], A. D. WASAN[6], R. R. EDWARDS[3], N. VITALY[1,2];
[1]Dept. of Physical Med. and Rehabil., Spaulding Rehabil. Hosp., Charlestown, MA; [2]Dept. of Radiology, Athinoula A. Martinos Ctr. for Biomed. Imaging, Massachusetts Gen. Hosp., Charlestown, MA; [3]Dept. of Anesthesiology, Perioperative and Pain Med., Brigham and Women's Hosp., Boston, MA; [4]Dept. of Physics and Computat. Radiology, Oslo Univ. Hosp., Oslo, Norway; [5]Dept. of Anesthesia, Critical Care, and Pain Med., Massachusetts Gen. Hosp., Boston, MA; [6]Dept. of Anesthesiol. and Perioperative Med., Ctr. for Innovation in Pain Care, Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Our prior study found that posterior cingulate cortex (PCC), a default mode network region engaged during self-referential processing, is activated during pain catastrophizing in fibromyalgia (FM) patients, with distinct roles for dorsal (dPCC) and ventral (vPCC) subregions (Lee et al. 2018). It is not clear, however, if engaging in pain catastrophizing thoughts also impacts interactions between vPCC, the core node for pain catastrophizing cognition, and other brain regions, and whether such interactions can be modulated by treatments such as cognitive behavioral therapy (CBT), which is known to reduce the frequency and impact of catastrophizing cognitions. To investigate PCC connectivity during catastrophizing, we performed a psychophysiological interaction (PPI) analysis on a dataset collected from 99 female FM patients (40.8 ± 11.9 years old, mean ± SD) as part of a longitudinal neuroimaging trial. FM patients provided self-reported outcomes such as Pain Catastrophizing Scale (PCS, 0 - 52) and Brief Pain Inventory (BPI interference, 0 - 10) as well as brain fMRI data at baseline and after 8-weeks of either CBT or education control (EDU) therapy. Functional MRI data were collected during a previously validated pain catastrophizing task (Lee et al. 2018), wherein patients engaged with pain-catastrophizing and neutral statements (CAT and NEU, respectively, presented in randomized order). A whole brain multiple linear regression model was used to correlate functional connectivity (PPI metrics) with clinical/behavioral outcome measures (PCS and BPI interference), cluster corrected at $p < 0.05$. After treatment, PCS and BPI interference scores

decreased more following CBT compared to EDU (PCS: CBT = -8.9 ± 9.3, P < 0.0001; EDU = -4.6 ± 9.1, P < 0.05; $P_{CBTvsEDU}$ < 0.05; BPI: CBT = -1.2 ± 1.4, P < 0.0001; EDU = -0.2 ± 2.0, P = 0.6; $P_{CBTvsEDU}$ < 0.05). After CBT, *increased* vPCC interaction with primary motor/somatosensory and posterior insular cortices was associated with greater PCS decrease. However, after EDU, *decreased* vPCC interaction with primary somatosensory, anterior insular, anterior cingulate, and medial prefrontal cortices was associated with greater PCS decrease. These results suggest distinct therapeutic mechanisms of CBT versus EDU for pain catastrophizing management, wherein increased processing of somatic self-awareness (i.e. greater self-referential PCC processing of FM pain) may be beneficial following CBT but detrimental for EDU treatment. Such findings highlight the putatively treatment-specific neural mechanisms underpinning the beneficial effects of various non-pharmacologic treatments for chronic pain.

Disclosures: J. Lee: None. **A. Lazaridou:** None. **M. Paschali:** None. **D. Ellingsen:** None. **A. Grahl:** None. **M.L. Loggia:** None. **A.D. Wasan:** None. **R.R. Edwards:** None. **N. Vitaly:** None.

Poster

127. Human Chronic Pain Including Post-Injury

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 127.15

Topic: D.08. Multisensory Integration

Support: John. J Kopchick Graduate Student Fellowship, Ohio University

Title: Transient knee deafferentation impacts neural activity for knee movement: A preliminary analysis

Authors: *M. CHAPUT, J. E. SIMON, B. T. FARRAYE, D. R. GROOMS;
Ohio Univ., Athens, OH

Abstract: Ligament rupture is a deafferentation injury and contributes to widespread nervous system plasticity. For knee injuries, the effect of deafferentation on plasticity is unknown, limiting advancing rehabilitation interventions. The purpose of this study was to determine the neural activity associated with transient knee joint deafferentation as a model for knee injury. Eleven recreationally active individuals (7 female, 23.6± 0.9yrs, 171.6± 13.2cm, 75.0± 20.4kg) volunteered. Participants were right leg dominant with no history of right knee surgery, leg injury, or concussion in the previous 6 months. Functional magnetic resonance imaging was used to quantify blood-oxygen-level-dependent signal with a 3T MR scanner and 16-channel head coil. Each participant was scanned under two experimental conditions (sham [staged injection] vs deafferentation [Lidocaine]) separated by at least 3 days. The injection of Lidocaine (5mL 2% HCL 20mg/mL) was performed by a general surgeon via a standard lateral approach, 27-gauge 1.5-inch needle, and sterile preparation. A right knee kicking task was performed for each condition with 30 second blocks of alternating rest (5) and movement (4) paced to an auditory

metronome (1.2Hz). Task-related neural activity was contrasted between conditions with a single-group paired t-test analysis. An a priori significance level of $p<0.05$, z-threshold>3.1, and cluster corrected for multiple comparisons was applied. Two separate psychophysiologic interaction analyses were performed from the significant group contrast clusters ($p<0.05$, z-threshold>3.1 subject and >2.3 group level, cluster corrected) to determine functional connectivity. Significant regions are reported from peak voxel location. After deafferentation, neural activity decreased in the ipsilateral lingual gyrus ([LG] z-max=5.84, 408 voxels) and contralateral intracalcarine cortex ([ICC] z-max=4.73, 196 voxels). The ICC demonstrated positive interaction to the contralateral occipital cortex (z-max=3.68, 406 voxels) and contralateral middle frontal gyrus (z-max=3.57, 1238 voxels) and LG positively interacted with the contralateral middle frontal gyrus (z-max=3.51, 731 voxels) and ipsilateral superior frontal gyrus (z-max=3.59, 731voxels) in the sham condition. After deafferentation, the ICC negatively interacted with right cerebellar lobule VI (z-max=3.59, 465 voxels) and LG negatively interacted with the cuneal cortex (z-max=3.64, 624 voxels). Experimental deafferentation resulted in decreased activation and connectivity in regions responsible for multimodal sensory integration and visual memory.

Disclosures: **M. Chaput:** None. **J.E. Simon:** None. **B.T. Farraye:** None. **D.R. Grooms:** None.

Poster

127. Human Chronic Pain Including Post-Injury

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 127.16

Topic: D.08. Multisensory Integration

Support: National Athletic Trainers' Association Foundation
National Strength and Conditioning Association Foundation
The Ohio State College of Medicine

Title: Unique sensorimotor cortical organization in individuals with anterior cruciate ligament reconstruction

Authors: *A. J. SCHNITTJER[1], A. S. LEPLEY[2], J. A. ONATE[3], H. W. KIM[1], C. R. CRISS[1], P. LEE[1], J. E. SIMON[1], D. R. GROOMS[1];
[1]Ohio Univ., Athens, OH; [2]Univ. of Michigan, Ann Arbor, MI; [3]Ohio State Univ., Columbus, OH

Abstract: Anterior cruciate ligament rupture can lead to surgical reconstruction (ACLR) and extensive rehabilitation, but poor outcomes like quadriceps weakness and performance deficits persist after ACLR. Recent data suggest a cascade of peripheral and central nervous system changes after ACLR, however, sensorimotor cortical organization for the involved limb is unknown. The purpose of this study was to examine cortical areas of functional activity overlap and nonoverlap for involved knee movement between ACLR and control groups. Eighteen

participants with left knee ACLR (8 males, 21.67±2.63 yrs, 171.72±10.28 cm, 70.48±15.70 kg, 45.94±32.04 mo. post-surgery) and 18 healthy controls (7 males, 23.11±3.03 yrs, 173.28±10.87 cm, 69.66±15.09 kg) were enrolled. Participants performed a unilateral knee motor control task for each limb separately during functional magnetic resonance imaging (fMRI), consisting of 30-sec blocks, 4 blocks of knee flexion/extension movement and 5 rest blocks. The independent variable was group (ACLR and control). Imaging data were preprocessed using FSL (FMRIB, Oxford UK) including brain extraction, motion correction, 6-mm spatial smoothing, mean-based intensity normalization, denoising with Independent Component Analysis-based strategy for Automatic Removal of Motion Artifacts (ICA-AROMA), high-pass temporal filtering at 100 Hz, and non-linear anatomical and standard space registration. A second-level analysis was conducted to contrast between limb movement (involved>uninvolved) within ACLR and control groups. A conjunction analysis was conducted to determine the degree of statistical overlap in functional brain activity between groups for the involved limb. All fMRI data analyses were conducted with an *a priori* threshold of $z>3.1$, $p<0.05$ and cluster corrected for multiple comparisons. Brain activation during involved>uninvolved limb movement between groups statistically overlapped in one cluster, including areas of the precentral gyrus, postcentral gyrus, superior parietal lobule, and supplementary motor area (SMA) (voxel: 571, $z_{max}=4.74$, MNI_{xyz}: 10, -34, 72, $p<0.0001$). ACLR nonoverlapping areas included parts of the precentral gyrus, postcentral gyrus, SMA, superior parietal lobule, lateral occipital cortex (superior division), and precuneus cortex. Control group nonoverlapping areas included parts of the precentral gyrus, postcentral gyrus, SMA, and superior parietal lobule. The cortical reorganization following ACLR may indicate a shift of involved knee sensorimotor representation potentially elevating motor planning, attention and visuospatial perception associated neural activity.

Disclosures: **A.J. Schnittjer:** None. **A.S. Lepley:** None. **J.A. Onate:** None. **H.W. Kim:** None. **C.R. Criss:** None. **P. Lee:** None. **J.E. Simon:** None. **D.R. Grooms:** None.

Poster

128. New Models, Methods, and Approaches in Pain Research

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 128.01

Topic: D.02. Somatosensation – Pain

Support: NIGMS Grant 1DP2GM140923-01
NIDA Grant 5T32DA028874-11

Title: Viral strategies for targeting and manipulating mu opioidergic neuronal populations for cell specific studies and therapeutic interventions

Authors: *G. J. SALIMANDO[1], S. TREMBLAY[1], J. LI[5], B. A. KIMMEY[1], S. ROGERS[1], N. M. MCCALL[1], T. BORNER[2], K. L. GARDINER[3], S. JAYAKER[6], I. SINGEC[7], C. J. WOOLF[6], M. R. HAYES[2], B. C. DE JONGHE[2], J. A. BLENDY[1], M. L. PLATT[1], W. R. RENTHAL[5], C. RAMAKRISHNAN[8], K. DEISSEROTH[9], G. CORDER[4];

[1]Dept. of Neurosci., [2]Dept. of Biobehavioral Hlth. Sci., [3]Dept. of Systems Pharm & Translational Therapeut., [4]Dept. of Psych., Univ. of Pennsylvania, Philadelphia, PA; [5]Dept. of Neurobio., Brigham and Women's Hosp. and Harvard Med. Sch., Boston, MA; [6]F.M. Kirby Neurobio. Ctr., Boston Children's Hosp. and Harvard Med. Sch., Boston, MA; [7]Natl. Ctr. for Advancing Translational Sci., NIH, Bethesda, MD; [8]CNC Program, [9]Dept. of Psych. & Behavioral Sci., Stanford Univ., Stanford, CA

Abstract: With concurrent global epidemics of chronic pain and opioid use disorders, there is a critical need to identify, target, and manipulate specific cell populations in the peripheral and central nervous systems expressing the mu-opioid receptor (MOR). To gain long-term access to neural cell-types and circuits involved in modulating pain, analgesia and addiction, we have developed a catalog of MOR promoter (MORp) constructs for driving transgene expression in MOR+ cells that can be packaged within adeno-associated viral (AAV) vectors. Working off the mouse *Oprm1* promoter, we created an initial set of AAV1-mMORp-eYFP viruses and tested for transduction efficacy in cultured cortical neurons. To validate *in vivo* selectivity, we then performed intracranial injections of mMORp viruses into several structures implicated in pain-processing, opioid analgesia and drug reward in C57BL6/J male and female mice, including: prefrontal cortex (PFC), central amygdala (CeA), ventral tegmental area (VTA), dorsomedial striatum and spinal cord. Robust expression of fluorophore transgenes were observed in all regions, with immunohistochemistry and fluorescent *in situ* hybridization studies demonstrating significant overlap of viral signal with putative MOR+ cells, as well as co-expression on Cre+ cells in two Oprm1-Cre transgenic mouse lines. Furthermore, we evaluated mMORp transduction across other non-transgenic animal models and found comparable reporter expression in the CeA and VTA of Sprague-Dawley rats and Asian musk shrews. Next, to demonstrate functional utility, mMORp constructs designed to drive expression of the chemogenetic receptor hM4Di and calcium activity indicator GCaMP6f were injected into mouse spinal cord and CeA, respectively. Pain-related behaviors in response to noxious mechanical stimuli, heat and formalin were observed to markedly decrease following clozapine-n-oxide administration in hM4Di spinal-expressing mice, and calcium mediated events observed in the CeA of GCaMP6f injected mice in response to noxious heat stimuli were significantly reduced in amplitude and frequency following systemic morphine administration. In addition to mouse promoter driven constructs, we created a human *OPRM1* promoter driven construct and confirmed its selective expression in *OPRM1*+ neurons in macaque PFC, insula, thalamus, and amygdala. Taken together, our new MORp viral toolkit provides researchers cell-type specific genetic access to putative MOR+ neurons in order to facilitate monitoring and manipulation of opioidergic neural circuits across a range of vertebrate species and translational screening models for pain and addiction.

Disclosures: G.J. Salimando: None. **S. Tremblay:** None. **J. Li:** None. **B.A. Kimmey:** None. **S. Rogers:** None. **N.M. McCall:** None. **T. Borner:** None. **K.L. Gardiner:** None. **S. Jayaker:** None. **I. Singec:** None. **C.J. Woolf:** None. **M.R. Hayes:** None. **B.C. De Jonghe:** None. **J.A. Blendy:** None. **M.L. Platt:** None. **W.R. Renthal:** None. **C. Ramakrishnan:** None. **K. Deisseroth:** None. **G. Corder:** None.

Poster

128. New Models, Methods, and Approaches in Pain Research

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 128.02

Topic: D.02. Somatosensation – Pain

Support: NIH 1DP2GM14092301

Title: Modeling expectation-driven endogenous analgesia in mice

Authors: *L. EJOH[1], G. F. CORDER[2];
[2]Psychiatry, [1]Univ. of Pennsylvania, Philadelphia, PA

Abstract: The experience of pain is highly modifiable by an individual's expectations, which can induce placebo analgesia. Placebo analgesia is an expectation-driven reduction in pain perception that can be attributed to a treatment context or operant-induced internal states, such as suggested safety after escape. Some current placebo models in mice and humans rely on a pharmacological conditioning design, where an administered drug, such as an opiate, is paired with cues over many days. Such designs can confound interpretations of reward motivation versus analgesia and may induce compensatory changes related to opioid-induced hyperalgesia, tolerance, or alterations in opioid peptide expression. Here, we developed a novel non-pharmacological placebo model that utilizes instrumental conditioning to drive expectation-mediated analgesia. In our optimized endogenous analgesia conditioning (EAC) paradigm, mice are placed in an open two-chamber maze with distinct visual contexts and a temperature-programmable floor plate, with continuous free access to explore either chamber. During the instrumental conditioning, the experimental context plate is set at a noxious temperature for EAC-conditioned mice, or an innocuous temperature, for non-conditioned controls, while the other plate remains stably innocuous to serve as the expected safe/pain-free environment. Following multiple within and across-day conditioning sessions where mice can instrumentally escape to the innocuous context, both context plates are set to noxious temperatures and multiple cameras record exploration, motor actions, and nocifensive behaviors as subjects freely explore the inescapable noxious contexts. We found that EAC mice prefer to spend significantly more time in the formerly innocuous paired context and display attenuated nocifensive behaviors, compared to non-conditioned controls. We are now exploring the role of multiple neuromodulatory systems in the learning and expectation phases of the EAC paradigm, as well as the specific neural circuits involved in the analgesic effects. Collectively, the EAC model demonstrates that context-based nociceptive conditioning can be used as a paradigm to induce endogenous analgesia in mice and may serve as a strong platform to investigate the malleable nature of pain perception in preclinical pain models.

Disclosures: L. Ejoh: None. **G.F. Corder:** None.

Poster

128. New Models, Methods, and Approaches in Pain Research

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 128.03

Topic: D.02. Somatosensation – Pain

Support: 1DP2GM140923-01

Title: An automated open-loop platform for the detection of pain and analgesia in mice

Authors: J. JAMES[1], M. WACHIRA[1], A. HSU[2], E. A. YTTRI[2], ***G. CORDER**[1];
[1]Univ. of Pennsylvania, Philadelphia, PA; [2]Carnegie Mellon Univ., Pittsburgh, PA

Abstract: The ability to observe and quantify pain in non-verbal animals remains a challenge and barrier to the basic neurobiological understanding of pain and for the preclinical screening of novel analgesics. Given the complexity of pain as a sensory and emotional experience, and the richness of naturalistic pain-related behaviors, we have developed an automated platform for studying pain in mice that allows for streamlined behavior classification using a controlled environment and open-source, machine learning algorithms. In its design, high-speed videography captures the spatiotemporal kinematics of mouse limb and body positions from a bottom-up perspective through a glass floor contained within a dark chamber encircled with infrared lighting. This setup removes the human experimenter—both as a looming threat administering noxious stimuli, and as the data-acquirer providing subjective determination of putative pain responses—with greater focus placed on a diverse range of ethological motor and nocifensive behaviors. For video processing, we first employed DeepLabCut (DLC) to create male and female-specific pose estimation networks built on videos of mice performing nocifensive behaviors in response to diverse noxious stimuli. Next, transitioning the DLC data output to B-SOiD—an unsupervised pattern recognition algorithm with supervised classification of behaviors—we generated a semi-biased model that classifies, quantifies, and analyzes nocifensive and general locomotive activities. Using this platform and trained deep learning networks, we then determined the efficacy of morphine analgesia by calculating the changes in behavior dynamics and clustering classifications across varying dosages of the opioid during acute inflammatory noxious events. We are now expanding this system's capabilities to incorporate optogenetic control and calcium imaging of nociceptive and endogenous analgesia neural circuits in the periphery, spinal cord, and brain.

Disclosures: J. James: None. **M. Wachira:** None. **A. Hsu:** None. **E.A. Yttri:** None. **G. Corder:** None.

Poster

128. New Models, Methods, and Approaches in Pain Research

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 128.04

Topic: D.02. Somatosensation – Pain

Support: NINDS R21 NS121946

Title: Sting expression in peripheral sensory neurons leads to dna virus recognition and pain

Authors: *S. LEE[1], F. BONIFACIO[2], A. SILVEIRA PRUDENTE[1], J. ROH[3], S. JUNG[4], C.-K. PARK[3], T. M. CUNHA[2], T. BERTA[1];
[1]Univ. of Cincinnati, Cincinnati, OH; [2]Univ. of São Paulo, Ribeirão Preto, Brazil; [3]Gachon Univ., Incheon, Korea, Republic of; [4]Hanyang Univ., Seoul, Korea, Republic of

Abstract: Pain is an early and common symptom of viral infections, and yet we have a limited understanding about the mechanisms through which viruses induce pain. Viral recognition depends mainly on the detection of viral nucleic acids, RNA and DNA, which are detected Pattern recognition receptors (PRRs). Among PRRs, Stimulator of interferon genes (STING) plays a key role in innate immune cells in detecting cytosolic DNA and induces type I interferon (IFN-I) for host detection and defense against viral pathogens. Although this PRR and interferon signaling has been recently proposed as a critical regulator of physiological pain and a promising new target for treating chronic pain, whether and how STING in peripheral sensory neurons participate in virus recognition, defense and pain is still completely unknown. Here, we report that intradermal delivery of viral oligonucleotides induced pain responses in mice via the expression of STING and the transient receptor potential vanilloid subtype 1 (TRPV1) in sensory neurons. In particular, we found that intradermal injections in mouse hindpaw of double-stranded DNA (dsDNA) oligonucleotides derived from the herpes simplex virus (HSV-60) induced immediate spontaneous pain responses (hindpaw lifting, shacking and licking), as well as transitory mechanical pain hypersensitivities lasting up to 4 h. Remarkably, mice treated with the TRPV1 antagonist AMG9810 or resiniferatoxin, an ultrapotent TRPV1 agonist leading to the peripheral denervation, abrogated both HSV-60 induced pain responses. STING expression is enriched in TRPV1+ peripheral sensory neurons, and similar abrogation of HSV-60 induced pain responses was observed in conditional knockout mice lacking the expression of STING uniquely in peripheral sensory neurons. In support of these data, we also found that STING agonists can directly activate sensory neurons *in vitro* calcium imaging analysis and elicited pain responses in control wild-type mice, but not TRPV1 knockout mice. Thus, our initial findings provide a previously undiscovered mechanism by which DNA viruses are recognized by peripheral sensory neurons and induce pain.

Disclosures: S. Lee: None. **F. Bonifacio:** None. **A. Silveira Prudente:** None. **J. Roh:** None. **S. Jung:** None. **C. Park:** None. **T.M. Cunha:** None. **T. Berta:** None.

Poster

128. New Models, Methods, and Approaches in Pain Research

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 128.05

Topic: D.02. Somatosensation – Pain

Title: Dorsal root ganglion delivery of test articles in rats; proof-of-concept method and efficacy of RLVT-14-02 in a rat partial sciatic nerve ligation model

Authors: A.-M. KARKKAINEN[1], ***M. DUDEK**[1], S. BÄCK[1], D. MISZCZUK[1], S. SIKORA[2]; [1]Charles River Discovery Services, Kuopio, Finland; [2]Releviate Therapeut. LLC, Oceanside, CA

Abstract: Neuropathic pain (NP) is caused by an injury/disease within nervous systems. Current first-line managements involve e.g. opioids and anticonvulsants, to which NP however usually responds poorly. There thus is a crucial need for new, specific, and effective drugs to treat NP. Matrix metalloprotease 14 (MMP-14) is a master-switch for the development of NP via proteolytic activation of MMP-2, and a positive feed-back loop with myelin basic protein degradation fragments. Pharmacologic inhibition of MMP-2 has been proven to result in reversal of MMP-14-mediated pathophysiology associated with NP. Therefore, inhibition of MMP-14 may have potential as a novel target to treat NP. Upon testing novel drugs, their full potential - including the correct administration route - requires to be evaluated. In this study, we provide PoC data on rat intra-DRG (i.DRG) delivery , and a beneficial effect of RLVT-14-02 (anti-MMP-14 human monoclonal antibodies) on rat tactile allodynia, evoked by the PSNL model. CD rats (n=10) were subjected to PSNL by performing a ligature around the dorsal 1/3 - 1/2 of the common sciatic nerve. Mechanical sensitivity was defined at baseline (pre-PSNL), D6 (post-PSNL, pre-treatment), and D8, D14, D16 D21 post-dosing, using electronic von Frey (evF). The RLVT-14 02 was administered on D7, via intrathecal (i.t.), intravenous (i.v.), or intra-DRG (i.DRG) route. The i.DRG delivery involved surgical exposure of lumbar 4 (L4) and L5 DRGs ipsilateral to the PSNL surgery, followed by a slow infusion of the substances (2-µl/DRG), with custom made glass capillary needle attached to Hamilton syringe. Tactile allodynia was measured by evF, to evaluate model induction and RLVT-14 02 efficacy. Our data shows highly repeatable i.DRG administration in rats, through optimized experimental procedure and with confirmed focal localization by dyes, and later, by immunohistochemical verification. Mere i.DRG administration did not affect tactile allodynia within an up to 2-month follow-up. In RLVT-14-02 efficacy study, PSNL surgery evoked robust tactile allodynia. RLVT-14-02 significantly reduced the mechanical allodynia at days D16 and D21 (1 and 2 weeks post-administration), compared to the pre-dosing (D6) values. Importantly, delivered by i.t. and i.v. infusions, the described beneficial effect of RLVT-14-02 was either nonsignificant, or indistinguishable from unspecific control treatment. These data highlight the need of careful evaluation of correct delivery routes, which are specific to the disease model of interest, and mechanism of action of new treatments.

Disclosures: A. Karkkainen: None. **M. Dudek:** None. **S. Bäck:** None. **D. Miszczuk:** None. **S. Sikora:** None.

Poster

128. New Models, Methods, and Approaches in Pain Research

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 128.06

Topic: D.02. Somatosensation – Pain

Support: CIHR Foundation Grant

Title: Optogenetic activation of sensory afferents: precise transdermal photostimulation and paw withdrawal measurement in mice

Authors: *C. DEDEK, M. AZADGOLEH, S. PRESCOTT;
SickKids, Toronto, ON, Canada

Abstract: Optogenetic activation of primary afferents to study pain behaviour in mice is increasing in popularity, but the techniques being employed are often rudimentary; A handheld fiber optic is used to stimulate while an experimenter gauges the behaviour by eye. Variation in fiber optic positioning introduces variance in the delivered light intensity, while subjective measures result in experimenter bias. To address these issues, we developed a combined photostimulator and withdrawal detector that produces reproducible photostimuli while precisely measuring the latency of responses. This photostimulator consists of a red and blue LED mounted on a mobile platform. The red and blue light are mixed and focussed at a fixed distance onto a plexiglass stage, where mice are free to move. An infrared laser can also deliver radiant heat. Using a substage camera to visualize the paw, the photostimulator is moved to aim at the target paw using visual feedback from the red light. A photodetector senses the red light reflected off the paw and is used to measure withdrawal latency from onset of the blue photostimulus. By measuring the intensity of light delivered to the target, we confirmed that our photostimulator delivered more consistent stimuli than a handheld fiber optic across repeated trials by the same experimenter, and across different experimenters. In Advillin-ChR2, TrpV1-ChR2 and vGlut1-ChR2 mice, we used this reproducible photostimulus and high resolution red-light reflectance measurement to precisely determine the response threshold and the latency of withdrawal to suprathreshold stimuli. Latencies measured with red light were comparable to those measured from high-speed video. We show that, with less expensive hardware and less intensive data processing, the former method has the same level of performance. Our results indicate that latency to paw withdrawal decreases with increasing stimulus intensity, suggesting withdrawal latency may be a simple and useful proxy for inferring the painfulness of a stimulus in mice. Interestingly, we found that withdrawal latencies at low intensity follow a bimodal distribution, with a mix of fast and slow responses; As stimulus intensity increases, latencies shift to the fast distribution. Our system will allow experimenters to deliver precise photostimuli and accurately measure the resulting behaviours.

Disclosures: C. Dedek: None. **M. Azadgoleh:** None. **S. Prescott:** None.

Poster

128. New Models, Methods, and Approaches in Pain Research

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 128.07

Topic: D.02. Somatosensation – Pain

Support: Columbia University Startup
Brain Research Foundation Seed Grant
Rita Allen Foundation Grant
Sloan Neuroscience Fellowship

Title: Investigation of pain linked escape behavior using C57 sublines

Authors: *J. BURDGE, W. MAYISENI, I. ABDUS-SABOOR;
Biol. Sci., Columbia Univ., New York, NY

Abstract: The same pain can cause wildly different reactions depending on who experiences it. The key to understanding why lies in the genetics that underlies the pain pathway. Studying genetic differences in pain has led to the identification of multiple components of the peripheral pain pathway and could in the same way be used to elucidate the pain pathway in the brain. Identifying genetically linked differences in pain behavior linked to the brain would allow for the study of the neural pathways that the brain uses to construct the sensation of pain and execute pain behaviors in response to noxious stimuli. Here we use the model of thermal escape jump, a behavior that originates from the brain, to examine how genetic variation leads to differences in pain behavior independent of pain sensitivity. We tested 18 genetically diverse inbred mouse lines to determine the levels of escape jump behavior they showed when placed on a hot plate at either extreme hot or cold temperatures, and then tested them for thermal sensitivity to heat and cold for comparison. This testing found heightened jumping behavior without any significant difference in thermal sensitivity, with C57BL/10SnJ mice, a subline of C57 mice, showing more than 10 times the jumping behavior exhibited by C57/BL6J wildtype mice. Critically, these findings indicate that these differences in jumping behavior are not caused by changes in nociception, resulting from differences in the periphery, but instead by the behavioral response itself which could only result from changes in the brain. When tested for general escape behavior using the tail suspension assay, C57/10SnJ mice showed twice the escape behavior as wild-type mice. Further testing of different types of escape behavior found that in scenarios where a painful stimulus was not present including the deluge escape test and jumping during baseline open field no significant difference in behavior was found between C57/10SnJ and wildtype. In escape scenarios including a painful stimulus such as tail suspension, thermal escape jump, and open field post hot plate C57/10SnJ mice showed heightened escape behavior compared to wildtype. Studying this heightened escape behavior linked to pain phenotype could reveal new interactions between the escape and pain behavioral pathways as well as specific neural types and projections relevant to each.

Disclosures: **J. Burdge:** None. **W. Mayiseni:** None. **I. Abdus-Saboor:** None.

Poster

128. New Models, Methods, and Approaches in Pain Research

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 128.08

Topic: D.02. Somatosensation – Pain

Title: Comparison between Manual and Electronic von Frey for the Evaluation of Mechanical Allodynia in Rat Models of Neuropathic Pain.

Authors: M. FEREYROLLES, V. MAFFRE, A. ZANON, Y. DARBAKY, ***L. DIOP**;
ANS Biotech, RIOM, France

Abstract: Tactile and mechanical allodynia are symptoms experienced by many patients suffering from different pathology especially from neuropathy. In patients with post-traumatic / postsurgical neuropathic pain, different methods were performed to evaluate tactile and mechanical allodynia. In rat, different models such as Chronic Constriction Injury (CCI) and Spared Nerve Injury (SNI) mimic neuropathic pain symptoms. The objective of pharmacological labs is to develop new antalgic to treat this specific pain and a growing need is observed in *in vivo* models of neuropathic pain but also in relevant tests able to detect the small variation of pain and especially tactile allodynia. The objective of this study was to assess the tactile and mechanical allodynia in rat models of neuropathic pain using manual and electronic of von Frey.
Methods: Male Sprague-Dawley rats (SPF status, Janvier, France), were used in the two neuropathic pain models. In the CCI model, rats (100-140 g the day of the surgery) underwent a sciatic nerve ligation. In the SNI model, tibial and peroneal nerves were sectioned on rats. Fourteen to twenty one days after surgery, tactile and mechanical allodynia were evaluate using manual von Frey and the up-and-down method described by Chaplan et al, 1994 or using the electronic von Frey, respectively. 50% response threshold and paw withdrawal thresholds were measured in rats treated with opioids and antiepileptics compounds.
Results: Tactile and mechanical allodynia was evidenced in both models. Marked increase in both paw withdrawal thresholds and 50 % response thresholds were observed in both neuropathic pain models after a single administration of morphine (3 mg/kg, s.c). However an acute administration of pregabalin (60 mg/kg, p.o.) did not show any significant variation in the paw withdrawal thresholds measured with electronic von Frey but a marked and dose related antiallodynic effects when tested with the manual von Frey.
Conclusion: In this study, manual von Frey using the Chaplan method showed more sensitive measurement of the tactile allodynia as evidence by a better detection of pharmacological efficacy of the antiepileptic compound, the pregabalin. Our study evidenced a difference of sensitivity of both technics of evaluation of tactile and mechanical allodynia and help to be more relevant in the choice of the technic used depending on the pharmacological treatment with the objective of development of new antalgic compounds for the neuropathic pain treatment.

Disclosures: **M. Fereyrolles:** A. Employment/Salary (full or part-time):; ANS Biotech. **V. Maffre:** A. Employment/Salary (full or part-time):; ANS Biotech. **A. Zanon:** A. Employment/Salary (full or part-time):; ANS Biotech. **Y. Darbaky:** A. Employment/Salary (full or part-time):; ANS Biotech. **L. Diop:** A. Employment/Salary (full or part-time):; ANS Biotech.

Poster

128. New Models, Methods, and Approaches in Pain Research

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 128.09

Topic: D.02. Somatosensation – Pain

Support: This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska Curie grant agreement No 814244.

Title: A high-capacity in vitro co-culture platform for the study of synaptic transmission

Authors: *L. MOLL[1,2], C. NODIN[1], C. I. SVENSSON[2], P. KARILA[1];
[1]Cellectricon AB, Mölndal, Sweden; [2]Karolinska Institutet, Solna, Sweden

Abstract: New targets and drugs are needed for the treatment of neurological disorders (ND) such as Alzheimer's disease, Parkinson's disease and chronic pain. To study changes in synaptic signal transmission (SST), a hallmark of many NDs, applications of more advanced microchannel-separated in vitro models have been described (Park et al., 2013). However, these models generally have low throughput, which limits their application in large-scale mechanistic or drug screening studies.

Here we present a high-capacity in vitro co-culture system for the study of SST in a recently developed microchannel plate (MC-plate) comprising 96 experimental units. We assessed SST between rat dorsal root ganglia neurons (DRG) and spinal cord neurons (SC) in microchannel-separated wells by applying electric field stimulation (EFS) to the DRG population while recording the response from the SC neurons on Cellectricon's optical electrophysiology platform (Sidders et al., 2018). The signal specificity was subsequently validated by pharmacological treatment of SC cultures with compounds modulating SST.

At 5 DIV DRGs grew extensive axons to adjacent wells, providing an opportunity for formation of synaptic connections with the subsequently added SC neurons. Functional EFS assessment at 13 DIV led to a response in 99 ± 1% of the DRG wells, with a calcium influx ratio of 1.14 ± 0.30 (mean ± SD). Moreover, SC wells displayed a significantly higher number of timed depolarizations in wells connected to pulsed DRG wells compared to wells not receiving EFS pulses (79 ± 17% vs 35 ± 9%; $P < 0.0001$, one-way ANOVA with Tukey post hoc, $N = 5$). Similarly, the response ratio in wells connected to a pulse-receiving well was significantly higher compared to non-pulsed wells (1.78 ± 0.26 vs 1.13 ± 0.20, $P < 0.0001$, $N= 5$). Taken together this indicates that SST occurred between the neuronal populations of spatially separated wells.The addition of synaptic modulators to SC wells did not affect the DRG response, whereas the AMPA antagonist NBQX induced a full block (EC_{50} = 27 nM) and the NMDA antagonist MK801 resulted in a partial block (EC_{50} = 127 nM) of the SST from DRGs to SC cells.

We have presented an approach to assess SST between discrete neuronal populations in a high-capacity MC-plate, allowing up to 96 parallel experiments. Moreover, the approach was validated with a set of tool compounds targeting SST. Given the high capacity, this platform can for example be used to assess effects of compounds along the pain pathway or to identify novel targets for NDs. Moreover, the platform may be extended to encompass cells from a peripheral target organ, e.g. bone or immune cells, to create a "disease in a dish" model for chronic pain.

Disclosures: **L. Moll:** A. Employment/Salary (full or part-time):; Cellectricon AB. **C. Nodin:** A. Employment/Salary (full or part-time):; Cellectricon AB. **C.I. Svensson:** F. Consulting Fees (e.g., advisory boards); Cellectricon AB. **P. Karila:** A. Employment/Salary (full or part-time):; Cellectricon AB.

Poster

128. New Models, Methods, and Approaches in Pain Research

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 128.10

Topic: D.02. Somatosensation – Pain

Title: Unveiling neurophysiological biomarkers and subjective predisposition to pain through artificial intelligence

Authors: *N. GOZZI[1], G. PREATONI[1], F. CIOTTI[1], M. HUBLI[2], P. SCHWEINHARDT[2], S. RASPOPOVIC[1];
[1]Dept. of Hlth. Sci. and Technol., ETH Zürich, Zürich, Switzerland; [2]Spinal Cord Injury Ctr., Balgrist Univ. Hosp., Zurich, Switzerland

Abstract: Pain is not just a simple physical reaction to an external stimulus, but rather a complex phenomenon comprising also emotional aspects. However, self-report scales are still considered the gold standard for pain assessment even though they are extremely biased by their subjective nature. Researchers have tried to achieve an objective measurement of pain and its relative biomarkers using machine learning (ML) algorithms. However, most of these studies search for biomarkers in specific pathologies or in reaction to single experimentally induced pain stimuli. Moreover, they do not consider the emotional components of pain. Consequently, today there are no objective tools to measure and treat pain in satisfactory manner. We investigate through Artificial intelligence (AI) how psychological and physiological components are impacting pain perception in different pathologies of chronic pain patients. To do so, we collected data from 40 chronic pain patients (spinal cord injury, low back pain, complex regional pain syndrome), who underwent two different types of experimentally induced pain: contact heat and pinprick experiments. Multidimensional data have been collected, including physiological recordings (i.e., electroencephalography (EEG), skin conductance (SC)) and complete psychological profiles (e.g., depression, anxiety, pain catastrophizing). Through explainable AI models, we first investigated which are the most important physiological features that characterize pain. Then, we exploited these reliable biomarkers using advanced hierarchical ML approaches to identify the subjective predisposition and bias to pain. Our models were able to reliably identify a painful stimulus. We found that the most important features to detect pain in the physiological recordings belong to the EEG power spectral density and amplitude measures of the SC. However, we also noticed differences between the two types of induced pain, highlighting the need of using a comprehensive experimental set-up to really find biomarkers of the pain experience and not only characteristic of the painful stimulus nature. Advanced ML techniques were instrumental to disentangle the physiological biomarkers with respect the subjective

predisposition to pain. Our model has the potential of opening the way to personalized therapies based on a comprehensive evaluation of everyone's pain experience.

Disclosures: **N. Gozzi:** None. **G. Preatoni:** None. **F. Ciotti:** None. **M. Hubli:** None. **P. Schweinhardt:** None. **S. Raspopovic:** None.

Poster

128. New Models, Methods, and Approaches in Pain Research

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 128.11

Topic: D.02. Somatosensation – Pain

Title: Long-term neuropathic pain and spinal cord pathology in an RNU rat model of L5 nerve root avulsion

Authors: J. LI, B. DE HARO, C. ABILAY, M. L. FU, D. PATEL, C. R. NICHOLAS, *C. A. PRIEST;
Neurona Therapeutics, Inc, South San Francisco, CA

Abstract: Nerve root avulsion injury occurs when a sudden tractive force on peripheral nerves causes the nerve roots to detach proximally from the spinal cord. This type of injury often leads to severe neuropathic pain that may be long-lasting and debilitating. Current methods of treatment are limited with variable outcomes, highlighting a medical need to develop novel therapeutic strategies. After avulsion injury, people often report chronic at-level neuropathic pain; however, most preclinical models of avulsion injury result in neuropathic pain that is either transient or below-level. In this study, the L5 nerve root avulsion model was evaluated for development of long-term, at-level pain. The L5 dorsal and ventral roots were unilaterally avulsed from the spinal cord by pulling the L5 dorsal root ganglion with steady force. Adult male immunodeficient RNU rats were observed for up to 11 months post-avulsion to gather data regarding long-term injury progression and recovery. Von Frey test results demonstrated that, compared to pre-injury and age-matched naïve control groups, avulsed animals developed stable mechanical allodynia in the ipsilateral hindpaw, and transient mechanical allodynia in the contralateral hindpaw. Nerve-avulsed animals also demonstrated a change of preference on a two-texture floor preference test compared to naïve controls. Spinal cord histopathology was progressive post-avulsion. In the acute phase after injury, the ipsilateral L5 superficial dorsal horn was damaged, and there was robust activation of microglia and astrocytes. By 11 months after injury, the ipsilateral L5 dorsal horn was dramatically smaller in area than the contralateral dorsal horn, and neuroinflammation and neuronal loss were persistent in ipsilateral laminae I-III. In summary, we validated L5 nerve root avulsion in the RNU rat as a long-term neuropathic pain model with stable mechanical allodynia, inflammation and neurodegeneration in the lumbar spinal cord. This model builds our understanding of chronic avulsion injury and may support development of novel treatments for chronic neuropathic pain.

Disclosures: **J. Li:** A. Employment/Salary (full or part-time):; Neurona Therapeutics, Inc. **B. De Haro:** A. Employment/Salary (full or part-time):; Neurona Therapeutics, Inc. **C. Abilay:** A. Employment/Salary (full or part-time):; Neurona Therapeutics, Inc. **M.L. Fu:** A. Employment/Salary (full or part-time):; Neurona Therapeutics, Inc. **D. Patel:** A. Employment/Salary (full or part-time):; Neurona Therapeutics, Inc. **C.R. Nicholas:** A. Employment/Salary (full or part-time):; Neurona Therapeutics, Inc. **C.A. Priest:** A. Employment/Salary (full or part-time):; Neurona Therapeutics, Inc.

Poster

128. New Models, Methods, and Approaches in Pain Research

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 128.12

Topic: D.02. Somatosensation – Pain

Support: SIP-MDC-20220300

Title: New N-benzylpiperidine compounds with antinociceptive properties in zebrafish

Authors: ***S. A. GIL-LÓPEZ**[1], J. SILES-GUEVARA[1], E. ROSALES-ORTEGA[2], G. NAVARRETE-VÁZQUEZ[2], M. DÉCIGA-CAMPOS[1];
[1]SEPI, Escuela Superior de Medicina, Inst. Politécnico Nacional, Ciudad de México, Mexico; [2]Facultad de Farmacia, Univ. Autónoma del Estado de Morelos, Morelos, Mexico

Abstract: Drugs uses to treat pain are associated with adverse effects, increasing the search for new drugs as alternative treatments for pain. Recently the sigma-one receptor (S1R) has been involved in the nociceptive process. In this sense, we synthesized a new drug class of analgesics considering LMH-2, antagonist S1RA, and haloperidol analog as base structural. Three compounds ROE-3, ROE-4, and ROE-6 were assayed in zebrafish (Danio rerio) as an alternative behavioral model of irritant compound-induced nociception. We evaluated the nociceptive effect of 1% acetic acid (10 µL/i.m, into the tail). Locomotor activity was quantified as nociceptive behavior, the number of times the fish crossed the lines between the quadrants of a glass Petri dish during 30 min. All compounds were prepared in a liter of water, and fish were exposed for 30 min before formalin or acetic acid injection. Buprenorphine and diclofenac, as standard antinociceptive drugs, were used as a positive control. Buprenorphine and diclofenac (3 mg/L and 30 mg/L, respectively) significantly inhibited nociception-induced acetic acid in a concentration-dependent manner. The results showed that the exposition of ROE compounds decreases the number of lines crossed on glass Petri; ROE-4 was more effective (92.3%) than ROE-3 (72.14%) or ROE 6 (69.45%). These compounds were compared with LMH-2 or haloperidol, which produced concentration-dependent antinociception. This preliminary assay describes the potential utility of these new compounds as analgesic. Further investigations are needed to characterize these compounds' pharmacological and toxicological properties.

Disclosures: **S.A. Gil-López:** None. **J. Siles-Guevara:** None. **E. Rosales-Ortega:** None. **G. Navarrete-Vázquez:** None. **M. Déciga-Campos:** None.

Poster

128. New Models, Methods, and Approaches in Pain Research

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 128.13

Topic: D.02. Somatosensation – Pain

Title: Behavioral characteristics during thermal preference plate test on the development of painful diabetic neuropathy for rats

Authors: *D. C. LEE[1], D. WANG[3], K. LEE[4], Z. B. KAGAN[5], K. BRADLEY[2];
[1]Nevro, Nevro, Agua Dulce, CA; [2]Nevro, Redwood city, CA; [3]Nevro Corp, Redwood City, CA; [4]Res., Nevro Corp, Mississauga, ON, Canada; [5]Nevro Corp., Lake Oswego, OR

Abstract: Introduction: Painful diabetic neuropathy (PDN) is a serious complication of diabetes and occurs in approximately 20% of patients with diabetes mellitus. In a recent randomized controlled clinical trial, 10kHz spinal cord stimulation (10kHz SCS) was shown to be a promising therapy for PDN, in both pain reduction and possible neurological improvements (Petersen et al 2021). To characterize possible sensory improvements with 10kHzSCS in PDN, we first sought to determine the most sensitive metrics of behavioral change during PDN development in a streptozotocin (STZ) animal model undergoing a 10 min Thermal Preference Plate Test (TPPT). **Methods:** Each rat was placed in a Plexiglas cage surrounding two adjacent thermal plates (30C vs. 45C) for 10 min. The location of the rat body was traced by a video camera and analyzed by custom image tracking software. The fraction of time the rat spent on the control side (30C) and the total distance traveled were computed to assess basic behaviors. In addition, dynamic behaviors over time were assessed by the time to travel 50% (T50) and 80% (T80) of the total distance as well as number of crossings between plates. TPPT was studied on day 0, 7 and 14 from STZ injection. Body weight, blood glucose and von Frey paw withdrawal threshold (VFPWT) on the left hind paw were collected on the same days as TPPT. **Results:** Ten rats were tested. A single effective dose (60 mg/kg) of the cytotoxic agent STZ caused the 7wk-old Sprague-Dawley rats to become hyperglycemic (>270 mg/dl) within 72 hours. On day 7, glucose, body weight, VFPWT and percentage of time spent on control side were significantly different ($p<0.05$) compared to those from day 0. Total distance traveled was not significant (day 0: 5.9±1.8m, day 7: 5.4±1.6m, $p=0.48$) until day 14 (3.7±1.1, $p=0.0004$). From day 0 to 14, the T50 dropped from 230±30s to 201±57s ($p=0.09$) and T80 dropped from 419±51s to 362±70s ($p=0.04$). For both T50 and T80, mean and variance changed together. These implied that average values showed the trend in the STZ group, but wide variance on day 14 may represent heterogeneous patterns for exploring plates. On day 14, 60% of rats traveled 50% of total distance before 200s (out of 600s), while on day 0, only 10% of rats did. **Conclusion:** Rat behaviors demonstrated both steady state and dynamic changes with the development of STZ-

based PDN. We found that total distance and percentage of time spent on control side may be most promising for tracking thermoceptive-based behavioral changes in the PDN animal model.

Disclosures: **D.C. Lee:** A. Employment/Salary (full or part-time):; Nevro. **D. Wang:** A. Employment/Salary (full or part-time):; Nevro. **K. Lee:** A. Employment/Salary (full or part-time):; Nevro. **Z.B. Kagan:** A. Employment/Salary (full or part-time):; Nevro. **K. Bradley:** A. Employment/Salary (full or part-time):; Nevro.

Poster

128. New Models, Methods, and Approaches in Pain Research

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 128.14

Topic: D.02. Somatosensation – Pain

Support: CIHR grant FDN-159906

Title: An improved conflict avoidance assay to investigate modality-specific nociception in rodent pain models

Authors: *S. FERLAND[1], F. M. FERRINI[2], Y. DE KONINCK[1];
[1]CERVO Brain Res. Ctr., Laval Univ. / IUSMQ, Quebec, QC, Canada; [2]Univ. of Turin, Grugliasco, Italy

Abstract: INTRODUCTION Reflex-based approaches in animal pain models have been largely used in research; however, it remains unclear whether differences in reflexes lead to significant changes in the decision-making of animals. This has sparked efforts to develop operant assays to study evoked pain in animals. To date, few of these methods can evaluate and compare sensitivity across nociceptive modalities. Understanding mechanisms underlying modality-specific hypersensitivity would lead to a better understanding of diverse pain pathologies and their treatment. Our aim is to improve an existing operant assay (conflict avoidance) to evaluate and compare modality-specific sensitivity in mice of both sexes and to test it in a nerve-injury model. **METHOD** The apparatus is composed of a lit and a dark chamber linked by a corridor where thermal and mechanical stimuli are presented. Two cold-hot plate (Bioseb) were used to deliver thermal stimuli (15°C to 50°C) and an array of height-adjustable pins (0 to 4 mm) served as mechanical stimuli. Mice naturally avoid light, but they must cross the nociceptive stimulus to escape it and move to the dark chamber. The testing protocol consisted of five days: acclimatation, training and three testing days where mice were presented over five trials with mechanical, cold and heat stimuli of ascending intensity. The latency to escape from the lit chamber and the time spent in the dark chamber were measured from videos and reported as the difference from the baseline taken at the beginning of each day. Results from the assay were compared to reflex-based measurements (von Frey, dry ice, Hargreaves). 8 to 12 weeks old C57BL/6J mice of both sexes were used. A polyethylene cuff (PE-20) was inserted around the main branch of the sciatic nerve to induce neuropathic pain in a subset of animals. **RESULTS**

We optimized the existing assay by validating the aversiveness of the lit chamber and its effect on training performances. We found that in optimized conditions, one or both measures scaled with stimulus intensity for all modalities tested. Significant differences in both measures were found between naïve males and females for cold and heat, females being less sensitive to cold and more sensitive to heat. The cuff model caused a significant change in mechanical sensitivity, but not heat or cold hypersensitivity. **CONCLUSION** Our results show that our modified assay is a promising new method to evaluate modality-specific sensitivity based on voluntary behavior rather than reflexive. This method is solid, objective and highly reproducible and is well suited for dissecting the contribution of specific sensory modalities in the onset of neuropathic p ain symptoms.

Disclosures: S. Ferland: None. **F.M. Ferrini:** None. **Y. De Koninck:** None.

Poster

128. New Models, Methods, and Approaches in Pain Research

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 128.15

Topic: D.02. Somatosensation – Pain

Support: SEP-Cinvestav Grant 269 to JM and 129 to VG-S
Conacyt Grant A1-S-40015 to VG-S

Title: Chronic restraint stress and social transfer of stress produce tactile allodynia mediated by the TNFα receptor in rats

Authors: *A. PLUMA-PLUMA[1], G. GARCÍA[2], V. GRANADOS-SOTO[2], J. MURBARTIAN[1]; [1]Cinvestav, Unidad Coapa, Cinvestav, Unidad Coapa, Ciudad DE Mexico, Mexico; [2]Cinvestav Sede Sur, Cinvestav Sede Sur, Mexico DF, Mexico

Abstract: Stress is a normal physiological response that promotes preservation and survival. However, chronic stress produces a dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis that contributes to developing depression- and anxiety-like behaviors as well as sensorial disorders. Exposure to chronic stress induces nociceptive hypersensitivity in rodents and humans. Previous studies have shown the relevance of HMGB1 and TNFα in nerve- or tissue injury-induced nociception. However, the role of these proteins in authentic and transmitted chronic stress-induced nociception is unknown. Thus, the purpose of this study was to determine the participation of the spinal HMGB1-TNFα signaling pathway and TNFα receptor 1 (TNFR1) in rats subjected to chronic restraint stress and social transfer of stress. Chronic stress induced tactile allodynia in rats. Non-stressed female rats showed increased sniff behavior of the anogenital area of stressed rats. Non-stressed rats also developed tactile allodynia. Intrathecal injection of glycyrrhizin (HMGB1 inhibitor), thalidomide (TNFα synthesis inhibitor) and R7050 (TNFR1 antagonist) reduced tactile allodynia in female and male rats with chronic restrain stress (authentic stress) or social transfer of stress (transmitted stress). Authentic and transmitted stress

enhanced HMGB1 and TNFR1 protein expression in DRG and dorsal spinal cord of rats. Our data suggests that the spinal HMGB1/TNFα signaling pathway and TNFR1 play a relevant role in the maintenance of authentic- and transmitted stress-induced nociceptive hypersensitivity in rats.

Disclosures: A. Pluma-Pluma: None. **G. García:** None. **V. Granados-Soto:** None. **J. Murbartian:** None.

Poster

128. New Models, Methods, and Approaches in Pain Research

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 128.16

Topic: D.02. Somatosensation – Pain

Title: Measuring pain in a chronic inflammatory rat model using a novel high speed videography-based pain scale

Authors: *C. DRESSLER[1], M. JIWANJI[3], B. DUNHAM[1], W. FOSTER[4], I. ABDUS-SABOOR[5], N. T. FRIED[6], M. E. WIMMER[2];
[2]Psychology, [1]Temple Univ., Philadelphia, PA; [3]Temple Univ. Undergraduate Neurosci. Program, Camp Hill, PA; [4]Biol., Columbia Univ., New York, NY; [5]Biol., Univ. of Pennsylvania, Philadelphia, PA; [6]Dept. of Biol., Dept. of Neurosci., Philadelphia, PA

Abstract: Chronic pain is a socio-economic burden affecting more than 30% of people worldwide. This multi-dimensional condition can lead to severe disabilities and has a significantly negative impact on the quality of life, increasing with the duration of pain. There is much literature on the mechanisms involved in the establishment of acute pain, however, the transition to chronic pain and its etiology and risk factors are poorly understood. We recently established a novel pain scale using high-speed video imaging, and combining face grimace with paw kinematics into a single reliable pain score in rats. By mapping sub-second mechanically-evoked behaviors to eight stimuli in both males and females, we transformed the data into a single dimension using statistical and machine learning approaches to generate an easily interpretable rat pain scale. Previous research has relied on reflexive paw withdrawal assays to measure pain that result in binary responses in rats and allows for limited interpretation. With the use of the rat pain scale, we can refine the analysis of each withdrawal response. This approach consistently distinguished innocuous stimuli from painful pinpricks, reliably predicting which stimuli would be perceived as innocuous or painful in rats. Utilizing this pain scale will aid in the investigation of the transition from acute to chronic pain, shedding light on the contributions and extent of involvement of the immune and nervous system, which remains unclear today. To study chronic pain, we combined the use of the rat pain scale and the Complete Freund's Adjuvant (CFA)-induced chronic pain rat model. The hind paw was injected with CFA (100 ul) to induce inflammatory pain, mimicking a wide variety of etiologies related to chronic pain; controls received saline. Using the CFA-induced chronic pain rat model, a pain assay was

applied to investigate pain-related behaviors at different time points. Over the course of 5 weeks, with the use of four different stimuli, VF60, VF100, light pinprick, and heavy pinprick, we were able to follow the pain levels, duration, recovery, and measure the pain behavioral response. We can establish a pain time course identifying each stimuli as producing allodynia or hyperalgesia symptoms, both of which are prominent in patients with chronic pain. Having a better understanding of chronic pain can provide novel à-la-carte therapeutical solutions, aiding in decreasing its increased reliance on the use of strong opioids as a current treatment option. These studies will provide us with tremendous biological information on pain levels, pain chronicity and pain pathways involved in a pro-inflammatory state induced by CFA.

Disclosures: C. Dressler: None. **M. Jiwanji:** None. **B. Dunham:** None. **W. Foster:** None. **I. Abdus-Saboor:** None. **N.T. Fried:** None. **M.E. Wimmer:** None.

Poster

128. New Models, Methods, and Approaches in Pain Research

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 128.17

Topic: D.02. Somatosensation – Pain

Title: Olfactory cues mediate the rapid social transfer of pain in mice

Authors: E. JONES[1], S. TUY[2], B. A. REIN[3], *M. L. SMITH[4];
[1]Univ. of San Diego, San Diego, CA; [2]Univ. of San diego, San Diego, CA; [3]Stanford Univ., Sunnyvale, CA; [4]UCSD, San Diego, CA

Abstract: Empathy is an essential component of social communication that involves experiencing others' sensory and affective states. Empathy-like behavior is evolutionarily conserved in a range of species, including rodents. For example, we developed a model of empathy where *bystander* mice rapidly adopt the sensory and emotional state of a social partner, a key component of empathy. During this "social transfer of pain," bystander mice socially interact with a familiar sex-matched cagemate that is experiencing inflammatory pain (due to an hindpaw injection of Complete Freunds Adjuvant; CFA). Following the one-hour social interaction, bystander mice demonstrate pain behavior that is indistinguishable from CFA-injected mice, including mechanical and thermal hypersensitivity and a negative affective state. To determine the sensory channel mediating this social communication, we assessed the ability of olfactory cues to provoke hyperalgesia in bystander mice during the social transfer of pain. First, we injected male and female mice with CFA and put them back into their homecages for 24hrs (for the control condition, we handled mice in the same manner, without giving any injection). After 24hrs, we took 30g of soiled bedding from the cages of either CFA injected mice or controls and spread it across clean, empty cages. Sex-matched naïve bystander mice were then placed in these cages for 1hr. Following 1hr of exposure to CFA bedding, bystander mice demonstrated significant and prolonged hyperalgesia that lasted for >72h. Bystanders that were exposed to control bedding did not demonstrate any changes in mechanical or thermal

sensitivity. To ensure scientific rigor, experimenters were blinded to group conditions. These findings demonstrate that olfactory cues released into the social environment by mice experiencing pain are sufficient to rapidly provoke hyperalgesia in nearby mice. In addition, these experiments highlight the need for proper consideration of how animals are housed and tested in pain studies.

Disclosures: E. Jones: None. **S. Tuy:** None. **B.A. Rein:** None. **M.L. Smith:** None.

Poster

128. New Models, Methods, and Approaches in Pain Research

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 128.18

Topic: D.02. Somatosensation – Pain

Support: New Frontiers in Research Fund-NFRFE (#01326)
Canadian Institutes of Health Research (#162211)

Title: Silencing nociceptor neurons with nanoparticles and light

Authors: *K. ROVERSI[1,2], M. TABATABAEI[2], N. DESJARDINS-LECAVALIER[2], T. CROSSON[1], M. BALOOD[1], S. CONSTANTINO[2], M. GRIFFITH[2], C. BOUTOPOULOS[2], S. TALBOT[1];
[1]Univ. de Montreal, Montreal, QC, Canada; [2]Ctr. de Recherche Hôpital Maisonneuve-Rosemont, Montreal, QC, Canada

Abstract: Introduction: Maladaptive interplay between the sensory and the nervous systems can drive chronic pathologies. Nociceptor neurons are critical drivers of allergy, inflammation and pain by responding to cytokines secreted by immunocytes. The selective silencing of nociceptors' response to such cytokines can transform established therapeutic approaches, but such a method is yet to be available. Here we introduce a novel approach to silence heat-sensitive nociceptors. Our approach exploits heat-sensitive channels as entry ports for selective drug delivery. Methods: We designed gold nanoparticles (AuNPs) functionalized to αIL1R and αIL5R. Those are cytokine receptors co-expressed with the heat-sensing channel TRPV1 in sensory neurons. We evaluated the ability of αIL1R-AuNPs and αIL5R-AuNPs to open the TRPV1 channel upon heat-stimulation with laser (488 nm). Furthermore, we tested if a cationic derivative of an N-type calcium channel blocker (CNCB2) can enter the neurons cytoplasm via the open channel to silence the targeted nociceptors. As a proxy for the channel opening and silencing, we monitored calcium flux using a mouse expressing a calcium indicator ($TRPV1^{cre}GCaMP6\text{-}eGFP^{fl/fl}$). Results: We found that laser-stimulation triggers calcium flux in neurons pre-exposed to αIL1R-AuNPs and αIL5R-AuNPs. We also found that laser-stimulation of neurons pre-exposed to the functionalized AuNPs and CNCB2 resulted in absence of response (i.e., no calcium flux) to capsaicin-stimulation (TRPV1 agonist), indicating successful silencing of those neurons. Theoretical modelling of the temperature rise as well as TRPV1 blockage

experiments confirmed “channel hijacking” as the silencing mechanism. Conclusion: Overall, this work constitutes the first paradigm of spatially targeted silencing of nociceptors. With further development this approach can result into novel treatments for allergy, inflammation and pain diseases.

Disclosures: K. Roversi: None. **M. Tabatabaei:** None. **N. Desjardins-Lecavalier:** None. **T. Crosson:** None. **M. Balood:** None. **S. Constantino:** None. **M. Griffith:** None. **C. Boutopoulos:** None. **S. Talbot:** None.

Poster

128. New Models, Methods, and Approaches in Pain Research

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 128.19

Topic: D.02. Somatosensation – Pain

Support: NIH Grant R01 HUM00120181

Title: Visual and auditory testing provides improved prediction of the nociplastic pain continuum over pressure pain testing

Authors: *N. C. WALLER[1], A. SCHREPF[2], I. A. MAWLA[3], E. ICHESCO[4], T. E. LARKIN, Jr.[5], C. KAPLAN[2], D. J. CLAUW[2], R. E. HARRIS[4], S. HARTE[2];
[1]Univ. of Michigan, [2]Univ. of Michigan, Ann Arbor, MI; [3]Univ. of Michigan Med. Sch., Univ. of Michigan Med. Sch., Ann Arbor, MI; [4]Univ. of Mchigan, Univ. of Mchigan, Ann Arbor, MI; [5]CPFRC At Michigan Med., CPFRC At Michigan Med., Ann Arbor, MI

Abstract: Chronic pain is characterized by a continuum of central nervous system pain sensitization, at the extremes of which amplified CNS activity manifests independently of peripheral drivers and contributes to pain pathophysiology (hereafter referred to as *nociplastic pain*). Quantitative sensory testing (QST) allows for systematic investigation of sensory responses to a variety of quantifiable stimuli. In this study, we hypothesize that the modality of QST distinguishes purely nociplastic versus nociceptive contributions across diverse chronic pain cohorts. Participants across chronic pain conditions and healthy controls (fibromyalgia [FM]: N = 16, rheumatoid arthritis: N = 14, hip osteo-arthritis: N = 18, carpal tunnel syndrome: N = 7, healthy controls: N = 16; sex = 23 male) were assessed for the contribution of nociplastic pain using the 2011 Survey Criteria for FM. Participants underwent QST assessments of pressure pain sensitivity at the thumbnail, auditory sensitivity, and visual sensitivity. Participants rated the unpleasantness of the auditory and visual stimuli on a scale of “not unpleasant” to “most unpleasant experience imaginable” (0-100). Response values from the brightest visual (500 lux), loudest auditory (90 dB), and highest pressure tolerable with the thumb pressure stimuli (kPa) were used to predict FM scores via regressions. A Step 1 multiple regression model of unpleasantness in response to a bright, aversive visual stimulus predicting participant FM score was significant, $F(1, 45) = 4.67$, $p < .05$, adjusted $R^2 = .074$. A Step 2 model adding thumb

pressure tolerance was also significant, $F(2, 44) = 2.76$, $p < .05$, $\Delta R^2 = -.018$, however the ΔR^2 between model iterations was not significant. The coefficient for thumb tolerance was not significant in the Step 2 model, suggesting that the painful thumb pressure does not provide added predictive ability of FM scores. The coefficient for visual unpleasantness maintained significance such that increased unpleasantness ratings positively predicted FM scores. A simple regression of FM scores on auditory unpleasantness showed that increased auditory unpleasantness ratings positively predicted FM scores, $F(1, 69) = 4.01$, $p < 0.05$, $R^2 = 0.041$. Unpleasantness ratings in response to bright visual and loud auditory stimuli were significant predictors of participant FM scores. However, the highest pressure tolerable to thumb pressure testing did not provide additional predictive ability of participant FM scores when added to the model. The key findings suggest that centrally-directed sensory testing may provide a transdiagnostic window into the nociplastic pain continuum.

Disclosures: **N.C. Waller:** None. **A. Schrepf:** None. **I.A. Mawla:** None. **E. Ichesco:** None. **T.E. Larkin:** None. **C. Kaplan:** None. **D.J. Clauw:** None. **R.E. Harris:** None. **S. Harte:** None.

Poster

128. New Models, Methods, and Approaches in Pain Research

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 128.20

Topic: D.02. Somatosensation – Pain

Support: CIHR - FRN154281

Title: Cryotherapy delays recovery of inflammatory pain in mice

Authors: *L. VASCONCELOS LIMA[1], J. S. MOGIL[3], C. PITTMAN[2];
[1]McGill Univ., [2]McGill Univ., Montreal, QC, Canada; [3]McGill Univ., McGill Univ. Integrated Program in Neurosci., Montreal, QC, Canada

Abstract: Background and aims: Previous data from our laboratory have demonstrated that interfering with the acute inflammatory response, using anti-inflammatory drugs such as dexamethasone and diclofenac, leads to pain chronification despite its acute analgesic effect. Our aim with this follow-up study was to test whether cryotherapy—i.e., the application of ice at a site of injury for analgesic/anti-inflammatory purposes—would produce similar effects.
Methods: CD-1 mice of both sexes were given inflammatory pain via an injection of complete Freund's adjuvant (CFA) into their left hind paw. Immediately thereafter, each mouse received either cryotherapy or control treatment in one of two protocols: 3 sessions of 30 minutes per day for three days, with one hour interval between sessions, or 1 session of 60 minutes per day for three days. All mice were anesthetized with isoflurane and had both of their hind paws submerged in iced water at 5° degrees Celsius (cryotherapy) or room temperature water at 20 °C (control). Mechanical paw-withdrawal threshold (PWT) was measured prior to treatment

(baseline) and at regular intervals until average PWTs returned to baseline values. Paw edema was assessed by measuring dorso-palmar diameter. Additionally, the 3x30 min protocol was tested in mice induced with exercise-enhanced pain (EEP), by dual injection of acidic saline (pH 5.0) into their left gastrocnemius muscle, followed by a bout of 2-h forced wheel running exercise. This model was used to simulate a sports-related injury, which is commonly treated with cryotherapy. **Results:** Cryotherapy produced an acute anti-allodynic effect shown by PWTs measured 1 h after the last treatment session, with both protocols and in both CFA and EEP injured mice, but significantly delayed PWT recovery to baseline levels when compared to controls (30 days versus 15 days for CFA and 15 days versus 3 days for EEP). **Conclusions:** Our observations suggest that blocking the acute inflammatory response with the application of cold to the site of injury (cryotherapy), despite having the immediate benefit of pain relief, might also lead to pain chronification. These results add to our recent findings demonstrating long-term deleterious effects of interfering with the acute inflammatory response (with both drugs and cryotherapy) that, if replicated in humans, might lead to changes in long-term established protocols for management of acute musculoskeletal injuries.

Disclosures: L. Vasconcelos Lima: None. **J.S. Mogil:** None. **C. Pittman:** None.

Poster

128. New Models, Methods, and Approaches in Pain Research

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 128.21

Topic: D.02. Somatosensation – Pain

Title: Brain-computer interface to deliver individualised multi sensory therapy for neuropathic pain

Authors: *G. PREATONI, V. AURUCCI, S. RASPOPOVIC;
Dept. of Hlth. Sci. and Technol., ETH Zurich, Zurich, Switzerland

Abstract: Chronic neuropathic pain is a distressing health problem affecting up to 8% of the general population. Due to side effects and limited efficacy of pharmacological approaches, novel therapies for the treatment of neuropathic pain are emerging. Some of them, such as Transcutaneous Electrical Nerve Stimulation (TENS), aim at targeting the physiological component of pain, while others, such as Virtual Reality (VR), try to address the cognitive components by modulating attention.However, there are no holistic therapies which simultaneously tackle pain in all its physical and cognitive components. Moreover, the treatment duration and frequency are based on patients' self-reported pain intensity (which is unreliable), while an optimal therapy should be driven and real-time adjusted based on reliable neurophysiological pain biomarkers.To address this need, our goal is to develop a Brain-Computer Interface (BCI) to detect in real-time neurophysiological signatures of neuropathic pain through Electroencephalography (EEG) and accordingly deliver a multisensory therapy combining VR and TENS. We successfully built a BCI detection framework that extracts and

classifies frequency and entropy based EEG features decoding pain in real-time, exploiting machine learning (ML) models. Neuropathic patients were asked to: 1) focus on their painful limb 2) focus on a non-painful limb or 3) to rest. This allowed the training of ML models to decode pain-related attentional features. Upon pain detection, subjects received visuo-tactile stimulation composed of a purposely developed multimodal therapy combining TENS and VR. During the offline phase, all patients reported increased perceived pain intensity while focusing on pain compared to resting and control conditions. Here, the EEG recordings showed common trends at specific EEG power bands while patients focused on their pain. This enabled us to construct an online decoder. When tested online, the performances of the BCI showed a high accuracy in identifying pain, hence the therapy was released when the patients were actually perceiving a higher pain. The proposed BCI opens the way toward real-time detection of neurophysiological pain biomarkers with the intent of providing personalized therapies. This holds promise to counteract the present opioid crisis induced by overuse of pain killers.

Disclosures: G. Preatoni: None. **V. Aurucci:** None. **S. Raspopovic:** None.

Poster

128. New Models, Methods, and Approaches in Pain Research

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 128.22

Topic: D.02. Somatosensation – Pain

Support: Foundation for Anesthesia Education and Research Mentored Research Training Grant (Washington D.C.)

Title: Focused Ultrasound Induced Inhibition of Peripheral Nerve Nociceptive Fibers in an Animal Model of Acute Pain

Authors: *T. ANDERSON[1], C. PACHARINSAK[2], J. VILCHES-MOURE[2], K. BUTTS PAULY[3], D. YEOMANS[4];
[2]Comparative Med., [3]Radiology, [4]Anesthesiology, Perioperative and Pain Med., [1]Stanford Univ., Stanford, CA

Abstract: Acute pain is prevalent in many healthcare settings, including the emergency department, among hospitalized patients, and after surgery. Despite many systemic medications and neuromodulating techniques, moderate-to-severe acute pain remains a common problem in these healthcare settings. Further acute pain is associated with adverse outcomes. Focused ultrasound is a non-invasive method of inhibiting the peripheral nervous system and has the potential to provide an acute pain management tool. However, investigations of its effect on peripheral nerve nociceptive fibers in animal models of acute pain are lacking in the literature. Focused ultrasound was applied directly to the sciatic nerve of rats who also received an acute pain (hindpaw) incision. Behavioral testing (thermal and mechanical hyperalgesia, hindpaw extension and flexion) took place for four weeks after focused ultrasound application. Changes to

peripheral nerve structure after focused ultrasound application (and non-focused ultrasound controls) were assessed on the day of focused ultrasound application and two weeks after focused ultrasound application using light microscopy (hematoxylin and eosin, Luxol Fast Blue, Masson's Trichrome, and Bielschowsky silver) and transmission electron microscopy. After focused ultrasound application, animals had 1) animals had an increased threshold to nociception using Randall Selitto mechanical hyperalgesia testing, with a return to baseline 2.5 weeks after FUS application and acute pain incisional injury; 2) a sustained increased threshold to nociception of ≥4 weeks using modified Hargreaves thermal hyperalgesia; and 3) a small decrease in motor function, assessed by hindpaw extension after inducing the startle reflex, with a return to baseline by 2-4 weeks after focused ultrasound application. Changes to nerve structure by both light and electron microscopy are noted two weeks after focused ultrasound application (alterations to myelin sheaths and nerve fiber ultrastructure) but not on the day of focused ultrasound application. Focused ultrasound, using a distinct parameter set appears to have a greater effect on nociceptive fibers than motor fibers. As the greatest amount of pain occurs in the first 2 weeks after trauma and surgery, but there is continued pain for an extended period of time afterwards, it may be optimal to inhibit both A-delta and C fibers for approximately 2 weeks after injury and inhibit C fibers for weeks to months afterwards. Histological findings suggest FUS-induced alterations to both the myelin sheaths and the nerve fibers, but it is unclear what the clinical significance of the findings are.

Disclosures: **T. Anderson:** None. **C. Pacharinsak:** None. **J. Vilches-Moure:** None. **K. Butts Pauly:** None. **D. Yeomans:** None.

Poster

128. New Models, Methods, and Approaches in Pain Research

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 128.23

Topic: D.02. Somatosensation – Pain

Support: NIH grant R01 DE022757
USDVA grant 5I01BX000638

Title: Coronavirus-derived polypeptides can target epigenetic control in the nervous system

Authors: V. I. SHUBAYEV, J. DOLKAS, G. CATROLI, ***A. V. CHERNOV**;
Univ. of California San Diego, La Jolla, CA

Abstract: Human coronaviruses (HCoV) can cause long-lasting neurological sequelae, including neuropathic pain. The underlying molecular processes remain not well-understood. Molecular mimicry between the virus-encoded polypeptides and host proteins emerges as a driving force of viral pathogenesis in the peripheral nervous system. We previously reported a specific motif within the HCoV OC43 p65-like protein with a profound amino acid sequence and structural homology to the evolutionarily conserved domain of myelin basic protein (MBP), a major

component of the myelin sheath. Synthetic polypeptides derived from the respective homologous sequences of MBP and HCoV promoted robust pain-like behavior in female rats after injections into sciatic nerves. A significant elevation in genome-wide transcriptional activity in the dorsal root ganglia (DRG) and spinal cords, not directly exposed to pro-algesic polypeptides, suggested the involvement of upstream epigenetic mechanisms. We propose that molecular mimicry can target key epigenetic regulators and assist the virus in hijacking metabolic, cell energy, immune, and other functions in the peripheral and central nervous systems to promote virus spreading.The present study is focused on aberrant epigenetic transcriptional regulators using an animal model of rats treated with synthetic polypeptides derived from SARS-HCoV-2 or "common cold" HCoVs. Scrambled polypeptides or saline buffer were injected as controls. After single-bolus intraneural injections, sciatic nerves, DRG, and dorsal spinal cords were subjected to whole transcriptome sequencing, bioinformatics, and predictive system biology analysis. Direct HCoV-host molecular interactions were detected using affinity capture with biotinylated polypeptides as bait probes, followed by high-definition mass spectrometry.We identified upstream regulators and interactive networks potentially responsible for epigenetic regulation of gene expression, including molecular circuits controlled by long non-coding RNAs and chromatin remodeling factors. An unexpected upregulation of X-linked genes was observed, including chromatin remodeling helicases responsible for X chromosome inactivation in females. These results might provide a new paradigm for the X chromosome and epigenetic factors in viral pathogenesis, and related immune and (neuro)-inflammatory responses. The influence of sexual dimorphism in HCoV-induced damages to the nervous system and aberrant interference with nociceptive functions is a focus of ongoing research to benefit patients affected by HCoV infections.

Disclosures: V.I. Shubayev: None. **J. Dolkas:** None. **G. Catroli:** None. **A.V. Chernov:** None.

Poster

128. New Models, Methods, and Approaches in Pain Research

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 128.24

Topic: D.02. Somatosensation – Pain

Support: 5R21AI163621-02
1R01NS117513-01A1

Title: Wrangling Synapses to Catch Some Viruses: Examining Neuronal Viral Exocytosis Using NAPPA Technology

Authors: *W. M. TIERNEY[1], I. B. HOGUE[2];
[1]Arizona State Univ., Arizona State Univ. Interdisciplinary Grad. Program In Neurosci., Tempe, AZ; [2]Arizona State Univ., Arizona State Univ., Tempe, AZ

Abstract: Herpes Simplex Virus 1 infects approximately two-thirds of the world's population. While typically infecting the PNS and causing recurrent lesions, HSV-1 can also spread into the

CNS, where it can cause severe Herpes Simplex Encephalitis. Currently, HSV is thought to spread from epithelial tissues to sensory neurons via synapses. Due to large numbers of virus particles enter and exiting neurons simultaneously, studying intracellular transport/trafficking is difficult. This problem is compounded further by the unpredictability of synapse formation in cultured neurons. The mechanisms of viral egress from neurons is not well understood, but we hypothesize that the virus uses cellular secretory pathway mechanisms, including the post-Golgi secretory pathway. Synaptogenesis has been successfully modeled using protein micropatterning technology to coat substrates with synaptic adhesion molecules capable of promoting synaptogenesis in vitro. To study virus spread from the synapses of neurons, we are taking advantage of Nucleic Acid-Programmable Protein Array technology. A NAPPA array begins as a DNA microarray containing plasmids encoding proteins of interest. An in vitro transcription/translation reaction then produces purified proteins, immobilized in situ, on these arrays. This will be combined with our existing primary sensory neuron culture methods to study synaptogenesis and fluorescence microscopy methods to image trafficking and egress of HSV-1 particles. With this model, we aim to better examine viral egress specifically at synapses.

Disclosures: W.M. Tierney: None. **I.B. Hogue:** None.

Poster

128. New Models, Methods, and Approaches in Pain Research

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 128.25

Topic: D.02. Somatosensation – Pain

Support: Canadian Institutes of Health Research (FDN-148413)

Title: Towards the development of brain-penetrating neurotensin receptor type 2 (nts2) non-opioid analgescis

Authors: *N. MENEBOO, M. DESGAGNÉ, C. COMEAU, S. FERKOVA, A. MURZA, W. LANDRY, M. CHARTIER, I. BROCHU, J. CÔTÉ, J.-M. LONGPRÉ, P.-L. BOUDREAULT, P. SARRET;
Pharmacol., SHERBROOKE PHARMACOLOGY INSTITUTE, Sherbrooke, QC, Canada

Abstract: The ongoing opioid crisis and the dissatisfaction of chronic pain patients with currently available treatments underscore the importance of developing new, safer painkillers. The biologically active fragment of neurotensin NT(8-13), which exerts non-opioid analgesia via activation of NTS1 and NTS2 receptors, has emerged as a promising target for managing various types of pain. However, the bioavailability of peptide-based drugs such as NT(8-13) in the brain is limited by their inability to cross the blood-brain barrier (BBB). Moreover, NTS1 activation is also associated with other physiological effects, including hypotension and hypothermia that may preclude their clinical application. Here, we first used a structure-activity relationship approach to develop macrocyclic NT(8-12) analogs selective for NTS2. Substitution of Ile^{12} by

cyclopentylalanine and Pro^7/Pro^{10} with allylglycine residues, followed by ring-closing metathesis cyclization led to a macrocyclic peptide with high-affinity for NTS2 (3 nM) and high selectivity against NTS1 (> 5000). Importantly, this constrained NTS2 analog exerted dose-dependent analgesic effects after intrathecal delivery in acute, tonic, and chronic pain models, without causing the undesired effects associated with NTS1 activation. However, the main shortcoming of this type of molecules remains their inability to bypass the BBB, which limits their use as therapeutics. To address this issue, we used the ligand Angiopep-2 (An2) acting on LRP1 receptors highly expressed at the BBB interface as a Trojan horse strategy to enhance brain uptake of covalently conjugated drugs. As a proof of concept, we fused the 19 amino-acid An2 ligand to the N-terminal residue of NT(8-13). We first reported LRP1-dependent transport of the ^{64}Cu-radiolabeled An2-NT(8-13) hybrid peptide across the BBB using PET-CT imaging after systemic administration. Systemic injection of this bifunctional ligand was also found to reverse the nociceptive behaviors in the formalin model of persistent pain and chronic constriction nerve injury model of neuropathic pain. In parallel, we also monitor some physiological variables associated with NTS1 activation and determine whether this chimeric compound induces the adverse effects of morphine. As expected, i.v. injection of An2-NT(8-13) causes a significant drop in blood pressure or change in body temperature. Importantly, unlike morphine, i.v. An2-NT(8-13) did not produce constipation or respiratory depression. Hence, the next step will be to conjugate An2 to our best NTS2-selective macrocycle. Together, this study opens the way to the development of safer non-opioid analgesics.

Disclosures: **N. Meneboo:** None. **M. Desgagné:** None. **C. Comeau:** None. **S. Ferkova:** None. **A. Murza:** None. **W. Landry:** None. **M. Chartier:** None. **I. Brochu:** None. **J. Côté:** None. **J. Longpré:** None. **P. Boudreault:** None. **P. Sarret:** None.

Poster

128. New Models, Methods, and Approaches in Pain Research

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 128.26

Topic: D.02. Somatosensation – Pain

Support: NIH RO1 grant NS107569

Title: Dysregulation of AMPK leads to enhanced excitability in nociceptive sensory neurons and thermal hyperalgesia in a lupus mouse model

Authors: *H.-R. WENG[1], V. VIATCHENKO-KARPINSKI[2], L. KONG[2];
[1]California Northstate Univ., Elk Grove, CA; [2]Mercer Univ., Macon, GA

Abstract: Systemic lupus erythematosus (SLE) is a chronic autoimmune disease in which the immune system mistakenly produces antibodies against the body's own tissues, resulting in damage in diverse tissues in the body, and various clinical manifestations. Majority of SLE patients live with chronic pain despite reduction in mortality associated with SLE in recent years.

We recently reported that MRL/lpr mice (an SLE mouse model) spontaneously develop hypersensitivity to thermal and mechanical stimuli in their hind paw. MRL/lpr mice with chronic pain have an increased production of IL-1beta and IL-18 in the spinal dorsal horn, resulting in enhanced glutamatergic synaptic activities in the spinal dorsal horn. In this study, we aimed to characterize the electrophysiological properties and signaling molecules in the first order sensory neurons in the dorsal root ganglion (DRG) in mice with chronic pain caused by SLE. We found that male MRL/lpr mice began to show thermal hypersensitivity at the age of 10 weeks in comparison with their own values at 8 weeks and MRL control mice. This difference became larger with age and reached plateau between ages of 15 to 16 weeks. There were no spontaneous action potentials in nociceptive sensory neurons in the DRG in either the MRL/lpr mice or control mice. Action potential firing patterns evoked by current injection in nociceptive sensory neurons in MRL/lpr mice with chronic pain were similar to those in normal control mice. Nociceptive sensory neurons from MRL/lpr mice with chronic pain had an increased excitability, characterized by elevation of resting membrane potentials, lower rheobase and action potential thresholds. Input resistances in neurons from MRL/lpr and those from controls were similar whereas membrane capacitances in neurons from MRL/lpr mice with chronic pain were significantly smaller than those in the normal control group. These changes of electrophysiological properties in MRL/lpr mice were associated with suppression of AMP-activated protein kinase (AMPK) activity in the DRG as indicated by a significant reduction of phosphorylated AMPK protein levels. More importantly, subcutaneous intraplantar injection of an AMPK inhibitor (compound C) caused hypersensitivity to radiant heat on the injected hind paw in normal control mice. Compound C treatment also changed the electrophysiological properties of the nociceptive sensory neurons from the normal mice to those found in MRL/Lpr mice with chronic pain. Our study suggests that dysregulation of AMPK activity in the DRG leads to enhanced excitability in nociceptive sensory neurons and thermal hyperalgesia in mice with SLE.

Disclosures: **H. Weng:** None. **V. Viatchenko-Karpinski:** None. **L. Kong:** None.

Poster

128. New Models, Methods, and Approaches in Pain Research

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 128.27

Topic: D.02. Somatosensation – Pain

Support: NIH Grant DP2-NS106664
The New York Stem Cell Foundation
NIA Grant R21-AG075419

Title: Potassium channel overexpression as a novel strategy to silence nociceptors and reduce severe pain

Authors: *G. CHAHYADINATA[1], A. BATTENBERG[1], B. JOHNSTON[2], S. BAZAREK[2], D. DUBREUIL[1], A. HELD[1], M. ADLER[1], J. BROWN[2], B. WAINGER[3];
[1]Neurol., [2]Neurosurg., [3]Anesthesia, Critical Care & Pain Medicine, Neurol., Massachusetts Gen. Hosp., Boston, MA

Abstract: Chronic pain affects one quarter of adults in the US, a third with impairment of function, and costs over $500 billion annually. Many current efforts to treat pain by reducing the excitability of nociceptors, the first order pain-sensing neurons, have focused on the NaV1.7 sodium channel, since SCN9A (NaV1.7) knockout humans have congenital insensitivity to pain, whereas NaV1.7 gain-of-function mutation causes the severe painful syndrome familial erythromelalgia. However, to date, strategies to block NaV1.7 voltage-gated sodium channels have had limited success. Nonetheless, the basic strategy of reducing nociceptor excitability is well-validated in both humans and animal models. A major limitation of many current clinical pain treatments is side effects. These include central nervous system effects of neuropathic pain treatments, gastrointestinal and renal effects of non-steroidal anti-inflammatories, as well as multiple adverse effects of opioids, including risks of tolerance, dependence, addiction, and respiratory depression. Despite the fact that most pain conditions are focal, most treatments are systemic and thus expose patients to potentially unnecessary systemic adverse side effects. Thus, a strategy that addresses pain in specific locations may help reduce unwanted side effects of current approaches. We have developed a novel AAV-based approach of potassium channel overexpression that achieves spatial precision to silence nociceptors and thus has potential to abrogate pathological pain while minimizing side effects. Using a human synapsin promoter, we show that intrasciatic injection of AAV potassium channel viral particles yields channel expression in ipsilateral murine dorsal root ganglia in both dissociated DRG explants and sectioned DRG tissue. We validate the analgesic effect of our approach in several ways: Mice injected with AAV potassium channel viral particles exhibit higher mechanical thresholds compared to AAV GFP controls. Injection of AAV potassium channels into TrpV1::ChR2-EYFP mice, which express the light-sensitive ion channel channelrhodopsin (ChR2) in nociceptors, require higher light intensities to evoke pain responses. DRGs explanted from these animals also showed lower excitability in a calcium imaging-based in-vitro assay of neuronal excitability. Our results validate the overexpression of potassium channels as a promising alternative for pain treatment and support the use of spatial restriction to achieve precision in AAV-mediated gene therapies.

Disclosures: G. Chahyadinata: None. **A. Battenberg:** None. **B. Johnston:** None. **S. Bazarek:** None. **D. Dubreuil:** None. **A. Held:** None. **M. Adler:** None. **J. Brown:** None. **B. Wainger:** None.

Poster

128. New Models, Methods, and Approaches in Pain Research

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 128.28

Topic: D.02. Somatosensation – Pain

Support: NIH Grant K08NS099503

Title: A month of window watching: How the activity patterns of individual spinal somatosensory neurons evolve during inflammatory pain

Authors: *S. J. SULLIVAN, A. D. SDRULLA;
Anesthesiol. and Perioperative Med., Oregon Hlth. and Sci. Univ., Portland, OR

Abstract: Injury and inflammation can induce long-term changes of the nervous system that give rise to chronic pain. It is thought that plasticity within the superficial dorsal horn (SDH) of spinal cord, where somatosensory information from primary afferents first converges with the central nervous system, acts to amplify nociceptive signaling to pain centers of the brain. Recent advances in in vivo optical recording methods have revealed how SDH neurons are recruited by natural innocuous and noxious stimuli. However, to date, no published studies have tracked and characterized how the activity patterns of individually SDH neurons evolves over extended periods of pain. Here we present a method for chronically tracking the calcium activity of registered neurons in mice for one month. In a Complete Freund's Adjuvant (CFA) inflammatory pain model, excitatory SDH neurons showed early signs of sensitization to innocuous touch stimuli that persisted throughout the testing period. By one week, a brief noxious pinch stimulus (1 sec) induced fits of activity that lasted for nearly one minute. On closer examination of individual neurons, it was found that these population-level changes were non-uniformly distributed, with some neurons showing more sensitization to a given stimulus than others. Combining this history of functional remapping with molecular markers for neural subtypes may provide more specific therapeutic targets for treating chronic pain while retaining normal nociceptive function.

Disclosures: S.J. Sullivan: None. **A.D. Sdrulla:** None.

Poster

129. Responses to Touch and Map Organization in the Somatosensory System

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 129.01

Topic: D.03. Somatosensation – Touch

Support: JSPS/19K19898
JSPS/22H03500
JSPS/19H01092

Title: Gating of proprioceptive signals in the primate cuneate nucleus during voluntary hand movement

Authors: *S. KUBOTA[1], S. KIKUTA[1], C. SASAKI[1], T. OYA[1,2], K. SEKI[1];
[1]Dept. of Neurophysiol., Natl. center of Neurol. and Psychiatry, Kodaira, Japan; [2]Dept. of

Physiol. and Pharmacol., The brain and Mind Institute, Univ. of Western Ontario, London, ON, Canada

Abstract: During voluntary actions, somatosensation and the concomitant self-generated sensory signals from the periphery are known to be attenuated. This modulation, known as the sensory gating or sensory gain modulation, may be influenced by a descending signal, and therefore occur at several relays where sensory and motor commands converge. The one likely site for the modulation could be the cuneate nucleus in the medulla, the first relay in the ascending lemniscus pathway, as it does not only receive ascending somatosensory information of the upper body, but also receive descending signals from cortical and/or subcortical motor areas. This convergent projection from both afferent and efferent pathways implies that the sensory gain modulation may take place at the first relay, whereby influencing the somatosensory processing at the all subsequent stages. However, since due to technical difficulties, few studies have been done to examine the sensory gating in the cuneate nucleus during voluntary movements. To address this issue, we assessed the neuronal responses of the cuneate nucleus to the electrical stimulation to peripheral nerves in alert monkeys performing a voluntary motor task. We trained two macaque monkeys (Macaca fuscata and Macaca mulatta), to perform a wrist flexion-extension movement with the aid of visual feedback of wrist position using spring-loaded manipulandum. During the performance of the task, we recorded local field potentials (LFPs) and single neuron discharges of the cuneate nucleus that were evoked through electrical stimuli delivered at a constant current to the forearm muscle afferent (deep radial nerve; DR). We observed suppression of the evoked LFP during both wrist flexion (the evoked response decreases to 33 % of the rest) and extension (decrease to 24% of the rest). Similarly, in some DR-responsive neurons, the firing rate also decreased during both wrist flexion and extension. These results suggest that, indeed, the sensory gating occurred in the cuneate nucleus whenever the wrist is moved in either direction. This is a stark contrast with the evoked responses found in the spinal cord showing that proprioceptive inputs were specifically facilitated during relevant movements (Confais et al., 2017). Our results suggest that proprioceptive signals are differentially modulated in the spinal cord and the cuneate nucleus, and attenuation of proprioceptive signals in the cuneate nucleus probably points to a mechanism that gates predicted sensory signals in reference to efference copy of motor command.

Disclosures: **S. Kubota:** None. **S. Kikuta:** None. **C. sasaki:** None. **T. oya:** None. **K. Seki:** None.

Poster

129. Responses to Touch and Map Organization in the Somatosensory System

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 129.02

Topic: D.03. Somatosensation – Touch

Title: Live-cell imaging of the response of human Merkel cells to skin deformation induced by a microscope-mounted mechanical stimulation device.

Authors: *S. SAKAGUCHI[1,2], M. TSUTSUMI[1], N. ARAKAWA[1], K. KAJIYA[1], M. KONYO[2]; [1]MIRAI Technol. Inst., Shiseido Co., Ltd, Yokohama-Shi, Japan; [2]Grad. Sch. of Information Sci., Tohoku Univ., Sendai-shi, Japan

Abstract: Merkel cells (MCs) are known to sense mechanical forces applied to the skin and produce tactile sensations. It was reported that 0.5 mN of contact force with a fine needle can induce a human touch sensation, and 1 um displacement of cultured MCs by glass pipette showed the direct response to the membrane stretch of these cells. However, how much skin deformation can stimulate MCs present in human skin is still unknown. In this study, we aimed to construct an experimental system to evaluate MC response to quantitative mechanical stimuli applied to semi-intact human skin tissue. First, MCs were identified in semi-intact human skin using FFN206 and Quinacrine, which were reported to have MC specificity in the epidermis. Perfusion experiments were performed to depolarize MCs with high potassium solutions to evaluate the validity of FFN206 release used as an indicator of MC response. As a result, we confirmed FFN206 was specifically taken up by MCs in semi-intact epidermal sheets, and the destaining of the FFN206 signal after 5 minutes of exposure to the high-potassium stimuli using multi-photon microscope. We then developed a device with 2 mm diameter suction holes in contact with the sample and capable of applying various negative pressure (0-40 kPa) in order to perform live-cell imaging while applying mechanical stimuli to skin samples. This mechanical stimulation can be applied to excised skin tissue and the human body. By mounting this device on a multi-photon microscope, it's possible to deform the skin sample and observe the FFN206 signal simultaneously. To account for the effect of changes in fluorescence values due to skin variations caused by mechanical stimuli, FFN206 fluorescence values were normalized based on the other fluorescent dye observed at the same time at the same location. 5 kPa was used as the maximum presenting mechanical stimulus based on human data that the stimulus intensity is above the stimulus threshold. As a result, a decrease in normalized FFN206 fluorescence values was observed at a negative pressure intensity of 5 kPa. This response was not observed by the removal of extracellular Ca^{2+} or the addition of FM1-43, an inhibitor of Piezo2, a mechanotransduction channel of MCs. In conclusion, the use of MC-specific indicators and the development of a unique stimulus presentation device allowed us to perform live-cell imaging of MCs in semi-intact human skin tissue in response to skin deformation.

Disclosures: **S. Sakaguchi:** A. Employment/Salary (full or part-time):; Shiseido Co., Ltd. **M. Tsutsumi:** A. Employment/Salary (full or part-time):; Shiseido Co., Ltd. **N. Arakawa:** A. Employment/Salary (full or part-time):; Shiseido Co., Ltd. **K. Kajiya:** A. Employment/Salary (full or part-time):; Shiseido Co., Ltd.. **M. Konyo:** None.

Poster

129. Responses to Touch and Map Organization in the Somatosensory System

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 129.03

Topic: D.03. Somatosensation – Touch

Support: European Research Council (ERC) (FeelAgain grant agreement No. 759998)
Swiss National Science Foundation (SNSF) (MOVEIT No. 197271)
Innosuisse ICT program (n. 47462.1 IP-ICT)

Title: Towards neuroprostheses for diabetic peripheral neuropathy

Authors: *L. CHEE[1], N. GOZZI[1], G. PREATONI[1], G. VALLE[1], F. BEUSCHLEIN[2], C. ZIPSER[3], N. PFENDER[3], S. RASPOPOVIC[1];
[1]Hlth. Sci. and Technol., ETH Zürich, Zürich, Switzerland; [2]Dept. of Endocrinology, Diabetology and Clin. Nutr., Univ. Hosp. Zürich, Zürich, Switzerland; [3]Spinal Cord Injury Center, Balgrist Univ. Hosp., Zürich, Switzerland

Abstract: Diabetic Peripheral Neuropathy (DPN) is characterized by peripheral nerve damage caused by chronically high blood sugar. It has a variety of consequences including neuropathic pain and sensory loss that can lead to reduced balance and mobility. Transcutaneous electrical nerve stimulation (TENS) holds potential to non-invasively target the branches of nerves that innervate the area of sensory loss. We developed a fully portable neuroprothesis employing a smart stimulating system to proximally stimulate the distally damaged nerves of DPN patients. This neuroprothesis was used to assess DPN residual nerve function and finally restore lost sensation while performing functional tests. To do so, first sensory loss was evaluated through quantitative sensory testing (QST). Then, optimized electrode matrices placed at anatomically plausible positions were able to target nerves to restore missing somatotopic sensation. The electrical parameters required to evoke a somatotopic sensation were personalized and the sensitivity of patients to these parameters was evaluated. Then the smart stimulation system used these personalized parameters to provide foot ground interaction feedback during functional tasks. Functional tasks were performed with and without somatotopic sensory feedback to assess its effects. DPN patients were confirmed to have significant sensory loss in their feet as measured by the QST. The smart stimulation neuroprosthesis was able to restore part of the lost sensation in all tested patients. However, the measured charge thresholds and sensitivity of these damaged nerves were shown to be significantly lower than healthy nerves. Furthermore, in a set of patients, the neuroprothesis using electrically evoked somatotopic feedback provided functional improvements related to movement ability. These results suggest that neural stimulating prostheses are amenable to restoring lost sensation in DPN patients and have valuable functional benefits. These findings take steps towards the development of an at home usable system for treating long term DPN symptoms and related complications.

Disclosures: L. Chee: None. **N. Gozzi:** None. **G. Preatoni:** None. **G. Valle:** None. **F. Beuschlein:** None. **C. Zipser:** None. **N. Pfender:** None. **S. Raspopovic:** None.

Poster

129. Responses to Touch and Map Organization in the Somatosensory System

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 129.04

Topic: D.03. Somatosensation – Touch

Support: NIH DP5-OD029571
Meta Reality Labs Award #2990450277899571

Title: Transcutaneous Wrist Stimulation for Haptic Feedback from the Hand in Virtual and Augmented Reality

Authors: *A. HARRISON[1], M. TROUT[2], A. CITTERMAN[2], J. A. GEORGE[3];
[1]Univ. of Utah, salt lake city, UT; [3]Univ. of Utah, [2]Univ. of Utah, Salt Lake City, UT

Abstract: The long-term goal of this research is to provide intuitive and natural-feeling haptic feedback for interactions with objects in virtual and augmented reality. Our sense of touch plays a critical role in our manual dexterity and our ability to explore the world around us. Haptic information in virtual reality is primarily conveyed through sensorized gloves, which tend to use methods like mechanical vibrations or force feedback. These gloves are bulky and limit our natural ability to simultaneously interact with physical objects, as would be needed for seamless interactions in augmented reality. Here we introduce a new way to provide haptic feedback from the hands by electrically stimulating the median, ulnar, and radial nerves through the skin at the wrist. Electrically stimulating these nerves at the wrist produces a sense of touch that can be localized at the fingertips, palm of the hand, or the back of the hand. Sensations were evoked in seven human subjects using common electrodes traditionally used for monitoring heart rate (30 x 24 mm in diameter). Currents of 2 - 4.7 mA were passed between two electrodes to create sensations ranging from 1 to 5 cm^2 in size within a localized area. A higher current amplitude corresponded to a more intense sensation, often coming from a larger localized area on the hand. A higher frequency of electrical stimulation corresponded to a more intense sensation with minimal changes in size or location. Using classical psychophysical experiments, we calculated the just-noticeable difference in stimulation frequency that could be reliably detected as a more intense sensation. We found that a 26.8 ± 7.96% increase in stimulation frequency was the smallest perceivable percent change in stimulation frequency when using 50 Hz as a reference. Based on this information, we estimate that this form of haptic feedback could reliably convey up to 19 different magnitudes of tactile sensations by modulating the stimulation frequency from 1 to 300 Hz. The ability to evoke artificial sensations from electrical stimulation at the wrist presents an exciting opportunity to provide intuitive and anatomically congruent haptic feedback for virtual and augmented reality in an elegant form factor such as a wristwatch or bracelet.

Disclosures: **A. Harrison:** None. **M. Trout:** None. **A. Citterman:** None. **J.A. George:** None.

Poster

129. Responses to Touch and Map Organization in the Somatosensory System

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 129.05

Topic: D.03. Somatosensation – Touch

Support: DOE Grant DE-SC0022150

Title: Long-term sensory mapping and detection sensitivity of targeted transcutaneous electrical nerve stimulation

Authors: *K. DING[1], M. M. ISKAROUS[1], L. E. OSBORN[3], N. V. THAKOR[1,2];
[1]Biomed. Engin., [2]Electrical and Computer Engin., Johns Hopkins Univ., Baltimore, MD; [3]Res. & Exploratory Develop., Johns Hopkins Univ. Applied Physics Lab., Laurel, MD

Abstract: Sensory stimulation provides sensation back to individuals with upper limb amputations. Researchers have shown that transcutaneous or implanted electrical interfaces induce sensations in the phantom hand, which improve perception and prosthesis usage. Longitudinal studies provide insights into the stability of phantom sensation locations and stimulation detection sensitivity. For transcutaneous stimulation, how stimulation session recurrence affects the perceived sensation regions and detection thresholds is unknown. In this study, we sought to answer whether perceived sensation regions of the phantom hand and stimulation detection sensitivity changed after years of not receiving sensory stimulation. We applied targeted transcutaneous electrical nerve stimulation (tTENS) to two subjects with arm amputations, one had undergone targeted sensory reinnervation surgery (A01), and one did not receive any reinnervation surgery (A02). We mapped the locations of sensations each perceived in their phantom hand. Then, we conducted psychophysical experiments to measure tTENS detection thresholds at different frequencies, pulse widths, and amplitudes. Over 5 years, we conducted two sensory mapping and psychophysics sessions (1653 days apart) for subject A01. For subject A02, we tracked 12 sessions of sensory mapping and up to 5 sessions of detection thresholds. We used structural similarity (SSIM) index and perceived sensation coverage area to compare sensory mapping results. We found that within each subject, SSIM showed high similarities (>0.75) for each median and ulnar nerve region. For subject A01, we observed an increase in overall coverage area (82.3%) between the two experimental sessions. Detection thresholds were stable (within 3 dB of difference, dB in power ratio). For A02, overall coverage area showed an initial increase during the first three weeks. The area then remained relatively stable, especially between the last two entries that were over 3 years apart. Detection thresholds at median nerve region were within 3 dB of difference. At ulnar nerve region, detection thresholds showed a maximum difference of 7 dB. Altogether, these results suggest that phantom sensation activation regions remain similar, even when subjects did not undergo any tTENS sessions over long periods of time (>3 years). This study has implications for understanding long-term detection sensitivity changes and whether such trend differs between periods with regular stimulation sessions and periods without receiving stimulation. This study also provides insights into designs of optimal stimulation strategies and rehabilitation regimens.

Disclosures: K. Ding: None. **M.M. Iskarous:** None. **L.E. Osborn:** None. **N.V. Thakor:** None.

Poster

129. Responses to Touch and Map Organization in the Somatosensory System

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 129.06

Topic: D.03. Somatosensation – Touch

Support: NINDS NS122333

Title: A computational model of stereognosis

Authors: *D. E. G. SHEETS[1], A. R. SOBINOV[2], S. J. BENSMAIA[2];
[1]Computat. Neurosci., [2]Univ. of Chicago, Chicago, IL

Abstract: When we interact with an object, we sense its shape via signals from our hands, allowing us to identify the object or manipulate it without even seeing it. This sensory ability, termed stereognosis, relies on two distinct streams of sensory information: cutaneous signals from the fingertips contacting the object convey information about local features (e.g., curvature, texture, edge), and proprioceptive signals about the posture of the hand conformed to the object convey information about its global shape. In the present study, we used a computational approach to better understand how these two disparate streams of information are integrated. Specifically, we trained neural networks to identify objects based on simulated tactile signals about object contact and simulated proprioceptive signals about hand conformation. Having first established that these networks can recognize objects with high accuracy, we then identified the conditions under which object recognition was possible. First, we found that integrating tactile and proprioceptive signals is critical; segregating these two streams of information before the network non-linearity had a catastrophic impact on performance. Second, we found that integrating sensory signals across digits is critical, and performance increased as information was combined across a larger number of digits. We conclude that tactile and proprioceptive signals need to be integrated across digits to achieve stereognosis. We then relate these computational principles to the known response properties of neurons along the somatosensory neuraxis. While early stages of processing comprise neurons that respond to either touch or proprioception and have small receptive fields, Brodmann's area 2 comprises neurons multi-digit receptive fields that exhibit cutaneous and proprioceptive properties. We conclude that this area is ideally suited to contribute to stereognosis.

Disclosures: D.E.G. Sheets: None. **A.R. Sobinov:** None. **S.J. Bensmaia:** None.

Poster

129. Responses to Touch and Map Organization in the Somatosensory System

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 129.07

Topic: D.03. Somatosensation – Touch

Support: Schindler Foundation
University of Rochester Intellectual and Developmental Disabilities Research Center (IDDRC)

Title: Higher Sensitivity to Duration Differences in Tactile Stimulation in Young Adults with Autism Spectrum Disorder

Authors: *E. ISENSTEIN[1], J. XU[4], I. DEANDREA-LAZARUS[1], L. OAKES[2], E. G. FREEDMAN[5], J. J. FOXE[3];
[1]Univ. of Rochester, [3]Univ. of Rochester Sch. of Med., [2]Univ. of Rochester, Rochester, NY; [4]Gallaudet Univ., Gallaudet Univ., Washington, DC; [5]Univ. of Rochester - Neurosci., Univ. of Rochester - Neurosci., Rochester, NY

Abstract: Both hyper and hypo-sensitivity to tactile stimuli are commonly reported in people with autism spectrum disorder (ASD), yet little is known about the neurological underpinnings of this atypical tactile sensitivity. Few studies exist that examine the neurophysiology of tactile perception in ASD. Limited evidence shows mixed results, but all known research has used repetitive, identical stimuli with a predictable intensity or duration. Here, we clarify the role of predictability in how the brain responds to tactile stimulation in neurotypical and autistic young adults. Objective: To measure whether people with and without ASD have different patterns of cortical response to predictable and unpredictable passive somatosensory stimulation. This study used a somatosensory duration mismatch negativity (MMN) paradigm to assess vibrotactile novelty detection in 20 neurotypical and 11 autistic young adults. ASD diagnoses were confirmed by administration of the Autism Diagnostic Observation Schedule by a trained clinician. The MMN is a specific event-related potential that occurs when a repeated sequence of identical, predictable ‘standard’ stimuli is interrupted by a novel, unpredictable 'deviant' stimulus that differs from the standard majority. By maintaining one stimulus as the majority of the input (80%), any perceived deviation from the anticipated stimulus results in a distinct, measurable electrophysiological response known as the MMN. Vibrations of standard (100 ms) and deviant (115, 130, 145, and 160 ms) durations were presented during an electroencephalogram (EEG). Data collection is ongoing. Difference waves were calculated by subtracting the standard waveform from each respective deviant waveform. The mean amplitudes of the difference waves were extracted from fronto-central electrodes between 160 and 210 ms after stimulus presentation. The difference wave amplitudes did not differ significantly between groups: 115 ms: $t=-1.85$, $p=.07$; 130 ms: $t=.91$, $p=.37$; 145 ms: $t=-.39$, $p=.70$; 160 ms: $t=-.67$, $p=.50$. For the NT group, the 115 ms did not differ significantly from zero ($t=.02$, $p=.98$), but the 130 ms ($t=-7.94$, $p<.01$), 145 ms ($t=-3.36$, $p<.01$), and 160 ms ($t=-4.75$, $p<.01$) all differed significantly from zero. For the ASD group, the 115 ms ($t=-3.02$, $p=.01$), 130 ms ($t=-4.06$, $p<.01$), 145 ms ($t=-2.45$, $p=.03$), and 160 ms ($t=-6.79$, $p<.01$) all differed significantly from zero. These preliminary results trends toward higher sensitivity of early low-level processing of temporal vibrotactile information in the ASD group compared to the NT group. Additional data collection is needed to properly compare these two groups with appropriate power.

Disclosures: E. Isenstein: None. **J. Xu:** None. **I. DeAndrea-Lazarus:** None. **L. Oakes:** None. **E.G. Freedman:** None. **J.J. Foxe:** None.

Poster

129. Responses to Touch and Map Organization in the Somatosensory System

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 129.08

Topic: D.03. Somatosensation – Touch

Support: NIH Grant UL1TR003096

Title: Tactile modality changes primary somatosensory cortex overlap of adjacent fingers

Authors: M. WAQAS, D. JANKO, R. JHANJEE, M. BOLDING, ***W. R. WILLOUGHBY**; Univ. of Alabama, Birmingham, Birmingham, AL

Abstract: Within the primary somatosensory cortex, finger representations are organized lateral-to-medial with the thumb being most lateral and the little finger being most medial. Prior studies have shown Brodmann area (BA) 3b is the most finger specific and has the most cortical space dedicated to the fingers. More posterior parts (BA 1 and 2) are less finger specific, show more overlap and smaller distances between the thumb and the little finger resulting in smaller cortical space usage. We used functional magnetic resonance imaging (fMRI) to examine whether the amount of overlap between adjacent fingers (thumb and index) on the right hand differs based on tactile modality. We hypothesize that fingers stimulated using a tactile stroking stimulus will show less overlap compared to fingers stimulated by a vibrotactile stimulus. Two devices were used to deliver touch stimuli in a 3T Prisma MRI scanner (Siemens Healthineers). The tactile device delivered a stroking-motion stimulus with a plastic stylus, while the vibrotactile device used an electric motor for stimulation. Both devices were set up to stimulate the distal phalanx of each finger. Each 7 minute run used an ON-OFF block design with each block being 30 seconds, and one run was performed per device on each finger. Activation and overlap were calculated using FSL software. The vibrotactile stimulus showed a tighter activation spread and slightly greater overlap between the thumb and index finger in the primary somatosensory cortex as compared to the tactile stroking stimulus, which supported our hypothesis. The stroking stimulus tended to have broader activation for each finger, and this increased spread reduced the overall overlap between fingers for this modality.
The results indicate that the thumb and index finger representations are sensitive to different tactile modalities. A stroking stimulus produced less localized and less overlapped activation of adjacent fingers as compared to a vibrating stimulus. A stimulus that travels across the skin might activate a greater respective portion of the somatosensory cortex as opposed to a stimulus that acts on the same area because the brain tends to prioritize changing data and dedicates more resources to interpreting them, thus recruiting additional portions of the cortex. Future research will focus on differences between and within other modalities and also on why the somatosensory cortex is sensitive to different modalities.

Disclosures: **M. Waqas:** None. **D. Janko:** None. **R. Jhanjee:** None. **M. Bolding:** None. **W.R. Willoughby:** None.

Poster

129. Responses to Touch and Map Organization in the Somatosensory System

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 129.09

Topic: D.03. Somatosensation – Touch

Support: Mitacs Research Training Award
NSERC Grant

Title: Inter-point distance and frequency influence two-point discrimination of vibration on the thigh

Authors: *D. E. GENARO, L. C. MARRELLI, E. E. HOWE, M. APOLLINARO, L. R. BENT; Human Hlth. and Nutritional Sci., Univ. of Guelph, Guelph, ON, Canada

Abstract: Sensory substitution is a technique that enables the replacement of one sensory input for another. For instance, vibration has been shown to be an effective sensory substitution for muscle stretch, whereby an increase in flexion joint angle was successfully perceived via the number of active vibrating tactors in a linear array located on a limb of interest. For this application, it is critical to understand the resolution of an input sensation to ensure that the signal perceived matches the signal delivered. Establishing the minimum distance between two loci that enables two distinct points to be perceived, known as two-point discrimination (2PD), is a vital aspect in deciphering the resolution of this sensory language. 2PD, though, is greatly influenced by vibration frequency as specific frequency ranges activate cutaneous receptors that have varying receptive field sizes. The present study investigates vibration frequency and inter-point distance on the ability to distinguish two points at the skin of the thigh. Healthy, young, female participants took part in the study. Vibratory perceptual thresholds (VPT) were assessed on the thigh at two frequencies, 30 Hz and 150 Hz. Vibration was then delivered at 30 Hz or 150 Hz (2xVPT) using inter-point distances of 20, 25, or 30 mm. Six trials were completed for each condition (frequency x distance) where the vibrating probe was applied, at random, in the vertical or horizontal orientation and participants were asked to identify the orientation. Percent correct response was used as the outcome measure. The 30 mm inter-point distance exhibited significantly greater 2PD than either 25 mm or 20 mm ($p<0.05$) at both 30 Hz and 150 Hz. Interestingly, at 20mm, the 30 Hz vibration displayed greater 2PD than 150 Hz, implicating specific cutaneous receptor contributions. Our findings provide insight on the inter-point distances and frequency at the thigh that may optimize current sensory substitution applications such as military navigation and mobility aid devices for individuals living with lower limb amputation or diabetes.

Disclosures: D.E. Genaro: None. **L.C. Marrelli:** None. **E.E. Howe:** None. **M. Apollinaro:** None. **L.R. Bent:** None.

Poster

129. Responses to Touch and Map Organization in the Somatosensory System

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 129.10

Topic: D.03. Somatosensation – Touch

Support: This work was supported by Electronics and Telecommunications Research Institute(ETRI) grant funded by the Korean government.[22ZB1100]

Title: A decoding model of spike firing in the slowly-adapting receptors for encoding the natural tactility

Authors: Y. KANG[1], Y. CHOI[2], C. JE[1], K.-H. PARK[1], S. JUNG[2], *S.-Q. LEE[1];
[1]ETRI, Daejeon, Korea, Republic of; [2]Hanyang Univ. Med. Sch., Seoul, Korea, Republic of

Abstract: An emerging metaverse technology demands a natural touch sense as well as vision and auditory in virtual space. In realization of encoding natural tactility, accurate decoding of spike firing that the brain senses for mechanical stimuli is required. Among the tactile receptors, slowly adapting (SA) neurons show a gradual decrease in spike firing rate over time for a given pressure stimulus. However, previous methods have limitations in accurately modeling these features in spike patterns. In this work, we propose a novel decoding method that reflects the decrease in the spike firing pattern over time. In order to obtain a decoding model, an experiment was devised to extract the SA of a mouse and obtain a spike-firing response pattern according to the magnitude and time of the pressure stimulus. To extract the skin and nerves, the mice (C57bl/6, 8-10 weeks) were sacrificed under CO_2 anesthesia. The spike signal generated by the saphenous nerve was recorded by the Au electrode in an additional paraffin oil chamber electrochemically separated from the synthetic interstitial fluid chamber, with a pH of 7.4 and a temperature of 29-30 ℃. Using a stimulating rod, a neural spike response was obtained by applying a force of 10 to 100 mN for 6 seconds or varying the time from 1.0 to 5.0 seconds at the same 30 mN. It shows that even with stimulation times longer than 1.0 seconds, the spike firing is concentrated within approximately 1.0 seconds. In addition, the spike firing pattern can be divided into two sections within 1.0 second. One is the transient state in which physical stimulation is applied to nerve cells, and the other corresponds to the steady-state after reaching the target force: while the spike firing increases as time increases in the transient section, it decreases in the steady-state. To improve the decoding accuracy of the spike firing pattern, exponential regression analysis was performed on each of the two divided sections. As a result, the coefficient of determination in each exponential regression model showed similarities of 0.89 and 0.90, respectively. By using the regression model proposed in this paper, the tactile receptors decoding accuracy is highly improved. If electrical stimulation is performed with the encoding signal obtained based on the inverse model derived using the proposed model, more natural tactility can be implemented.

Disclosures: Y. Kang: None. **Y. choi:** None. **C. Je:** None. **K. Park:** None. **S. Jung:** None. **S. Lee:** None.

Poster

129. Responses to Touch and Map Organization in the Somatosensory System

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 129.11

Topic: D.03. Somatosensation – Touch

Support: SFB 1436 B05

Title: Exciting a traveling wave of steady-state somatosensory evoked field response along the somatosensory cortex

Authors: *C. MERKEL, J.-M. HOPF, M. A. SCHOENFELD;
Otto-von-Guericke Univ., Magdeburg, Germany

Abstract: Functional topographies of early sensory areas within the cortex can be measured with high spatial accuracy using fMRI-techniques. A common approach analyzes the phase shift of a periodic BOLD modulation along the topologically organized area evoked by a stimulus systematically cycling through the sensory information of interest (traveling wave method). In the present work we investigate, for the first time, the feasibility of reliably measuring such a traveling wave of cortical excitation using magnetoencephalographic signals for the purpose of topographical mapping. In order to analyze the modulation of a sustained signal representing the neural response to a sensory stimulus we utilized a steady state response to a vibro-tactile stimulation at 27Hz shifting from one fingertip to the next every 5sec from D2 to D5 creating a stimulus cycle at 0.05Hz. Magnetoencephalographic signal modulations over time were analyzed in individual high-resolution source spaces using beamformer techniques. The 0.05Hz modulations of the 27Hz response to the vibrotactile stimulation were highly localized within the hand-knob of S1 for all of the six analyzed subjects. These signals in turn showed a systematic phase shift along the medio-lateral direction of S1, consistent with the cycling of the stimulus across the finger-tips. The spatial phase distributions acquired with MEG showed hereby topological deformations highly consistent with topographical S1 maps of the same finger-map measured with fMRI (using the same stimulation protocol) for each subject. The current data suggests the possibility of mapping the spatial functional topology of early somatosensory areas in single subjects using MEG. The outlined method uses a traveling wave approach, creating phase maps and therefore complex topological information across cortical space, substantially improving on current methods merely localizing stimulation response maxima.

Disclosures: C. Merkel: None. **J. Hopf:** None. **M.A. Schoenfeld:** None.

Poster

129. Responses to Touch and Map Organization in the Somatosensory System

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 129.12

Topic: D.03. Somatosensation – Touch

Support: DFG KU 3711/2-1 423633679
DFG 425899996- SFB 1436
ESIF/ESF 2014-2020 FKZ: ZS/2020/05/141591

Title: The fine-grained inhibitory functional architecture of neighboring representations in primary somatosensory cortex of humans and mice

Authors: *P. LIU[1], J. U. HENSCHKE[1], S. STOLL[1], J. M. P. PAKAN[1], E. KUEHN[2];
[1]Inst. for Cognitive Neurol. and Dementia Res., Otto von Guericke Univ. Magdeburg, Magdeburg, Germany; [2]Hertie Inst. for Clin. Brain Res., Eberhard Karls Univ. Tübingen, Tübingen, Germany

Abstract: As we interact with the world around us, tactile stimulation can co-activate spatially extensive parts of the somatosensory system, however, it is important that sensory precision is maintained. This may be accomplished through inhibitory receptive field (RF) interactions within the cerebral cortex, with cortical RF suppression commonly used to describe the functional architecture of the primary somatosensory cortex (SI) in both health and disease. In humans, studies have reported response suppression during double-finger stimulation in comparison to the sum of single-finger stimulation, which was interpreted as a marker for inhibition. However, these studies focused on limited fingertip regions, leaving the dynamics of larger spatial extents, such as consecutive phalanges, unaddressed. Moreover, the fine-grained layer-specific architecture of RF inhibition in SI remains unknown. To address these issues, we investigated the inhibitory architecture of human index (D2) and middle finger (D3) representations, to quantify suppressive interactions in SI in fine-grained detail. We collected 7T fMRI data from human participants undergoing tactile stimulation of different phalanges of D2 and D3, as well as 3T structural MRI data. We applied phase-encoded mapping and population receptive field (pRF) modeling, and calculated the signal change for three stimulation conditions: D2+D3, D2 only, and D3 only. Both phase-encoded maps and pRF position maps indicated a posterior-to-anterior organization, oriented orthogonal to the central sulcus, corresponding to the proximal-to-distal surface of each finger. We also found that the signal change of D2+D3 was significantly lower than the sum of D2 and D3. Moreover, averaged pRF size for D2+D3 tended to be smaller than the sum of D2 and D3. To further investigate suppressive interactions in SI at the level of cortical layers and single cells, we then used a mouse model of neighboring whiskers and performed two-photon calcium imaging of cortical layers 2/3 (L2/3) and 5 (L5) barrel cortex during whisker stimulation. We quantified the responses of excitatory neurons to single and paired whisker stimulation and found that nearly half showed lower responses to dual compared to single whisker stimulation, similar to the suppressive effects we observed in humans. We also found differences in suppressive potential between L2/3 and L5. More fine-grained analyses compare the inhibitory architecture between human finger and mouse whisker representations. Together, our results reveal architectural principles of SI inhibition across species, ranging from topographic scales down to the single-cell level.

Disclosures: P. Liu: None. **J.U. Henschke:** None. **S. Stoll:** None. **J.M.P. Pakan:** None. **E. Kuehn:** None.

Poster

129. Responses to Touch and Map Organization in the Somatosensory System

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 129.13

Topic: D.03. Somatosensation – Touch

Support: NIH U19 NS107466
NIH U24 EB028942

Title: Biomechanics links contact angle, force, and phase during exploration

Authors: *R. LIU[1], K. DEKEL[4], P. YAO[2], A. AGGARWAL[7], K. PODGORSKI[7], D. H. O'CONNOR[8], D. GOLOMB[4,5,6], D. KLEINFELD[1,3];
[1]Dept. of Physics, [2]Neurosciences Grad. Program, [3]Dept. of Neurobio., Univ. of California San Diego, La Jolla, CA; [4]Dept. of Physiol. and Cell Biol., [5]Dept. of Physics, [6]Zlotowski Ctr. for Neurosci., Ben Gurion Univ., Beer-Sheva, Israel; [7]Allen Inst. for Neural Dynamics, Seattle, WA; [8]Zanvyl Krieger Mind/Brain Inst., Johns Hopkins Univ., Baltimore, MD

Abstract: The perception of object location arises from the interpretation of a tactile signal, in contrast to the sensation of touch produced by contact per se. In tactile sensing, transient adjustments are triggered when encountering an unexpected object to achieve "minimal impingement" (Grant, Mitchinson, Fox and Prescott, J Neurophysiol 2009) for optimal sensation. Such adjustments require rapid perception. We consider the possibility that perception is derived from the mechanics of a sensorimotor plant and directly encoded by thalamocortical afferents, with limited neuronal processing. Our experiments make use of the rhythmically active rodent vibrissa system in combination with high-resolution imaging of glutamate activities from thalamocortical inputs in mouse layer 4 barrel cortex. First, we establish that spiking at a preferred phase in the free whisking cycle is a reliable and spatially-ordered metric to label thalamocortical afferents. Next, using moving contacts, we observe that the torque upon touch of a vibrissa is proportional to phase during contact for small deflections, and reaches saturation for large deflections. Further, the azimuthal angle of contact of a vibrissa relative to the face is also proportional to phase. Theoretical modeling shows that the mechanics of the vibrissae, follicles, and mystacial pad can directly connect sensation to the perception of angular location. This connection is purely mechanical for contact angle at minimum impingement. Finally, the response probability to the contact location indicated by phase is in line with the preferred phase of free whisking across a large number of thalamocortical boutons. In summary, angular position, torque, and phase at contact are mechanically linked; phase provides a label for the response of thalamic afferents and directly indexes contact angle at minimum impingement. Interestingly, thalamocortical boutons with similar phase preferences are spatially clustered.

Disclosures: R. Liu: None. **K. Dekel:** None. **P. Yao:** None. **A. Aggarwal:** None. **K. Podgorski:** None. **D.H. O'Connor:** None. **D. Golomb:** None. **D. Kleinfeld:** None.

Poster

129. Responses to Touch and Map Organization in the Somatosensory System

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 129.14

Topic: D.03. Somatosensation – Touch

Support: NIH/NNDS R01 Grant NS107599
Whitehall Foundation Grant 2017-05-71

Title: Frontal Cortex Gates Distractor Stimulus Encoding in Sensory Cortex

Authors: *Z. ZHANG[1], E. ZAGHA[2];
[1]Neurosci. Grad. Program, UC Riverside, Riverside, CA; [2]Neurosci. Grad. Program; Psychology Dept., Univ. of California Riverside, Riverside, CA

Abstract: Suppressing behavioral responses to distractor stimuli is a fundamental cognitive process, essential for performing goal-directed tasks. A common framework for the neuronal implementation of distractor suppression is the attenuation of distractor stimuli from early sensory to higher-order processing. However, details of the localization and mechanisms of attenuation are poorly understood. In this study, we trained mice to selectively respond (lick) to whisker deflections from one whisker field and ignore identical deflections from the opposite whisker field. We found that suppression of frontal cortex, aligned to the target stimulus or the distractor stimulus, increases responses to distractors (false alarms). By simultaneously recording spiking activity in the mouse whisker region of primary somatosensory cortex (S1), we found that frontal cortex selectively suppresses the neuronal encoding of distractor stimuli in target-aligned S1. Frontal cortex decorrelates the encoding of target and distractor stimuli in single units, thereby increasing stimulus selectivity across the population of target-aligned S1 neurons. Even before stimulus onset, effects of frontal cortex on S1 were robust and context-dependent, indicating proactive modulation. Overall, our study provides important mechanistic details about the roles of frontal cortex in gating sensory responses in sensory cortex.

Disclosures: Z. Zhang: None. **E. Zagha:** None.

Poster

129. Responses to Touch and Map Organization in the Somatosensory System

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 129.15

Topic: D.03. Somatosensation – Touch

Support: K22 DE029779

Title: S100b-positive trigeminal sensory neurons innervate the dentinal tubules of murine molars

Authors: *A. R. GANDHI, B. S. C. CONSTANTINESCU, M. E. GUENTHER, E. A. RONAN, J. J. EMRICK;
Dept. of Biologic and Material Sci., Univ. of Michigan Sch. of Dent., Ann Arbor, MI

Abstract: Teeth are vital for survival and thus have robust innervation that serves as a sentinel for damage. Indeed, bacterial infection of the tooth causes caries (i.e., decay) and may result in excruciating pain - the toothache. Our recent retrograde tracing and transcriptomic analysis suggests that the murine dental pulp is richly innervated by a subset of trigeminal somatosensory neurons that are putatively Aδ;-nociceptors and low threshold Aβ;-mechanoreceptors. We find that expression of S100b marks the majority of tooth-innervating neurons from these functional classes; however, to-date the morphology and localization of associated neural terminals in the tooth pulp have not been described. Based on the tooth's capacity to detect external damage, we would predict that these molecularly-defined somatosensory endings should terminate in close proximity to the mineralized layers of the tooth (i.e., the dentin and enamel). In order to test this hypothesis, we sought to label and evaluate the projection patterns of trigeminal S100b-positive neurons targeting the dental pulp. S100b-Cre mice were injected with adeno associated viral vectors (AAVs) to induce expression of the red fluorescent protein, tdTomato, in this subset of neurons. Using an orbital approach, we targeted expression to trigeminal sensory neurons. Following a two week incubation period, tissues from both dental arches were harvested, demineralized, and sectioned. From there we used fluorescent immunohistological staining to amplify TdTomato expression and visualize it in the dental tissues. Confocal imaging of dental pulp tissue revealed stochastic, robust innervation by S100b-positive fibers. Morphologically, we found that a dense plexus of nerve endings give rise to terminals that traverse the odontoblast layer and extend into dentinal tubules. Often a single terminal appeared to target tubules and extend roughly halfway into the dentin. Interestingly, terminals demonstrated puncta along their length corroborating other reports of myelinated neurons. These anatomical findings are consistent with a proposed role for sensory neurons in detecting damage to the exterior tooth structure.

Disclosures: A.R. Gandhi: None. **B.S.C. Constantinescu:** None. **M.E. Guenther:** None. **E.A. Ronan:** None. **J.J. Emrick:** None.

Poster

129. Responses to Touch and Map Organization in the Somatosensory System

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 129.16

Topic: D.03. Somatosensation – Touch

Support: K22 DE029779

Title: Determining the function of tooth-innervating trigeminal sensory neurons

Authors: *E. A. RONAN[1], M. E. GUENTHER[1], M. NAGEL[2], B. S. C. CONSTANTINESCU[1], A. R. GANDHI[1], N. GHITANI[2], A. T. CHESLER[2], J. J. EMRICK[1];
[1]Dept. of Biologic and Material Sci., Univ. of Michigan Sch. of Dent., Ann Arbor, MI; [2]Sensory Cells and Circuits Section, NIH/NCCIH, Bethesda, MD

Abstract: We use our teeth to efficiently disrupt food to initiate the digestive process that is essential for nourishment and survival. Teeth are particularly vulnerable to environmental perturbation (i.e., heavy forces applied by the jaw muscles) while performing their essential role in mastication. Our previous work demonstrated that the teeth are richly innervated by a subset of trigeminal sensory neurons that express Piezo2 and likely detect mechanical forces. The precise "tuning" of these neurons to mechanical stimulation is not yet known. Here, we sought to explore the nature of dental pulp mechanoreception. To this end we developed a platform to distinguish dental pulp-innervating sensory neurons and evaluate their responses to tooth stimulation in vivo using calcium imaging of the trigeminal ganglion. Our paradigm allows us to locate "pulp neurons" using electrical pulses then follow their activity in response to subsequent mechanical stimulation. We find that tooth-innervating neurons respond to mechanical damage of the tooth, but fail to respond to neither direct application of any forces (low, medium, or high) nor vibration unlike other sensory neurons in the ganglion. Interestingly, we find that pulp neurons also respond to noxious cold. However, none of these multimodal responses depend on Piezo2. Our findings reveal that innervation serving separate components of the tooth apparatus are tuned to innocuous and damaging stimulation. Tooth damage converges on the activation of pulp neurons and relies on unknown molecular mechanotransducer(s). Conversely, detection of innocuous stimulation is more likely mediated by sensory neurons that innervate surrounding structures (i.e., the periodontium). Our platform serves as the basis to uncover the molecular mechanisms underlying tooth sensation and pain. Ultimately, these insights will aid in the development of novel clinical therapies to address toothache, the most common form of orofacial pain, as well as provide insight into general mechano-nociception.

Disclosures: E.A. Ronan: None. **M.E. Guenther:** None. **M. Nagel:** None. **B.S.C. Constantinescu:** None. **A.R. Gandhi:** None. **N. Ghitani:** None. **A.T. Chesler:** None. **J.J. Emrick:** None.

Poster

129. Responses to Touch and Map Organization in the Somatosensory System

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 129.17

Topic: D.03. Somatosensation – Touch

Support: 774989

Title: The penis is not necessary the glands penis: dorsal root recordings from L1to S1in the rat

Authors: *M. OLOARTE FLORES[1], Y. M. DE LEÓN RAMYREZ[1], O. LARA GARCIA[2], M. A. LARA GARCIA[3], Y. CRUZ[1], P. PACHECO[4];
[1]Univ. Autónoma de Tlaxcala, Tlaxcala, Mexico; [2]Univ. Autónoma de Tlaxcala, Xalapa, Mexico; [3]Inst. de Neuroetologia, Univ. Veracruzana, Xalapa, Mexico; [4]Inst. de Investigaciones Biomédicas, Univ. Nacional Autonoma de México, Xalapa, Mexico

Abstract: Penis innervation has been widely studied; however, little is known regarding glans penis sensorial contribution, e.g., sensorial pathway entering spinal cord or the kind of sensory information arising from the glands penis has been poorly described. In the present study, through dorsal roots electrophysiological recording, and performing glans penis mechanical stimulation such as brushing, traction and pressure; as well as thermal stimulation using cold or hot water, we were able to identify the sensory path arising in the glans penis and entering the central nervous system. Results: mechanical stimulation i.e., brushing, traction or pressure to glans penis produced electrophysiological activity from L1 to S1 spinal roots, this activity was mostly accompanied by phasic or tonic "on" but phasic or tonic "off" responses were rarely present. Thermal stimulation by hot water elicited activity in most dorsal roots but not in L2 and L5; while, cold water produced activity in all but L5. These results suggests that penis innervation must be further analyzed as glands penis sensory information enters from L1 to S1 spinal segments and carries thermal information that had not been previously described.

Disclosures: M. Oloarte Flores: None. **Y.M. De León Ramyrez:** None. **O. Lara Garcia:** None. **M.A. Lara Garcia:** None. **Y. Cruz:** None. **P. Pacheco:** None.

Poster

130. Peripheral Mechanisms of Chemosensation

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 130.01

Topic: D.04. The Chemical Senses

Support: ONR Grant (N00014-16-1-2829)
NIH Grants (RF1MH117155 and R01NS109553)
Intel Corp Grant (CG42647565 FE2018)
NSF Grant (IIS-1724405)
Obra Social La Caixa (ID 100010434)
Intramural grant from NIH/NICHD

Title: Olfactory receptor neurons generate multiple response motifs, increasing coding space dimensionality

Authors: B. KIM[1], S. HANEY[2], A. P. MILLAN[4], **S. JOSHI**[2], Z. ALDWORTH[1], N. RULKOV[3], A. T. KIM[1], M. BAZHENOV[2], *M. STOPFER[1];
[1]NIH-NICHD, Bethesda, MD; [2]Dept. of Med., [3]UCSD, La Jolla, CA; [4]Dept. of Clin. Neurophysiol. and MEG Ctr., Vrije Univ. Amsterdam, Amsterdam, Netherlands

Abstract: There are hundreds of thousands of detectable odorant molecules with different shapes, sizes, and charge distributions. Furthermore, odorants are often contained in turbulent plumes with complex temporal structures that can convey important information about the surroundings. To make use of this information, the olfactory system must generate a high dimensional representation describing this information in a coding format usable by downstream circuits. Odorants binding to olfactory receptor neurons (ORNs) trigger bursts of action potentials providing the brain with its only experience of the olfactory environment. To characterize ORN responses, we made hundreds of extracellular recordings from ORNs on the locust antenna while presenting odors. We found that ORNs can respond to odorants with four distinct types of firing pattern motifs - excitatory, delayed, offset, and inhibitory - each with a reliable temporal profile. Also, a given ORN could respond to different odors with different motifs, a phenomenon we termed 'motif switching'. Further, we found that each motif undergoes its own form of sensory adaptation when activated by repeated plume-like odor pulses. To determine how these motifs contribute to representations of odor plumes, we built a computational model, consisting of 10,000 ORNs, constrained by our *in vivo* recordings. The model revealed that including multiple motifs improved odor classification, and that even infrequent motif switching further improved classification by increasing the distance between spatiotemporal representation of odors. These results reveal a new property of ORNs: they can encode differences between odor stimuli through switches in response motifs, thus increasing contrast. Behavioral (Demir et al., 2020; Álvarez-Salvado et al., 2018) and modeling (Jayaram et al., 2022) studies have shown that the first layer of the insect olfactory system extracts information useful for navigation from temporal statistics of plumes. Using our model, we found that providing multiple ORN motifs significantly improved the ability to classify distance to source. Our model also predicted that classifiers including the excitatory and delayed motifs were most successful in determining distance to the source, suggesting that these two motifs extract complimentary information about the odor statistics most needed to characterize distance. Together, these results reveal new ways ORNs utilize the temporal domain to expand their coding space dimensionality, providing significant benefits for both odor classification and for processing complex natural odor inputs.

Disclosures: B. Kim: None. **S. Haney:** None. **A.P. Millan:** None. **S. Joshi:** None. **Z. Aldworth:** None. **N. Rulkov:** None. **A.T. Kim:** None. **M. Bazhenov:** None. **M. Stopfer:** None.

Poster

130. Peripheral Mechanisms of Chemosensation

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 130.02

Topic: D.04. The Chemical Senses

Support: National Science Foundation Next Generation Networks for Neuroscience Award 2014217 (MW)
Medical Research Council (UK) Next Generation Networks for Neuroscience Award MR/T046759/1 (MS)

EU H2020 Grant 945539 (Human Brain Project SGA3) (MS)
NIH F32MH115448 and NS109979 (MW,SB)

Title: Meaningful and descriptive chemical features for odorant structure-activity relationships in the main olfactory system

Authors: *M. SCHMUKER[1], S. D. BURTON[2,3], M. WACHOWIAK[2];
[1]Biocomputation Group, Univ. of Hertfordshire, Hatfield, United Kingdom; [2]Dept. of Neurobio., Univ. of Utah, Salt Lake City, UT; [3]Dept. of Biol. Sci., LeHigh Univ., Bethlehem, PA

Abstract: The sense of smell enables humans and animals to investigate their chemical environment. The accurate detection and identification of chemicals plays a crucial role in foraging, finding mates, detecting predators, self-monitoring and -maintenance, and other aspects of life. Yet, despite decades of olfaction research, our understanding of the organization of odorant space still lags far behind other sensory modalities.
In the visual system for example, the quantification of stimulus features like local contrast edges and moving gratings that are directly related to peripheral mechanisms of detection has enabled breakthroughs in our understanding of how this system works. In olfaction, the discovery of similarly essential stimulus properties has been limited in part by the fact that chemical features available through software packages are often cryptic and difficult to interpret.
During the analysis of a recent dataset [1], we compared the ability of features obtained from physicochemical descriptors (e.g., from the widely-used eDragon software) to fragment-based fingerprints to predict the chemical selectivity of glomeruli in the dorsal olfactory bulb of mice. Fragment-based fingerprints typically outperformed physicochemical descriptors in capturing structure-activity relationships (SAR). Moreover, adding physicochemical features to fragment-based fingerprints led to a decline in prediction accuracy.
In addition, since fragment-based fingerprints are directly linked to structural motifs, they are easier to interpret in a chemical and ecological context.
The dataset in [1] was obtained using very low odorant concentrations at which most glomeruli responded to only one or two odorants and each odorant activated only one or a few glomeruli. This narrow tuning likely increased the probability of extracting a consistent set of features that describe SAR. Future work is planned to compare these SAR with those obtained previously, at higher odorant concentrations and broader glomerular tuning (e.g. [2]).
References [1] Burton SD, et al. (2022) *Biorxiv*:2022.05.11.491539. https://doi.org/10.1101/2022.05.11.491539 [2] Soelter J, et al. (2020) *Sci Rep* 10:77. https://doi.org/10.1038/s41598-019-56863-4

Disclosures: M. Schmuker: None. **S.D. Burton:** None. **M. Wachowiak:** None.

Poster

130. Peripheral Mechanisms of Chemosensation

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 130.03

Topic: D.04. The Chemical Senses

Title: Type 2 cytokines IL-4 and IL-13 directly activate murine olfactory sensory neurons

Authors: *Y. HARA[1], M. K. JHA[1], P. PIEPENHAGEN[2], H. MATTOO[3], A. HICKS[1]; [1]Immunol. & Inflammation, Sanofi, Cambridge, MA; [2]Global Discovery Pathology, [3]Precision Med. and Computat. Biol., Sanofi, Framingham, MA

Abstract: Patients with severe chronic rhinosinusitis with nasal polyps (CRSwNP), a type 2 inflammatory disorder driven by cytokines, including interleukin (IL)-4 and IL-13, experience loss of smell (anosmia), which is one of the most troublesome and difficult-to-treat symptoms. Recent clinical trials show that treatment with dupilumab, a human monoclonal antibody that specifically binds with the IL-4 receptor alpha (IL-4 Rα) to inhibit IL-4 and IL-13 signaling, improves sense of smell in patients with CRSwNP, however the exact mechanism of action is unknown. We analyzed single cell RNA sequencing data of mouse nasal mucosa and identified that the IL4-Rα receptor is widely expressed in the olfactory epithelium. The presence of IL-4 Rα in murine olfactory sensory neurons (OSNs) is confirmed by immunostaining of dissociated olfactory sensory neurons positive for CamKII, a specific marker of OSN. To determine if the OSNs are responsive to type 2 cytokines IL-4 and IL-13, we measure intracellular calcium responses. We found OSNs are activated by capsaicin and surprisingly that IL-4 and IL-13 similarly directly increase calcium uptake in these capsaicin-sensitive neurons, indicating for the first time that these neurons are responsive to these major type 2 cytokines. These findings suggest that IL-4 and IL-13 via modulation of olfactory sensory neuronal activity may play an important role in smell pathophysiology and suggest that the therapeutic benefit of dupilumab may be due to a direct modulation of the effects of these cytokines.

Disclosures: Y. Hara: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Sanofi. **M.K. Jha:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Sanofi. **P. Piepenhagen:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Sanofi. **H. Mattoo:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Sanofi. **A. Hicks:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Sanofi.

Poster

130. Peripheral Mechanisms of Chemosensation

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 130.04

Topic: D.04. The Chemical Senses

Support: NRF Korea Grant 2020R1C1C101024513
NRF Korea Grant 2020R1A3A300192913
NRF Korea Grant 2022M3E5E801739511
KIST Grant 2E31502

Title: Ano9 activation via phosphorylation of serine 245 amplifies olfactory signals in mammals

Authors: S. LIM, H. KIM, *P. LEE, U. OH;
Brain Sci. Inst., Korea Inst. of Sci. and Technol. (KIST), Seoul, Korea, Republic of

Abstract: Intracellular Ca^{2+} and cAMP play a major role in transducing odorant inputs to electrical activity in OSNs. Here we show ANO9, expressed in OE, specifically the cilia of OSN, is activated by odorants through their respective receptors. We also identified the phosphorylation site of ANO9, Serine 245, which is essential for activation. *Ano9*-deficient mice elicited reductions in olfactory behavioral sensitivity, electro-olfactogram signals, and neural activity in the olfactory bulb. In line with the difference in olfaction between birds and other vertebrate phyla, chick ANO9 failed to respond to odorants, whereas chick CNGA2, a major transduction channel, showed greater responses to cAMP. Importantly, single-cell transcriptome data from Covid-19 patients revealed that only *Ano9* transcripts were markedly suppressed. Thus, the signal amplification by ANO9 is important for mammalian olfactory transduction, whose downregulation may be a risk factor for the olfactory dysfunction in Covid-19 patients.

Disclosures: S. Lim: None. **H. Kim:** None. **P. Lee:** None. **U. Oh:** None.

Poster

130. Peripheral Mechanisms of Chemosensation

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 130.05

Topic: D.04. The Chemical Senses

Support: NIH Grant 5R01DC016859-04

Title: Loss of EED in olfactory basal stem cells impairs neurogenesis

Authors: *T. KO[1], B. GOLDSTEIN[2], R. GUPTA[2], E. LLINAS[3];
[1]Dept. of Neurobio., [2]Head and Neck Surgery & Communication Sci., Duke Univ. Sch. of Med., Durham, NC; [3]Duke Univ., Durham, NC

Abstract: The olfactory epithelium (OE) is one of the few neurogenic niches in adult humans. Olfactory basal stem cells proliferate and differentiate into mature OE cell types, including olfactory sensory neurons (OSNs). How the olfactory basal cells regulate renewal and differentiation is still unclear. We have previously identified Polycomb group (PcG) proteins as candidates for epigenetic regulation of neurogenesis in the OE. Polycomb repressive complexes (PRCs) modify chromatin; the PRC2 complex deposits the H3K27me3 repressive mark

regulating target gene expression. Based upon the expression in basal cells and immature neurons, we hypothesized that PRC2 is likely to control aspects of adult neurogenesis in the OE. We used *KRT5*^{CreER}; Ai9;*Eed*^{flox} mice to conditionally delete the PRC2 subunit Embryonic Ectoderm Development (Eed) in olfactory basal stem cells. After Cre recombination, the methimazole chemical lesion model was used to activate basal cells to reconstitute the mature OE cell populations, including neurons and sustentacular cells. Mice were then sacrificed after 2 weeks. We assessed the differentiation of lineage-traced cells in the OE from *Eed*^{KO} (*KRT5*^{CrerER};Ai9;*Eed*$^{fl/fl}$) and *Eed*^{Het} (*KRT5*^{CreER};Ai9;*Eed*$^{fl/wt}$) mice by immunohistochemistry using a panel of cell type-specific markers and cell morphology. Our initial analyses identify a reduction of Cre-reporter-labeled neurons in *Eed*^{KO} mice compared to *Eed*^{Het} mice, and a higher percentage of sustentacular cells in *Eed*^{KO} mice when compared to *Eed*^{Het} mice. Our data suggest that PRC2 functions in the olfactory neuron lineage to regulate aspects of neuron differentiation. Ongoing studies are evaluating the specific Polycomb target genes involved in this process.

Disclosures: **T. Ko:** None. **B. Goldstein:** None. **R. Gupta:** None. **E. Llinas:** None.

Poster

130. Peripheral Mechanisms of Chemosensation

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 130.06

Topic: D.04. The Chemical Senses

Title: Deciphering new pheromone receptors and cell types through single nuclei RNAseq in the rabbit male and female vomeronasal organ

Authors: *P. RODRIGUEZ VILLAMAYOR[1,2], R. RUIZ-DANIELS[2], P. MARTINEZ[1], D. ROBLEDO[2];
[1]Departament of Genet., Univ. of Santiago de Compostela, Lugo, Spain; [2]The Roslin Institute, Univ. of Edinburgh, Edinburgh, United Kingdom

Abstract: Pheromones are chemosignals involved in fundamental innate socio-sexual behaviors such as mating and fighting, essential for animal reproduction and survival. These cues are mainly perceived by the vomeronasal organ (VNO), traditionally considered as a hardwired system with two main types of vomeronasal receptors (V1Rs and V2Rs) linked to G-protein coupled receptors (Gαi2 and Gα0) and the transient receptor potential channel 2 (Trpc2) to induce signal transduction. However, pheromone-evoked behavior is not stereotyped across individuals and therefore VNO undergoes experience and state-dependent plasticity to be able to cope with environmental changes and internal states of conspecifics. Understanding this plasticity is not straightforward considering the ’one neuron-one receptor’ nature of the VNO and the repertoire of species-specific pheromone receptors (formyl peptide receptors in mice).To obtain a comprehensive view of the cell-types and receptors in the VNO and ultimately understand the mechanisms behind its plasticity, we have generated the first cell atlas of the VNO using single-nuclei RNAseq (snRNAseq) of the rabbit VNO –two males and two female

adults–, a well-known model of chemical communication. Nuclei were processed using Chromium 10X pipeline, sequenced by Illumina, and analysed with STAR and Seurat. We identified 31 cell clusters, with no differences between sexes, consistent with our previous bulk RNAseq data. Seven clusters were vomeronasal sensory neurons (VSNs) containing either Gαi2a or Gα0 expression. Remarkably, not all of these clusters showed V1R/V2R or Trpc2 gene expression, suggesting that other unknown species-specific receptors might also be involved in pheromone sensing and signal transduction. Five additional clusters expressing sex steroid-receptors (progesterone, prostaglandin F2α receptor, etc.) fit within the VSNs category despite not showing Gαi2/Gα0 expression. VSNs expressing VRs and sex-steroid receptors were clustered separately, raising the question of whether sex-steroid receptors act as a first screening of sensory perception in response to specific internal states followed by the activation of VRs VSNs or if instead both groups of VSNs sense pheromones independently. Finally, we also found five clusters of immune cells, which supports the fact that the VNO acts as an interface between the immune and the nervous system.All in all, understanding the cellular rationale of the VNO will provide the needed framework for deciphering how pheromonal inputs are mediated by sensory neurons, potentially placing VSNs as a peripheral center that integrates internal states with external chemosignals.

Disclosures: P. Rodriguez Villamayor: None. **R. Ruiz-Daniels:** None. **P. Martinez:** None. **D. Robledo:** None.

Poster

130. Peripheral Mechanisms of Chemosensation

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 130.07

Topic: D.04. The Chemical Senses

Title: Smell alive: dynamic sensing by vomeronasal sensory neurons in behaving animals

Authors: *J. JENSEN[1,2], K. SCHUSTER[1], L. STOWERS[1];
[1]Scripps Res. Inst., La Jolla, CA; [2]UCSD, San Diego, CA

Abstract: Olfaction is a critical mode of social communication in rodents. In particular, the accessory olfactory system (AOS) encodes social chemical cues and powerfully shapes interactions and reciprocal communication. Though social behavior is highly dynamic, most previous studies of AOS functioning have relied upon static or *ex vivo* analysis of neural activity in the AOS. The dynamics of AOS stimulus encoding during stimulus investigation and social interactions and how these dynamics predict social behavioral responses remain unknown. To fill this gap, we are performing *in vivo* calcium imaging of vomeronasal sensory neuron axons in the accessory olfactory bulb in freely behaving, male and female mice. This is allowing us to define the relationship between properties of social stimuli, investigative behavior, VSN activity patterns and innate behavioral responses, such as ultrasonic vocalizations, urine marking, and aggression. Our results reveal that while stimulus identity determines the pattern of activated

glomeruli, active stimulus investigation shapes the magnitude and temporal dynamics of glomerular responses. Our approach is providing fundamental insights into AOS sensory coding during ongoing behavior and the role of chemical communication in shaping interactions.

Disclosures: J. Jensen: None. **K. Schuster:** None. **L. Stowers:** None.

Poster

130. Peripheral Mechanisms of Chemosensation

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 130.08

Topic: D.04. The Chemical Senses

Support: NSF Next Generation Networks for Neuroscience Award 2014217 (JPC, ACT)
MRC Next Generation Networks for Neuroscience Award MR/T046759/1 (MS, SS, MP)
EU H2020 Human Brain Project SGA3 Award 945539 (MS)

Title: About plume dynamics: extracting meaningful odor features for active sensing

Authors: S. SUTTON[1], ***M. PSARROU**[1], A. C. TRUE[2], J. P. CRIMALDI[2], M. SCHMUKER[1]; [1]Biocomputation group, Univ. of Hertfordshire, Hatfield, United Kingdom; [2]Univ. of Colorado Boulder, Boulder, CO

Abstract: Insects and mammals sampling an odorant in a turbulent plume will perceive spatiotemporal fluctuations in the odor concentration, which can contain information about odor source distance [1]. They can decode these fast odor transients and adjust their behavior according to the specific odor landscape [2]. We have previously introduced the *bout* analysis, a biologically inspired method for detecting rising portions of odor signal related to plume encounter events [3]. It is an effective method to estimate odor source proximity independent of gas concentration. Here, we quantify the relationship between bout features and source distance in free-stream (airborne) and near-bed (ground-based) odor release configurations, recorded by PLIF (planar laser induced fluorescence) in a wind tunnel [4]. We extracted four bout features (count, amplitude, duration, inter-bout interval - IBI) and examined their distribution over the wind tunnel. Both free-stream and near-bed plumes exhibited characteristic and unique bout feature profiles in down- and cross-wind direction from the source. Bout counts decreased more rapidly downwind in the free-stream condition, while the near-bed configuration was characterized by a slower bout count decrease. Bout amplitudes decreased downwind for both configurations, but the amplitudes of the bouts created by near-bed release were larger on average and exhibited greater variation than in the free-stream configuration. Bout durations appeared unaffected by distance for both configurations. However, on average the free-stream bouts were of greater duration regardless of the distance from the source. For both conditions, the length and variance of the IBI increased further downwind, whist the free-stream showed a greater increase with distance. In addition, for both, cross-wind bout counts decreased and their

variance increased away from the plume center. Generally, bouts became shorter with smaller amplitudes downwind, but longer and sparser with higher IBI crosswind away from the midline of the plume. Our results suggest that bout statistics can represent parameters like down- and cross-wind distance from an odor source. Further investigations will focus on how animals could exploit these features for navigation and sensing strategies in odor landscapes they encounter.

References

[1] Mylne & Mason (1991) *Q J Roy Meteor Soc* https://doi.org/10.1256/smsqj.49708
[2] Crimaldi et al. (2021) *J Comp Neurosci*, https://doi.org/10.1007/s10827-021-00798-1
[3] Schmuker et al. (2016) *Sens Act B Chem*, https://doi.org/10.1016/j.snb.2016.05.098
[4] Connor et al. (2018) *Exp Fluids*, https://doi.org/10.1007/s00348-018-2591-3

Disclosures: S. Sutton: None. **M. Psarrou:** None. **A.C. True:** None. **J.P. Crimaldi:** None. **M. Schmuker:** None.

Poster

130. Peripheral Mechanisms of Chemosensation

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 130.09

Topic: D.04. The Chemical Senses

Title: Optimized functional imaging of mosquito olfactory sensory neuron activity

Authors: *D. GIRALDO[1], A. M. HAMMOND[1], M. WOHL[1], C. J. MCMENIMAN[1,2];
[1]W. Harry Feinstone Dept. of Mol. Microbiology and Immunol., Johns Hopkins Bloomberg Sch. of Publ. Health, Johns Hopkins Malaria Res. Institute, Johns Hopkins Univ., Baltimore, MD;
[2]The Solomon H. Snyder Dept. of Neurosci., Johns Hopkins Univ. Sch. of Med., Baltimore, MD

Abstract: The yellow fever mosquito *Aedes aegypti* and the malaria mosquito *Anopheles gambiae* are highly anthropophilic and exhibit strong innate sensory drives to seek out humans. Females of these mosquito species use different physical and chemical cues emanating from the human body to locate a potential host. Odorants emanating from hosts are crucial for long range host detection and are sensed by specialized olfactory sensory neurons (OSNs) in sensilla that are primarily localized to the antennae and maxillary palps in the mosquito head, and project to the antennal lobe in the brain. These neurons can be divided into different classes based on their expression profile of chemoreceptor genes. To date, heterologous expression systems and electrophysiological approaches such as single sensillum recordings and electroantennography have facilitated studies of the ligand tuning dynamics of different OSN populations and target chemoreceptors from these disease vectors. Recent advances in mosquito genome editing allowed us to generate transgenic lines that express genetically encoded calcium indicators targeted to specific OSN populations and permitted recording of activity from multiple neurons at the same time. We applied CRISPR-Cas9 T2A-In Frame Fusions and the QF2-QUAS system to gain genetic access to broad OSN subsets in both species, including those expressing the olfactory co-receptors Gr1/Gr22, IR8a, IR25, IR76b and Orco. We have used these reagents in

conjunction with QUAS-GCaMP responder lines to visualize peripheral and central responses to CO_2 and other ligands present in human scent. These optimized methods for imaging mosquito neural activity have the potential to be applied to study the molecular and cellular basis of mosquito attraction to humans and improve our fundamental understanding of the ligand tuning dynamics of their olfactory systems.

Disclosures: D. Giraldo: None. **A.M. Hammond:** None. **M. Wohl:** None. **C.J. McMeniman:** None.

Poster

130. Peripheral Mechanisms of Chemosensation

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 130.10

Topic: D.04. The Chemical Senses

Title: Atropine facilitates initiation of swallowing reflex evoked by distilled water in anesthetized rats

Authors: *Y. NAKAJIMA, T. TSUJIMURA, K. NAGOYA, T. CHOTIRUNGSAN, Y. TSUTSUI, M. INOUE;
Niigata Univ. Med. and Dent. Hosp., niigata, Japan

Abstract: [Background and aims]Major side-effects of anticholinergic medications are xerostomia and dysphagia. However, few studies have evaluated how anticholinergic drugs have an impact on the swallowing neural network. This study aimed to investigate the effect of a muscarinic acetylcholine receptor (mAchR) non-specific antagonist atropine on the initiation of swallowing. [Methods]Experiments were carried out on 76 urethane-anesthetized Sprague-Dawley male rats (1.3 g/kg, ip). Swallowing reflex was evoked by either topical laryngeal application of a small amount (3 μl) of distilled water (DW), saline, citric acid (10^{-2} M) or capsaicin (10^{-9} - 10^{-5} M), upper airway (UA) distention with a continuous airflow (8 ml/s) or electrical stimulation of the right side of superior laryngeal nerve (SLN, 30 Hz, 0.2-ms pulse duration, 10-s train, 4.8-125 μA). A swallow was identified by electromyographic burst of the left side of suprahyoid and thyrohyoid muscles. To investigate anticholinergic effects on the initiation of swallowing, following reagents were delivered intravenously: atropine (0.01 - 1 mg/kg), methylatropine (a CNS-impermeant form of atropine, 1 mg/kg), mAChR subtype (M1 - M5) antagonist or saline (for vehicle of atropine). The effect of atropine administration on DW-evoked swallows was compared between with and without decerebration. After the swallowing assay, the amount of salivary secretion elicited by mAChR3 agonist pilocarpine was measured with a cotton ball placed on the oral floor.[Results]After administration of 1 mg/kg atropine, the number of DW-evoked swallows was significantly larger than baseline, while atropine did not change the saline, citric acid and capsaicin and UA-evoked swallows. The number of DW-evoked swallows was not changed following methylatropine, each M1- M5 antagonist or saline administration. The swallowing threshold of SLN stimulation was significantly decreased

following atropine administration than baseline and bilateral transection of the SLN abolished DW-evoked swallow. The number of DW-evoked swallows was significantly smaller in decerebrated rats than control rats and atropine did not facilitate DW-evoked swallows in this condition. Finally, pilocarpine-induced salivation was significantly reduced in atropine- or methylatropine-administrated rats compared with control rats[Conclusions] These results suggest atropine facilitates DW-evoked swallows via central mAChR actions.

Disclosures: Y. Nakajima: None. **T. Tsujimura:** None. **K. Nagoya:** None. **T. Chotirungsan:** None. **Y. Tsutsui:** None. **M. Inoue:** None.

Poster

130. Peripheral Mechanisms of Chemosensation

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 130.11

Topic: D.04. The Chemical Senses

Support: NSERC Grant 05571

Title: A role for dopamine D_2 receptors in hypoxia signalling in the zebrafish gill

Authors: *M. REED, M. JONZ;
Univ. of Ottawa, Ottawa, ON, Canada

Abstract: Adequate oxygen delivery to tissue is important for maintaining cellular homeostasis. Thus, an animal's ability to detect low oxygen, or hypoxia, is crucial for survival. Oxygen sensing in aquatic vertebrates occurs via chemoreceptive neuroepithelial cells (NECs) of the gills. NECs respond to decreased partial pressure of oxygen (PO_2) with Ca^{2+}-dependent vesicular recycling. This response is consistent with neurotransmitter release into the synaptic cleft, which leads to activation of sensory nerve fibres that initiate compensatory hyperventilation. Currently, there is no direct evidence for which neurotransmitters are released within the gills during hypoxia, and the receptors they act on remain uncharacterized. In zebrafish (Danio rerio), the neurotransmitter, dopamine, suppresses ventilation, whereas specific activation of D_2 receptors abolishes the hyperventilatory response to hypoxia. These results suggest a role for D_2 receptors in mediating the ventilatory response to hypoxia. We therefore hypothesized that dopamine D_2 receptors are involved in mediating hypoxia signalling by NECs within the gills of adult zebrafish. To first determine a relevant time scale during which zebrafish acclimate to hypoxia, we tested aquatic surface respiration (ASR) responses to acute hypoxia over a range of PO_2 in animals previously exposed to 24, 48, and 72 h hypoxia. We found the earliest evidence of acclimation after 48 h, as zebrafish acclimated to chronic hypoxia displayed a blunted ASR response to acute progressive hypoxia ($N=8$, $P<0.01$). Quantitative polymerase chain reaction confirmed expression of *drd2a* and *drd2b* (genes encoding zebrafish D_2 receptors) in isolated gill tissue, and 48 h hypoxia acclimation decreased the expression of *drd2a* by 4-fold and *drd2b* by 3.8-fold. Further, using confocal microscopy and immunohistochemical labelling, we localized

D_2 receptor immunoreactivity to the zebrafish gills. D_2 immunoreactivity was found in NECs and the nerve plexus of the filament epithelium, as well as in nerve fibers of the respiratory lamellae. Immunolabelling of NECs and nerves was verified using known markers of these structures, such as anti-synaptic vesicle protein and zn-12, respectively. Additionally, we discovered a previously undescribed cell type containing D_2 receptors on the afferent aspect of the gill filaments. Our results reveal D_2 receptors co-localize with chemosensory NECs and nerves, which may suggest roles for pre- and post-synaptic modulation of the hypoxic signal, similar to the mammalian carotid body. This work may suggest that a role for dopamine and D_2 receptors in O_2 sensing arose early in vertebrate evolution.

Disclosures: M. Reed: None. **M. Jonz:** None.

Poster

130. Peripheral Mechanisms of Chemosensation

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 130.12

Topic: D.04. The Chemical Senses

Support: NIH Grant U19 NS107466

Title: Chemosensory switch of breathing

Authors: *A. CALLADO-PÉREZ[1,2], M. DEMERS[1], B. FRIEDMAN[3], D. KLEINFELD[2,4], M. DESCHÊNES[1];
[1]CERVO Brain Res. Center, Laval Univ., Quebec, QC, Canada; [2]Dept. of Physics, [3]Dept. of Computer Sci. and Engin., [4]Dept. of Neurobio., Univ. Of California, San Diego, La Jolla, CA

Abstract: Under normal conditions, breathing is automatically -and unconsciously- controlled by several homeostatic mechanisms that regulate its depth and rate to protect the organism from chemical irritants. These protective airway reflexes include cough and forced expiration, as well as reflexive apnea. This apneic reflex is mediated by two major sensory pathways: the first pathway is mediated by vagal and glossopharyngeal afferents that project to the nucleus of the solitary tract (*Patrickson et al., 1991; Furusawa et al., 1996; Pascual-Font et al., 2011*); the second pathway involves trigeminal afferents from the nasal cavity that project mainly to the muralis subnucleus of the spinal trigeminal complex (SpVm), which lies at the transition between the interpolaris and caudalis subnuclei *(Anton and Peppel, 1991; Panneton, 1991; Matthews et al., 2015).* How these two pathways mediate the apneic reflex remains an open issue. Here we examine the anatomical circuit and physiological mechanisms through which trigeminal afferents from the nasal cavity trigger reflexive apnea induced by inhalation of ammonia vapors (a strong chemical irritant of the airway). First, we used the Nav1.8-YFP transgenic mouse line, in which c-afferents are fluorescently labeled, to demonstrate direct axonal input from c-afferents to SpVm neurons. We also show that apneic episodes upon ammonia inhalation are prevented after electrolytic lesion of SpVm. Using *in vivo* extracellular

recordings, we found that SpVm neurons respond to ammonia presentation as well as mechanical stimulation of the nasal and buccal mucosae. Using retrograde tracing with both chemical (ctB, Fluorogold) and viral (AAV-retrograde-Ef1α-mCherry) tracers, we demonstrate that SpVm neurons project to the PreBötzinger complex (preBötC), the oscillator for respiration. *In vivo* extracellular recordings additionally demonstrate that a subpopulation of expiratory units in the preBötC are activated by inhalation of ammonia vapors. Finally, we inject AAV2/1-Syn-Cre-mCherry in the SpVm and AAVDJ-Ef1α-DIO-ChR2-YFP in preBötC to show that optogenetic excitation of the specific population of neurons in preBötC that receive input from SpVm can elicit apnea. We propose that the trigeminal pathway necessary for reflexive apnea relies on brainstem circuits that involve projections from the trigeminal subnucleus muralis to preBötC. The irritant ammonia activates this pathway for chemosensation via the nasal c-afferents. These nerve afferents lead to activation of glutamatergic neurons in SpVm, which, in turn, activate expiratory glycinergic cells in the preBötC to increase the expiration period and protect the airway.

Disclosures: A. Callado-Pérez: None. **M. Demers:** None. **B. Friedman:** None. **D. Kleinfeld:** None. **M. Deschênes:** None.

Poster

130. Peripheral Mechanisms of Chemosensation

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 130.13

Topic: D.04. The Chemical Senses

Support: NIH DP1AT009497
NIH R01DK103703
NIH T32 HL007901
Food Allergy Science Initiative
Japan Society for the Promotion for Science

Title: Enteroendocrine cell lineages that differentially control feeding and gut motility

Authors: *M. HAYASHI[1], J. A. KAYE[1], N. R. JOSHI[1], E. R. DOUGLAS[2], F. REIMANN[3], F. M. GRIBBLE[3], S. LIBERLES[4];
[1]Dept. of Cell Biol., [2]Harvard Med. Sch., Boston, MA; [3]Univ. of Cambridge, Cambridge, United Kingdom; [4]Dept. of Cell Biol., Howard Hughes Med. Institute, Harvard Med. Sch., Boston, MA

Abstract: Enteroendocrine cells are specialized sensory cells of the gut-brain axis that are sparsely distributed along the intestinal epithelium. The functions of enteroendocrine cells have classically been inferred by the gut hormones they release. However, individual enteroendocrine cells typically produce multiple, sometimes apparently opposing, gut hormones in combination, and some gut hormones are also produced elsewhere in the body. Here, we developed approaches involving intersectional genetics to enable selective access to enteroendocrine cells

in vivo. We constructed Villin1-p2a-FlpO knock-in mice to restrict reporter expression to intestinal epithelium and through combined use of Cre and Flp alleles, effectively targeted major transcriptome-defined enteroendocrine cell lineages that produce serotonin, glucagon-like peptide 1, cholecystokinin, somatostatin, or glucose insulinotropic peptide. Chemogenetic activation of different enteroendocrine cell types variably impacted feeding behavior, nausea-associated behaviors (conditioned flavor avoidance), and gut motility. Defining the physiological roles of different enteroendocrine cell types provides an essential framework for understanding sensory biology of the intestine.

Disclosures: **M. Hayashi:** None. **J.A. Kaye:** None. **N.R. Joshi:** None. **E.R. Douglas:** None. **F. Reimann:** None. **F.M. Gribble:** F. Consulting Fees (e.g., advisory boards); Kallyope. **S. Liberles:** F. Consulting Fees (e.g., advisory boards); Kallyope.

Poster

131. Human Psychobehavior and Physiology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 131.01

Topic: D.05. Auditory & Vestibular Systems

Title: Body representation can curb auditory space processing

Authors: *D. PAROMOV[1,2], K. MOÏN-DARBARI[1,2], P. GERMAIN[1,2], M. MAHEU[1], B.-A. BACON[3], F. CHAMPOUX[1,2];
[1]Univ. of Montreal, Montreal, QC, Canada; [2]Ctr. de recherche de l'Institut Universitaire de Gériatrie de Montréal, Montreal, QC, Canada; [3]Carleton Univ., Ottawa, ON, Canada

Abstract: Sound localization is the result of computational processes anchored in binaural cues but which also includes the integration of information originating from the different senses. Notably, for the sounds to be localized, they must be perceived in relation to the body. This suggests strong interactions between the auditory system and the systems mapping the representation of the body in space, which include the somatosensory, vestibular and proprioceptive systems. The influence of auditory cues on postural stability and body orientation has been explored at length. However, the reverse interaction, namely the influence of body representation on sound localization, has never been investigated. In this study, we aim to determine if a change in body representation in space has an impact on sound localization. Twenty participants with normal auditory and vestibular function were asked to remain still while performing a task known to disrupt the spatial representation of the body in space. Participants performed the task in the presence of a constant auditory signal, and were asked to locate the sound before and after performing the task. Before the task, all participants were able to locate the sound source with precision. However, the degree of error in localization was significantly larger after the task. This illusory shift confirms the strong connections between sound localization processes and body representation in space, with the latter being shown, for the first time, to affect the former.

Disclosures: **D. Paromov:** None. **K. Moïn-Darbari:** None. **P. Germain:** None. **M. Maheu:** None. **B. Bacon:** None. **F. Champoux:** None.

Poster

131. Human Psychobehavior and Physiology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 131.02

Topic: D.05. Auditory & Vestibular Systems

Support: NIH Grant DC016363

Title: How many sounds can we hear?

Authors: C. WEISER[1], B. J. KING[2], M. PROVENCAL[2], *J. M. GROH[1], C. D. KING[2]; [1]Duke Univ., [2]Duke Univ., Durham, NC

Abstract: The visual system can detect many different simultaneous stimuli. This is achieved in part due to small neuronal receptive fields in primary visual cortex as well as neuronal multiplexing of simultaneously presented visual stimuli (Li et al, 2016; Caruso et al, 2018). However, the mammalian auditory system is thought to lack a map of auditory space, possibly limiting processing of multiple simultaneous auditory signals. Yost and colleagues have reported that humans can accurately detect between two and four simultaneous sounds, depending on the type of stimulus (eg, Yost and Zhong 2017; Yost et al 2019). METHODS. Many studies assessing human detection abilities of simultaneous auditory signals have focused on directly reporting the number of detectable sound locations. Such methods might be less sensitive than tasks involving comparisons between different numbers of sounds. Here we use a 2-interval-forced-choice task in which human subjects were asked which of two sets of spatially differentiated auditory stimuli had more distinct source locations. We controlled for frequency content to ensure subjects performed the task based on sound location alone. Each trial contained two presentations of 6 fixed-frequency noise bands, randomly spread across 1-6 of 8 speakers, positioned in an evenly spaced horizontal frontal field array. For each stimulus pair, the first stimulus (the benchmark) always played from 3 randomly assigned speakers. For the second stimulus the number of speakers was randomized between 1-6. Subjects indicated with a mouse click whether the first or second stimulus used more speakers. Subjects completed two 600-trial sessions (200ms and 1000ms stimulus duration). RESULTS. Our data align with results of previous experiments showing that humans can detect roughly 2-4 sound locations at a time. Some subjects show significant improvement in accuracy as the number of sound sources in the second stimulus increases from 3 to 6, but others are roughly uniform across that range, so the overall effect when averaged is small. We observe little difference between 200ms and 1000ms trials, suggesting that longer stimulus duration did not improve task performance. This suggests that, to the extent that multiple sound locations are multiplexed in the auditory system, providing additional time for detection does not increase the number of sounds encoded.

Disclosures: **C. Weiser:** None. **B.J. King:** None. **M. Provencal:** None. **J.M. Groh:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); book author, coursera instructor. **C.D. King:** None.

Poster

131. Human Psychobehavior and Physiology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 131.03

Topic: D.05. Auditory & Vestibular Systems

Support: Sasakawa Scientific Research Grant from The Japan Science Society 2022-6042

Title: Effect of the Timing Jitter in a Preceding Sound Sequence on Medial Olivocochlear Reflex and Reaction Time

Authors: *Y. ISHIZAKA[1], S. OTSUKA[2], S. NAKAGAWA[2];
[2]Ctr. for Frontier Med. Engin., [1]Chiba Univ., Chiba, Japan

Abstract: Medial olivocochlear fibers efferently project to the outer hair cells (OHCs) from superior olivary complex. The fibers are activated by acoustic stimulation and exert an inhibitory effect on OHC motility; this effect has been termed the medial olivocochlear reflex (MOCR). We have reported that the MOCR and phase locking of delta activity in cortical regions showed a similar decreasing tendency with increasing the jitter added to the preceding sound sequence. This suggests that processing of temporal expectation in the cortical regions is involved in the predictive control of MOCR. By contrast, delta-band oscillations were also shown to be involved in expediting reaction time (RT) to target occurrence which is predicted from temporal regularity. Therefore, we hypothesized that the prediction-related modulations of the MOCR and behavioral reaction are underlined by the same mechanism, namely delta-band oscillation. In this experiment, we compared dependency of the delta oscillation, MOCR and RT on the jitter added in a preceding sound sequence. The MOCR was evaluated by measuring otoacoustic emissions (OAEs), which are sounds that originate in the cochlea and reflect OHC motility. OAEs are suppressed by noise presented to the contralateral ear. The size of the MOCR suppression has been used as a measure of MOCR strength. OAEs were evoked by clicks presented at the rate of 40 clicks per second. A stimulus block for the contralateral ear was composed of target noise,which was a elicitor of MOCR, and three preceding tones whose duration were all 500 ms. Predictability of the timing of target noise was modulated by adding jitter (ΔT) to the inter-stimulus interval (ISI) among the tones and target noise, whose default was 500 ms. ΔT was randomly selected from 50, 100, 150, and 200 ms for each stimulus block and fixed within the block. Participants were instructed to press a button as soon as possible when the target noise occurred. The RT was defined as the time interval from the onset of the target noise to time point of the button press. We estimated the phase locking value (PLV) of the delta-band electroencephalogram oscillations during the noise presentation. The MOCR and the PLV of delta oscillations were decreased and the RT was increased with increasing the jitter up to 20%,

and they remained saturated above that percentage. This similar dependence on the jitter size suggests the involvement of delta oscillations in the increase of MOCR and the decrease of RT associated with temporal predictability of the target occurrence based on preceding sound sequence regularity.

Disclosures: **Y. Ishizaka:** None. **S. Otsuka:** None. **S. Nakagawa:** None.

Poster

131. Human Psychobehavior and Physiology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 131.04

Topic: D.05. Auditory & Vestibular Systems

Support: CERVO Brain Research Center

Title: Mistuned harmonic perception when the F_0 is missing : A new protocol to investigate pitch perception in humans

Authors: A. WHITTOM, F. COUTURE, C. NADEAU, L. CHAUVETTE, ***A. SHARP**;
Ctr. de Recherche CERVO, Univ. Laval, Québec, QC, Canada

Abstract: The missing fundamental is a well-known phenomenon in auditory neuroscience (Seebeck, 1841) and occurs when the pitch of a complex sound is perceived as its fundamental frequency (F_0) even if the F_0 is absent. This perception is predicated on the condition that enough F_0 harmonics are in the signal. A common example is the telephone, where the F_0 is not transmitted by the handset and humans are still able to perceive the voice pitch of the talker. Although this auditory illusion has been known for more than a century, the mechanisms underlying this auditory phenomenon remain under-investigated (Zatorre, 2005). Some studies have attempted to measure behaviorally the ability to extract the missing F_0 in humans (e.g. Ladd et al., 2013). However, their proposed methodologies did not allow to compare perception when the F_0 is present or absent. The main goal of the project was therefore to develop a new unified methodology to investigate the perception of pitch in the same way with both present and missing F_0. Using a MATLAB-based application developed in our laboratory, 10 healthy adults had to untune the frequency of the 2nd harmonic of a complex sound containing the F_0 and 6 harmonics until they perceived 2 distinct sounds. This task was repeated 10 times for three F_0 (125, 200, 440Hz). The results were compared to the results of Moore et al. (1985) suggesting that the frequencies of the lower harmonics in a complex tone can be shifted by 1-3% before these harmonics are heard as a second sound. Our results replicated this highly cited psychoacoustic study with thresholds of respectively 1% (440Hz) and 2% (125, 200Hz). A second group of healthy adults (N=30) completed the same task but this time with the F_0 missing. Our results suggest a low intra-individual variability across trials for all 3 F_0, which makes it possible to measure a precise mistuned harmonic perception threshold in a complex sound with and without F_0. In addition, the comparison between thresholds for present and missing F_0

revealed that participants had a higher threshold when the F_0 was missing for the 3 frequencies of F_0 investigated, suggesting that the perception of mistuned harmonics is harder for complex sounds with missing F_0. This new and more precise methodology not only already tells us more about the perception of pitch in humans but will allow us to investigate the impact of cortical reorganization following auditory deprivation or musical training on pitch perception. This method in pair with electrophysiology techniques will allow us to further deepen our understanding of the mechanisms allowing auditory perception in a context of missing F_0 which is a common situation in everyday life.

Disclosures: **A. Whittom:** None. **F. Couture:** None. **C. Nadeau:** None. **L. Chauvette:** None. **A. Sharp:** None.

Poster

131. Human Psychobehavior and Physiology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 131.05

Topic: D.05. Auditory & Vestibular Systems

Support: NIH F31-DC019291
NIH R01-DC011555

Title: Determining the Optimal Stimulus to Evoke the Binaural Interaction Component of the Auditory Brainstem Response

Authors: *Z. OWRUTSKY[1], J. PEACOCK[1], N. GREENE[1], D. J. TOLLIN[2];
[1]Univ. of Colorado, Aurora, CO; [2]Physiol., Univ. of Colorado Sch. of Med., Aurora, CO

Abstract: Auditory brainstem responses (ABRs) are widely used for non-invasive assessment of auditory function. A derived component of the ABR, known as the binaural interaction component (BIC) holds promise as a potential biomarker for spatial hearing ability. However, clinical use of the BIC has been limited because it is unreliably measured in humans using traditional click stimuli.Chirps are specifically designed to enhance temporal synchrony in the responses of the auditory nerve and brainstem by compensating for the frequency- and level-dependent delays accrued by the traveling wave in the cochlea. Chirps have been shown to produce larger responses in monaural ABR measurements. Here, we test the hypothesis that chirp stimuli evoke larger ABR-BIC amplitudes compared to traditional click stimuli.
ABRs were measured in response to tone bursts over a range of frequencies and intensities in chinchillas (n=7). Stimuli consisted of 5-ms tone bursts (1-16kHz) presented via calibrated insert earphones from 10 dB below to 50 dB above ABR detection threshold. Latencies of ABR waves I, IV and BIC were plotted against stimulus frequency and fit to a power function: Tau=k*f^(-d), where tau is latency in seconds, f is frequency in Hz, and k and d are derived constants. Values of k and d were used to construct a series of level-specific chirps at four stimulation levels (10-50 dB above threshold) based on monaural ABR waves I and IV (termed chirp-I and chirp-IV,

respectively) and BIC DN1 (chirp-BIC).
Consistent with previous reports, we show that all chirps tested evoked significantly larger monaural ABR amplitudes for waves I and IV compared to clicks at relatively low levels (50-60 dB SPL, $p<0.05$). Here, we report that the BIC is also enhanced at lower sound levels by using chirps. At 50 dB, both monaural chirps as well as the BIC chirp evoked significantly larger BIC amplitudes over the click (ttest, $p<0.05$). At higher intensity levels (80-90 dB SPL), we find no significant difference in BIC amplitude between chirps and clicks.
Chirp stimuli designed to optimize monaural ABR peak amplitudes appeared to produce similar gains in DN1 amplitude as chirps designed to optimize DN1 at relatively low stimulation levels. This is likely explained by the observation that upward spread of excitation in the cochlea is limited at lower sound levels, and that the cochlear-neural delay, which we exploit here in our chirp design, is more pronounced at lower stimulation levels as well. Surprisingly, we find no statistical difference in BIC amplitude between monaural and binaural chirps, suggesting that any chirp which compensates for cochlear delay may be sufficient to evoke optimal BIC responses.

Disclosures: **Z. Owrutsky:** None. **J. Peacock:** None. **N. Greene:** None. **D.J. Tollin:** None.

Poster

131. Human Psychobehavior and Physiology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 131.06

Topic: D.05. Auditory & Vestibular Systems

Support: NIH-NIDCD 5R01DC014279

Title: Electrocorticography-based auditory attention decoding with moving talkers and background noise

Authors: *V. CHOUDHARI[1,2], C. HAN[1,2], S. BICKEL[3,4], A. D. MEHTA[3,4], N. MESGARANI[1,2];
[1]Electrical Engin., Columbia Univ., New York City, NY; [2]Mortimer B. Zuckerman Mind Brain Behavior Inst., New York City, NY; [3]Hofstra Northwell Sch. of Med., Uniondale, NY; [4]The Feinstein Inst. for Med. Res., New York City, NY

Abstract: Hearing-impaired listeners experience difficulty in attending to a specific talker in the presence of interfering talkers. Cognitively-controlled hearing aids aim to address this problem by decoding the attended talker from neural signals using auditory attention decoding (AAD) algorithms, separating the speech mixture into individual streams and selectively enhancing the attended speech stream. Prior work investigating AAD algorithms for cognitively-controlled hearing aids often use simple acoustic scene settings for their experiments. In most of these studies, the attended and unattended talkers are of different sex and stationary in space with no relative motion. Background noise is often ignored. Such scenes do not mimic real-life settings.

More importantly, the talkers could also be engaged in conversations, which calls for attention switches during turn-taking. For AAD algorithms to be operable in real-world settings, it is imperative that they generalize to challenging and unpredictable changes in the acoustic scene. We designed an AAD task that replicates real-life acoustic scene settings. The task involved two concurrent talkers (either same/different sex) that are spatially separated and continuously moving in the presence of background noise. These talkers independently engaged in two distinct conversations. Different talkers took turns in these conversations. Electrocorticography (ECoG) data from two epilepsy patients was collected. The participants were instructed to attend to the conversation that was cued at the start of each trial. A deep learning-based binaural speech separation algorithm was used to causally separate the speech streams of the talkers in the acoustic scene while also preserving their location information (interaural time and level differences). Spatiotemporal filters were trained to reconstruct the spectrograms and the trajectories of the attended and unattended talkers from the neural recordings. These reconstructions were then compared with the spectrograms and trajectories yielded by the binaural speech separation algorithm to determine the attended and unattended talkers. The binaural speech separation algorithm helped in enhancing the attended talker both subjectively and objectively. Trajectories and spectrograms of the attended talker were reconstructed from neural data with accuracies significantly above chance levels. Attended talker could be correctly decoded with an accuracy of 82% using a window size of 4 seconds. These results suggest that our current speech separation and AAD algorithms can generalize well to challenging environments in daily settings.

Disclosures: V. Choudhari: None. **C. Han:** None. **S. Bickel:** None. **A.D. Mehta:** None. **N. Mesgarani:** None.

Poster

131. Human Psychobehavior and Physiology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 131.07

Topic: D.05. Auditory & Vestibular Systems

Title: Functionnal connectivity of silent gaps using a electroencephalogy

Authors: *T. AUGEREAU, F. CHAMPOUX, V. DUDA;
Ecole d'Orthophonie et d'Audiologie, Univ. de Montréal, Montréal, QC, Canada

Abstract: Background and Aim: Recent advances in multifocal transcranial direct current stimulation (tDCS) highlighted the enhanced effect when stimulating a set of areas involved in a cognitive process. Here, we target the temporal resolution in auditory processes as it is a key aspect in speech perception. The loss appearing in presbycusis could be thus countered using multifocal tDCS. A recent study aimed at highlighting differences in the connectivity patterns of the MMN succeeded in highlighting 11 potential areas for MMN generation for deviant stimuli over time. The objective of this study will be to identify the target areas involved specifically in

the processing of temporal resolution in the context of the multi-deviant paradigm. **Methods:** Twenty healthy normal hearing subjects will be tested to record the generation of the MMN and to measure its connectivity. Stimuli will be presented using a multi-deviant paradigm which consists of alternating a standard and 7 deviants in a pseudo-random order. The standard is a continuous 200 ms white noise (0Hz - 22kHz) and the deviants a 200 ms white noise with silent intervals of different durations (2, 5, 7, 10, 20, 30 and 40 ms). Each deviant has a 7.1% chance of being presented and the standard is presented every other noise (50% of stimuli). Stimuli will be presented every 500ms and sent via a script developed on Matlab through ER2 headphones. To confirm the target areas, a clustered connectivity analysis will be performed using the Source Information Flow Toolbox (SIFT) in EEGLAB conjointly with Fieldtrip. Independent components will be localized and clustered, then segmented in regions of interest (ROIs). Connectivity matrix will allow to determine links between ROIs and binarization of links will allow to construct the network model. **Results:** We expect the right Heschl's gyrus, the right dorsolateral prefrontal cortex, and the left dorsoanterior cingulate cortex will be activated in the generation of the MMN associated with the gapped stimuli. These results would concord with previous studies on the MMN using non-gapped stimuli. **Conclusion:** The cortical connectivity of temporal resolution is still not fully elucidated in the literature. Here we plan to use the Mismatch Negativity and the multi-deviant paradigm to demonstrate the cortical areas involved in processing auditory temporal cues.

Disclosures: **T. Augereau:** None. **F. Champoux:** None. **V. Duda:** None.

Poster

131. Human Psychobehavior and Physiology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 131.08

Topic: D.05. Auditory & Vestibular Systems

Support: FWO G0D6720N
FWO 1290821N

Title: Objectively assessing hearing and language abilities in patients with disorders of consciousness

Authors: *R. SONCK[1,2], J. VANTHORNHOUT[1], E. BONIN[2,3], A. THIBAUT[2,3], S. LAUREYS[2,3], T. FRANCART[1];
[1]Dept. of Neurosciences, KU Leuven - Univ. of Leuven, Leuven, Belgium; [2]GIGA-Consciousness, Univ. of Liège, Liège, Belgium; [3]Ctr. du Cerveau², Univ. Hosp. Ctr. of Liège, Liège, Belgium

Abstract: Objectives. Following a severe brain injury, some patients fall into a coma and may subsequently experience disorders of consciousness (DOC). When assessing a patient's consciousness level, the patient's hearing disability is a confounding factor that can interfere with

the assessment and lead to misdiagnosis. To reduce misdiagnosis, we propose to assess the hearing- and language abilities of patients with DOC using electroencephalography (EEG) to investigate their auditory steady-state responses (ASSR) and neural speech envelope tracking.
Methods. Sixteen normal-hearing adults participated in the first experiment. While their EEG was recorded, the participants listened passively to three ASSR stimuli, with amplitude modulation frequencies of 3.1 Hz, 40.1 Hz, and 102.1 Hz; each frequency provides information about different brain regions along the auditory pathway. These stimuli are presented both sequentially (i.e., single ASSR) and simultaneously (i.e., multiplexed ASSR). In a second experiment, which is still ongoing (n=2, but more are planned), patients with DOC first go through the same multiplexed ASSR set-up as in the first experiment. Then, we track their neural speech envelope after listening to a story in their native language, in a foreign language, and in noise.
Results. We have shown that the signal-to-noise ratio of neural responses evoked by a multiplexed ASSR stimulus does not significantly differ from evoked neural responses from sequentially presented single ASSR stimuli. Furthermore, our preliminary results indicate that neural speech envelope tracking is possible in patients with DOC.
Conclusion. Multiplexed ASSR is a valid replacement for single ASSR, which can help to shorten EEG measurements, crucial for patients with DOC as they quickly get exhausted. Moreover, neural speech envelope tracking might be a promising tool to analyze DOC patients' speech processing abilities, which cannot always be deduced with certainty by only relying on neurobehavioral testing.

Disclosures: R. Sonck: None. **J. Vanthornhout:** None. **E. Bonin:** None. **A. Thibaut:** None. **S. Laureys:** None. **T. Francart:** None.

Poster

131. Human Psychobehavior and Physiology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 131.09

Topic: D.05. Auditory & Vestibular Systems

Title: Auditory evoked response and auditory gamma oscillations measured by OPM-MEG

Authors: *K.-M. AN[1,2,3];
[1]Ctr. for Human Brain Hlth., Univ. of Birmingham, Birmingham, United Kingdom; [2]Res. Ctr. for Child Mental Develop., Kanazawa Univ., Kanazawa, Japan; [3]Korea Res. Inst. of Standards and Sci., Daejeon, Korea, Republic of

Abstract: Magnetoencephalography (MEG) is a functional neuroimaging method, which non-invasively measures brain neural activity. The conventional MEG system detects brain magnetic fields using Superconducting QUantum Interference Devices (SQUIDs). SQUIDs-MEG has a fixed sensor position and greater distance between sensors and cortical sources because of liquid helium and Dewar. Recently, small-sized optically pumped magnetometers (OPMs) have been

developed and commercialized. OPMs do not require a cryogenic environment and can be placed as close to the scalp as millimetres. Here, we developed an OPM-MEG system by arranging six OPM sensors and a 3D-printed curved plate that fitted the temporal head surfaces. In this study, we recruited 22 right-handed healthy participants (mean age: 27.05 ± 4.36 years; 11 females) to measure auditory-related brain responses using the OPM-MEG. To detect auditory evoked response and auditory steady-state gamma oscillations at 40 Hz, we presented the auditory stimuli of 1-kHz pure tone with 200-ms duration and the periodic stimuli with a 40-Hz repetition rate with 1-s duration. We observed the clear M50 and M100 components of auditory-evoked fields. We found the gamma-band power changes and inter-trial phase coherence of auditory steady-state responses at 40 Hz. Our results indicate the feasibility of using OPM sensors to detect auditory brain responses and gamma brain oscillations.

Disclosures: K. An: None.

Poster

131. Human Psychobehavior and Physiology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 131.10

Topic: D.05. Auditory & Vestibular Systems

Support: KIST Institutional Program (2E31084)
National Research Council of Science & Technology (NST) grant CAP21051-200
National Research Foundation of Korea NRF-2022R1I1A4063209
National Research Foundation of Korea NRF-2022R1A2C2005062

Title: The role of phase coherence in sound for signal detection in noise

Authors: *J. LEE[1,4], H. AN[4], S. JUN[1,2,3], Y. LIM[4];
[1]Electronic and Electrical Engin., [2]Brain and Cognitive Sci., [3]Grad. Program in Smart Factory, Ewha Womans Univ., Seoul, Korea, Republic of; [4]Ctr. for Intelligent & Interactive Robotics, Korea Inst. of Sci. and Technol., Seoul, Korea, Republic of

Abstract: Hearing in noise is a common problem in everyday life, yet how our auditory system successfully extracts sound of interest from superimposed background remains unclear. In this study, we defined the auditory stability based on the pairwise structural similarity between each contour derived from the sparse contour-based signal representation with multiple time scales and angle parameters. We assumed that auditory stability might contain important information for signal detection in noise that has not been revealed by the amplitude in the spectrogram. To test the hypothesis, we measured the statistical distance (Kolmogorov-Smirnov statistic) of energy or auditory stability for a chirp and white noise, and examined how these statistical distances correlate with human signal detection performance. Listeners performed a 2-Alternative Forced Choice (2-AFC) detection task between a chirp signal and a white noise under 3 different noise conditions (n=20, SNR:-2, -3, -4 dB). Pearson correlation showed that

statistical distance of energy and auditory stability were significantly correlated with hit rate in -3dB (energy: r=0.132, p<0.05; auditory stability: r=0.113, p<0.05) and -2dB (energy: r=0.141, p<0.05; auditory stability: r=0.097, p<0.05). However in the -4dB condition, we only found a significant correlation between auditory stability and hit rate (energy: r=0.0007, p=0.980; auditory stability: r=0.073, p<0.05). In summary, auditory stability based on sparse contour-based signal representation seems to successfully describe the human performance of signal detection in noise, including the lowest signal-to-noise (SNR) ratio condition in contrast to the measure based on the spectrogram. This result may suggest that the auditory stability derived from the phase coherence in sound may capture the information for the stable sound hearing even in more complex situations.

Disclosures: **J. Lee:** None. **H. An:** None. **S. Jun:** None. **Y. Lim:** None.

Poster

131. Human Psychobehavior and Physiology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 131.11

Topic: D.05. Auditory & Vestibular Systems

Support: NSF Grant OISE2020624
NSF Grant SMA1734892
NSF Grant CCF1552946
NIH Grant R01-DC019394
NIH Grant R01-DC014085
NIH Grant P01-AG055365
NIH Grant R21-AG068802

Title: Extracting directional connectivity via network localized Granger causality from MEG data

Authors: B. SOLEIMANI[1,2], I. KARUNATHILAKE[1,2], P. DAS[4], S. E. KUCHINSKY[5], J. Z. SIMON[1,2,3], *B. BABADI[1,2];
[1]Dept. of Electrical and Computer Engin., [2]Inst. for Systems Res., [3]Dept. of Biol., Univ. of Maryland, College Park, MD; [4]Dept. of Anesthesia, Critical Care and Pain Med., Massachusetts Gen. Hosp., Charlestown, MA; [5]Audiol. and Speech Pathology Ctr., Walter Reed Natl. Military Med. Ctr., Bethesda, MD

Abstract: Extracting the directed connectivity that underlies networked activity of various cortical areas is key to understanding the neural mechanisms of sensory processing. Granger causality (GC), as a measure of directed connectivity, has been widely used for this purpose in functional magnetic resonance imaging analysis. However, due to the relatively low temporal resolution there, capturing network interactions pertaining to the millisecond-scale is not possible. Magnetoencephalography (MEG), on the other hand, provides millisecond temporal

resolution, but only offers limited spatial resolution, which makes GC inference highly challenging. Existing methods typically proceed in two stages, by first performing MEG source localization, then followed by GC inference. Consequently, the spatiotemporal biases induced in favor of source localization in the first stage may propagate to the second stage and result in false alarms and missing the true GC links. To address this challenge, we introduce the network localized Granger causality (NLGC) inference paradigm, in which cortical source dynamics are modeled as latent sparse multivariate autoregressive processes whose parameters are directly estimated from the MEG measurements, without the need for intermediate source localization. NLGC is shown to be more reliable than the two-stage approaches in different practical scenarios such as in the presence of the model mismatch in the forward model and low signal-to-noise ratio conditions. We demonstrate the utility of NLGC inference using experimentally recorded MEG data from younger and older participants performing a tone processing task versus resting state. In analyzing the networked activity of frontal, temporal, and parietal areas, NLGC reveals novel lobe-specific dependence of network connectivity patterns in younger vs. older adults as well as tone processing vs. resting state conditions across different frequency bands. Our results suggest that NLGC inference can be utilized as a robust alternative to existing methods for directional connectivity analysis of MEG data.

Disclosures: **B. Soleimani:** None. **I. Karunathilake:** None. **P. Das:** None. **S.E. Kuchinsky:** None. **J.Z. Simon:** None. **B. Babadi:** None.

Poster

131. Human Psychobehavior and Physiology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 131.12

Title: WITHDRAWN

Poster

131. Human Psychobehavior and Physiology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 131.13

Topic: D.05. Auditory & Vestibular Systems

Title: Sensory attenuation and the sense of agency under the lens of EEG: What about action-effect relevance?

Authors: *E. LINDNER[1], F. P.-H. CHENG[1], A. DESANTIS[2], A. GAIL[1];
[1]Cognitive Neurosci. Lab., German Primate Ctr., Goettingen, Germany; [2]Dept. Traitement de l'Information et Systèmes, The French Aerospace Lab. ONERA, Salon-de-Provence, France

Abstract: Sensory processing of self-initiated action-effects leads to less intense perception and reduced neural responses compared to externally triggered stimuli (sensory attenuation). It is suggested that this sensory attenuation might help agents to differentiate between the sensory consequences of self-generated actions, because they are predicted and suppressed, and externally initiated actions, which are unexpected and enhanced. However, the link between sensory attenuation and the sense of agency remains unclear. For instance, it is unclear if sensory attenuation occurs in all cases of action-effect prediction (AEP). Specifically, we ask whether action-effects are attenuated when they are relevant to determine and plan follow-up actions. Lacking sensory attenuation in cases of AEP with enhanced behavioral relevance of the action-effect would contradict an immediate link of sensory attenuation to AEP and agency. Here, we quantified auditory evoked potentials in electroencephalography (EEG) when human participants created two-sound sequences by pressing keys on a keyboard. We assessed sensory attenuation using identity-specific AEP, as prediction-congruent sounds have previously been found to be attenuated in the event-related potential (ERP) N1 compared to prediction-incongruent sounds. The first sound of each sequence corresponded to (congruent) or violated (incongruent) a previously learned key-sound association. The identity of the first sound was either relevant for the selection of the second sound (keypress) to complete the sequence (Relevance) or irrelevant (No-Relevance), or there was only one keypress and sound (Baseline). In the ERPs, we found the P2 component to be modulated by congruency and condition. Post-hoc tests revealed a decrease in the incongruent P2 amplitude from Baseline to Relevance condition, as well as from No-Relevance to Relevance condition. Incongruent sounds resulted in a suppressed P2 compared to congruent sounds. Pupil size data yielded similar findings. Contrary to our expectation, we did not observe an N1 ERP modulation by congruency in any condition. These findings indicate that identity-specific AEP does not necessarily lead to sensory attenuation in N1. However, it led to a modulation of the P2 ERP and pupil size, if coupled with the relevance of the action-effect. This modulation was especially apparent in changes for incongruent stimuli. This might indicate an effect of relevance on the (conscious) processing of incongruent auditory stimuli.

Disclosures: **E. Lindner:** None. **F.P. Cheng:** None. **A. Desantis:** None. **A. Gail:** None.

Poster

131. Human Psychobehavior and Physiology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 131.14

Topic: D.05. Auditory & Vestibular Systems

Support: NIH F32-MH120886-01
NIMH MH117155
NINDS R01 NS123655-01

Title: Spatial and temporal characteristics of speech-selective columns in human superior temporal gyrus

Authors: *D. R. CLEARY[1], C. DICKEY[5], B. STEDELIN[7], Y. TCHOE[2], A. BOURHIS[3], D. SILER[7], S. LEE[3], E. KAESTNER[6], S. RUSSMAN[8], D. SOPER[10], S. J. HAN[11], J. C. YANG[12], A. M. RASLAN[14], S. S. CASH[13], S. DAYEH[9], E. HALGREN[4];
[1]Neurosurg., [2]Electrical and Computer Engin., [3]ECE, [4]Multimodal Imaging Lab. (MC0841), UCSD, La Jolla, CA; [5]Dept. of Neurosciences, Univ. of California San Diego, La Jolla, CA; [6]Univ. of California San Diego, San Diego, CA; [7]Oregon Hlth. & Sci. Univ., Portland, OR; [8]Bioengineering, UC San Diego, San Diego, CA; [9]Dept. of Electrical and Computer Engin., UC San Diego, La Jolla, CA; [10]Neurol., Massachusetts Gen. Hosp., Wenham, MA; [11]Stanford Med., Palo Alto, CA; [12]Dept Neurolog. Surgery, [13]Dept Neurol, Mass Genl Hosp, Boston, MA; [14]OHSU, Portland, OR

Abstract: Our understanding of the neural underpinnings of receptive speech remains incomplete. Limited direct evidence exists for the assumption that cerebral cortex is functionally organized into discrete columns. To study cortical processing of speech, we recorded from the surface of the awake human cortex during surgeries in 7 patients (of which 5 provided reliable data). Initial clinical mapping of eloquent cortex was performed, and we then recorded broad-band local field potentials from the superior temporal gyrus (STG) and adjacent areas with custom, high-density microgrids containing up to 1024 channels at 200 micron pitch. Patients listened to a series of consonant-vowel syllables, and a similar number of noise-vocoded stimuli that maintain the time-amplitude contour across frequency bands. Consistent spatial and temporal modulation patterns were observed across all patients, where auditory stimuli produced statistically significant cortical activation with phase-amplitude coupling between slower (2-8Hz) and faster frequencies (70-190Hz). Factorization was used to separate the channels by functional similarities, and spatially clustered groups showed similar patterns of gamma-band activation with high local correlation that dropped off rapidly. Clusters were consistently 1-2 mm in diameter, with distinct transitions. Boundaries between clusters appeared to co-localize with pial arterial supplies, suggesting an anatomical basis for the functional divisions. Most clusters responded more robustly to speech sounds compared to noise-vocoded controls, but others selectively responded to noise. Each speech-selective cluster exhibited a characteristic high gamma temporal profile, and a distinct pattern across the different speech stimuli. However, cluster responses were not simply related to particular classes of consonants or vowels. In summary, we report 4 main findings: (1) Human language-selective association cortex appears to be organized in modules of 1-2 mm, suggesting an optimal resolution for language prostheses. (2) Functional boundaries at this resolution appear to have some relation to vascular boundaries, a finding that has implications for the interpretation and ultimate resolution of the BOLD response. (3) Phoneme selectivity may be more complex than is often thought, and involve temporal and spatial patterns. (4) Some cortical modules selectively respond to non-speech stimuli, suggesting that instead of being organized in different laminae, error signals implementing predictive coding may be organized in different columnar modules.

Disclosures: **D.R. Cleary:** F. Consulting Fees (e.g., advisory boards); Advisory board (unpaid). **C. Dickey:** None. **B. Stedelin:** None. **Y. Tchoe:** None. **A. Bourhis:** None. **D. Siler:** None. **S. Lee:** None. **E. Kaestner:** None. **S. Russman:** None. **D. Soper:** None. **S.J. Han:** None. **J.C. Yang:** None. **A.M. Raslan:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Intellectual property. **S.S. Cash:** None. **S. Dayeh:** E. Ownership Interest (stock, stock options,

royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Intellectual property. **E. Halgren:** None.

Poster

131. Human Psychobehavior and Physiology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 131.15

Topic: D.05. Auditory & Vestibular Systems

Support: E. Matilda Ziegler Foundation Grant

Title: Neural dynamics of human echolocation

Authors: *H. GARCIA-LAZARO, S. TENG;
The Smith Kettlewell Eye Res. Inst., San Francisco, CA

Abstract: Echolocation is a strategy that leverages active sensing and spatial hearing to detect and localize objects and navigate through environments. Some blind individuals use echolocation to sense and navigate their surroundings, complementing other mobility methods. They emit mouth clicks and perceive the echoacoustic reflections to detect, localize, and discriminate the size, distance, shape and material of objects [1-3]. Spatial hearing acuity in these tasks is superior in blind individuals compared to sighted people [4-6], but little is known about the neural temporal dynamics that facilitate it.This study aims to elucidate the neural temporal dynamics underlying the perception of spatialized echo reflections produced by mouth clicks, which is a fundamental operation of human echolocation. Participants, blind and sighted individuals, performed a spatial perceptual auditory task while recording their brain activity using EEG. On each trial, they listened to a train of 2, 5, 8 or 11 synthesized mouth clicks of 5 ms duration each [7], with echoes spatialized 5-25° to either side of the midline). The distance of the virtual object reflector was 1 meter. The subject's task was to indicate whether the echo reflector was to the left or right of center. To decouple motor from perceptual processing, keyboard responses were collected after stimulus presentation and randomized relative to stimulus location. Behavioral performance varied according to visual experience; blind participants were more accurate in discriminating the location of echo reflections than sighted individuals. Using an MVPA approach for the EEG signal, we examine how well spatial information contained in the echo reflections was perceived and discriminated during the first two clicks. Interestingly, spatial information (left vs right) was distinguishable in the brain, indexed by decoding accuracy, during the first 200ms after the first click onset. Decoding accuracy increased notably before the onset of the second click in the trial suggesting the presence of sensory evidence for a given location even before a perceptual decisional process was in place and independent of performance.

Disclosures: H. Garcia-Lazaro: None. **S. Teng:** None.

Poster

132. Object Coding and Scene Perception

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 132.01

Topic: D.06. Vision

Support: AFOSR (FA9550-21-1-0088)
NSF (BCS-1945230, IIS-2114644)
NIH (R01MH129426)
Dana Foundation

Title: Feature-based encoding of objects by single neurons in the human amygdala and hippocampus

Authors: *R. CAO[1], X. LI[1], U. RUTISHAUSER[3], N. BRANDMEIR[2], S. WANG[4];
[1]Lane Dept. of Computer Sci. and Electrical Engin., [2]Dept. of Neurosurg., West Virginia Univ., Morgantown, WV; [3]Cedars-Sinai Med. Ctr., Cedars-Sinai Med. Ctr., Los Angeles, CA; [4]Washington Univ. in St. Louis, Washington Univ. in St. Louis, Saint Louis, MO

Abstract: Neurons in the human amygdala and hippocampus demonstrate category-specific visual responses and are thought to have invariant visual representations of faces and objects. A recent study challenged this view by showing that amygdala and hippocampal neurons encode faces based on shared visual features, suggesting the existence of feature-based coding in the amygdala and hippocampus. Yet, it remains unclear how amygdala and hippocampal neurons encode objects in general and whether feature-based coding also exists for objects. Here, we recorded from more than 2000 neurons in the amygdala and hippocampus while in total 26 neurosurgical patients viewed multiple sets of object images. We constructed object feature spaces using pre-trained deep neural network (DNN) models. First, we found that a subset of neurons in the amygdala and hippocampus encoded object images that are clustered in feature space, i.e., neurons responded only when an object fell into a specific region in the feature space and exhibited region-based feature coding. We validated this finding using a different set of object images. Second, by employing a free viewing task of natural scene images and constructing feature spaces using the content of fixations, we found that region-based feature coding generalized to the overtly attended parts of faces and objects in complex natural scenes. Third, by employing a visual search task of faces and objects and constructing feature spaces using the content of fixations, we again found region-based feature coding. Taken together, our results not only reveal a novel region-based code for objects in general but also suggest a general coding mechanism for visual images in the amygdala and hippocampus. This novel coding mechanism may serve as an intermediate code bridging perception-driven representations of visual features and mnemonic semantic representations for declarative memory.

Disclosures: R. Cao: None. **X. Li:** None. **U. Rutishauser:** None. **N. Brandmeir:** None. **S. Wang:** None.

Poster

132. Object Coding and Scene Perception

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 132.02

Topic: D.06. Vision

Support: a Royal Society and Wellcome Trust Sir Henry Dale Fellowship to AC (211200/Z/18/Z)

Title: Neuroscience in the wild: Using mobile EEG and augmented reality to study object recognition in real-world environments

Authors: *V. I. NICHOLLS[1], B. ALSBURY-NEALY[3], A. KRUGLIAK[2], S. PANDYA[4], A. CLARKE[1];
[1]Univ. of Cambridge, Cambridge, United Kingdom; [2]Psychology, Univ. of Cambridge, CAMBRIDGE, United Kingdom; [3]Univ. of Toronto, Toronto, ON, Canada; [4]Univ. of Miami, Miami, FL

Abstract: Our ability to recognise objects is impacted by the environment we find these objects in. This occurs through initial coding of global scene context, enabling the generation of predictions about potential objects in the environment (Bar, 2004; Trapp & Bar, 2015). When correct, these predictions facilitate object recognition, but when these predictions are violated object recognition is impeded, shown by slower reaction times, lower accuracy, and larger N300/400 event-related potentials (ERPs; Biederman, et al, 1982; Mudrik, et al, 2010; 2014; Lauer, et al, 2020). The majority of research on object recognition and visual contexts has been done in controlled laboratory settings, where objects and scenes often occur simultaneously, isolating objects from a coherent spatiotemporal context. However, in the real world, the environment is relatively stable over time while objects come and go. Research in real world environments is the ultimate test of how context changes our perceptions, and is fundamental in determining how we understand what we see. In this research, we asked how the visual context influenced object recognition in real-world settings through a combination of mobile electroencephalography (mEEG) and augmented reality (AR) in humans. During the experiment, participants (n=34, based on a power analysis of data from Draschkow, et al, 2018) approached AR arrows placed either in an indoor or an outdoor environment while mEEG was recorded. When participants reached the arrows, they changed colour indicating that a button could be pressed, which then revealed an object that was either congruent or incongruent with the environment. We analysed the data in two ways. First, we analysed the ERP data (aligned to the appearance of the objects) with hierarchical generalised linear mixed models with a fixed factor of congruency, and object and participants as random factors. Similarly to laboratory experiments, we found that scene-object congruency effects in N300/400 time windows over posterior electrodes. Second, using representational similarity analysis and computational models of vision and semantics we examined how visual and semantic processes were impacted by object congruency with real world settings, finding congruency effects linked to semantic information. Overall our findings suggest that visual contexts constrain our predictions of likely

objects even in real-world environments, helping to bridge between research in laboratory and real life situations.

Disclosures: V.I. Nicholls: None. **B. Alsbury-Nealy:** None. **A. Krugliak:** None. **S. Pandya:** None. **A. Clarke:** None.

Poster

132. Object Coding and Scene Perception

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 132.03

Topic: D.06. Vision

Support: NIH Grant R01 EY05864
NIH Grant F32 EY026791
NIH Grant T32 MH019524

Title: Behavioral and neural sensitivity to simple shapes in macaques with amblyopia

Authors: *B. BUSHNELL[1], N. J. MAJAJ[4], J. A. MOVSHON[2], L. KIORPES[3];
[1]New York Univ., New York City, NY; [2]Ctr. for Neural Sci., [3]Neural Sci., New York Univ., New York, NY; [4]NYU, New York City, NY

Abstract: Amblyopia is a developmental visual disorder caused by discordant binocular visual input in early life which leads to deficits in visual acuity, typically in one eye. Here we ask whether these deficits extend to shape perception, whether they can be predicted by losses in visual acuity or other metrics, and whether they can be explained by changes in the response properties of cells in V1, V2, and V4. To study form sensitivity, we used radial frequency stimuli (RFS), circular targets whose radii are modulated sinusoidally. Amblyopes often have higher thresholds when using their amblyopic eye (AE) than their fellow eye (FE). We measured monkeys' ability to discriminate RFS from circles as a function of the amplitude and frequency of modulation in 2-alternative forced-choice experiments in 6 amblyopic and 3 normal macaques. As in humans, behavioral thresholds for all subjects were in the hyperacuity range, and sensitivity was higher for RFS with 8 and 16 cycles than 4. Thresholds in the AE were higher than the FE, and the interocular sensitivity ratio increased with radial frequency. In 2 strabismic amblyopes and 1 control subject, we measured multi-unit activity with 96-channel "Utah" arrays in V1/V2, and V4. We estimated neural sensitivity for each channel by computing the discriminability (in d' units) between responses to circles and to each RF stimulus. We estimated selectivity for RF patterns from the relationship between d' and modulation amplitude at each frequency. Both selectivity (median d' for all channels) and sensitivity increased from V1/V2 to V4. Channels with significant selectivity usually preferred modulated patterns to circles: 15 to 25% of channels were tuned for circles, while 67% were tuned for RFS. In V4, fewer channels were tuned for RFS in the AE than the FE. The FE was more sensitive to changes in amplitude perceptually and physiologically in V4 (lower threshold, higher d') than the AE.

We conclude that amblyopic non-human primates have perceptual RFS deficits consistent with amblyopic humans. Increased sensitivity (d') and selectivity to RFS in V4 relative to V1/V2 is consistent with the notion that V4 plays a pivotal role in shape selectivity. Amblyopic deficits are also greater in V4 than V1/V2 degradation of signal along the visual hierarchy.

Disclosures: B. Bushnell: None. **N.J. Majaj:** None. **J.A. Movshon:** None. **L. Kiorpes:** None.

Poster

132. Object Coding and Scene Perception

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 132.04

Topic: D.06. Vision

Support: C14/18/100

Title: Invasive human recordings demonstrate diverse coding of the shape and category of visual objects in the Lateral Occipital Cortex

Authors: *V. BOUGOU, M. VANHOYLAND, A. BERTRAND, P. JANSSEN, H. OP DE BEECK, T. THEYS;
KU Leuven, Leuven, Belgium

Abstract: Invasive human recordings constitute a high-resolution approach to investigate the representation of objects, shapes, and categories in different brain areas. Noninvasive imaging studies have revealed the multidimensionality of the representations of shapes and categories in the human brain. Nevertheless, the selectivity at the level of single neurons and small neuronal clusters that underlie these macroscopic representations at the population level are still unknown. We used invasive recordings with a 96-channel microelectrode Utah-array in the Lateral Occipital Cortex of 4 neurosurgical patients (5 Utah-arrays) and analyzed both single-cell activity (multi-unit spiking activity or MUA) and the Local Field Potentials (LFPs). A stimulus set of 54 images in which shape and category were dissociated (Bracci et al., 2016) was presented. High-gamma power (60-120 Hz) and Multi-Unit Activity (MUA) per electrode were computed, normalized, and averaged over time for 100 - 300 ms after stimulus onset. Per pair of conditions, we correlated the spatial multi-channel response pattern per microarray. The resulting matrices were converted into dissimilarity matrices (1 - correlation) and were correlated with behavioral dissimilarity matrices for the shape and category dimensions. For 4 out of 5 microarrays, this multi-channel analysis confirmed previous fMRI data suggesting significant shape-based representations at the multi - unit level in the Lateral Occipital Complex, of which one microarray additionally showed a representation of the category dimension. A further analysis of individual visually-responsive electrodes (two-way ANOVA) revealed high diversity of neural tuning beyond these general shape and category effects. For 3 microarrays we found significant MUA responses for a sufficient number of electrodes (>25%). We found 164 visually responsive MUA sites, out of which 27 sites were significantly selective for the shape dimension

alone, whereas 113 sites also showed significant category effects (3 were category-selective, 10 were category & shape -selective and 100 had interactions between shape and category). Main and interaction effects of category were also abundant in arrays that showed no category effect in the multi-channel response patterns. These results suggest that the multichannel analysis offers a general description of the neural representation in an area, in line with functional imaging studies, but fails to capture the diversity of the underlying neuronal selectivity.

Disclosures: V. Bougou: None. **M. Vanhoyland:** None. **A. Bertrand:** None. **P. Janssen:** None. **H. Op De Beeck:** None. **T. Theys:** None.

Poster

132. Object Coding and Scene Perception

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 132.05

Topic: D.06. Vision

Support: ERC 2019-SyG-RELEVANCE-856495
HFSP RGP0036/2016
BMBF FKZ 01GQ1704

Title: Physiologically-inspired neural model for anorthoscopic perception

Authors: *M. GIESE[1], A. BOGNÁR[2], R. VOGELS[3];
[1]Hertie Inst. For Clin. Brain Sci. / CIN, Tuebingen, Germany; [3]Neurosciences, [2]KU Leuven, Leuven, Belgium

Abstract: Objects presented sequentially, translating behind a narrow slit are readily recognized by humans (anorthoscopic perception). This perceptual capability is not easy to explain with standard deep neural network (NN) models of visual object recognition. METHODS: We developed a deep NN that recognizes anorthoscopically presented body shapes, and reproduces properties of IT neurons during anorthoscopic perception (Bognar & Vogels, 2021). The initial layers of the model correspond to an Image net-pretrained standard deep NN model (VGG16). The intermediate levels are formed by special local nonlinear recognition units, which assess the similarity of features that are highly visible in the training and test stimuli, followed by holistic recognition units that integrate information over larger parts of the figure. Position-invariance is accomplished, combining weight sharing with maximum pooling of the holistic detector responses. RESULTS: The model recognizes shapes from sequentially presentation through a slit; it reproduces the following properties of IT neurons: (i) shape-selective neural responses to the full figure as well as to presentations through a slit; (ii) low influence of the sequential order of the slit views; (iii) partial transfer between activation patterns for vertical and horizontal slit views. CONCLUSION: Integrating mechanisms that prevent interference between slit and object features into deep NN models might allow to account for the behavior of neurons in area IT during object recognition during anorthoscopic perception.

Disclosures: **M. Giese:** None. **A. Bognár:** None. **R. Vogels:** None.

Poster

132. Object Coding and Scene Perception

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 132.06

Topic: D.06. Vision

Title: Immersing Yourself in a Virtual Story: Display Clutter Does Not Influence Accommodative Posture and Visual Discomfort Symptoms After Reading in a Virtual Environment

Authors: *O. RAMOS JACQUEZ, D. A. VIDAMUERTE, C. Y. DELGADO, B. S. ACEITUNO, H. I. KIM, S. A. DREW;
California State University, Northridge, Northridge, CA

Abstract: Reading through various digital mediums has become the norm in our society as new technologies emerge. Newer iterations of virtual reality (VR) systems allow the user to engage in simple and complex tasks, such as reading. Despite the improvements made in these systems, many users continue to experience visual discomfort symptoms after VR exposure. Previous research has established a link between display clutter and attentional costs. Additionally, attention has been associated with a poorer accommodative response, the ability of the lens of the eye to change in thickness to keep a target in focus. Recent research has now shown a bidirectional relationship between vergence accommodation conflict and cognitive load. Therefore, it is of interest to examine how visual discomfort relates to accommodative response and how the display clutter of VR environments may affect this relationship. This study aimed to investigate how the level of clutter in an environment changes the relationship between accommodative posture and reports of visual discomfort after VR exposure. We hypothesized that across groups viewing increasingly more cluttered environments, we would observe an accompanying increase in accommodative lag between groups. Data were collected from 46 college students located in Southern California. All of the participants read for 30 minutes using the Oculus Go head-mounted display in one of three VR environments of varying clutter (i.e., viewer placed outside a galaxy, on a snowy mountain, or in a library). After completing the reading task, participants completed a visual discomfort survey while remaining in VR. An open-field autorefractor was used to determine participants' accommodative posture before and after the VR experience. A one-way MANOVA was conducted to examine differences in change of accommodative posture across the different environments and reported visual discomfort symptoms. Results indicated no difference in accommodative posture or visual discomfort symptoms across the three virtual environments. Overall, this evidence suggests display clutter may not moderate the relationship between VR-induced visual discomfort and accommodative posture for VR reading scenarios.

Disclosures: **O. Ramos Jacquez:** None. **D.A. Vidamuerte:** None. **C.Y. Delgado:** None. **B.S. Aceituno:** None. **H.I. Kim:** None. **S.A. Drew:** None.

Poster

132. Object Coding and Scene Perception

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 132.07

Topic: D.06. Vision

Support: NIH R01 MH069456 (KAN and NTB)

Title: Synthesizing images to build layer-specific mappings between convolutional neural networks and the brain

Authors: *K. PENG[1,2], J. WAMMES[3,4], K. NORMAN[5,6], N. TURK-BROWNE[1,7];
[1]Dept. of Psychology, Yale Univ., New Haven, CT; [2]Interdepartmental Neurosci. Program, Yale Univ., New Haven, CT; [3]Dept. of Psychology, Queen's Univ., Kingston, ON, Canada; [4]Ctr. for Neurosci. Studies, Queen's Univ., Kingston, ON, Canada; [5]Dept. of Psychology, Princeton Univ., Princeton, NJ; [6]Princeton Neurosci. Institute, Princeton Univ., Princeton, NJ; [7]Wu Tsai Institute, Yale Univ., New Haven, CT

Abstract: Computational models can be used to generate hypotheses about the brain. This approach has been used in the visual system by relating representations of natural images in a convolutional neural network (CNN) to representations of the same images in visual regions of interest (ROIs). A limitation of this approach is that natural images are processed hierarchically across layers, meaning that the representational spaces of successive layers are similar. Any given ROI thus shares representational similarity with multiple layers across the network, making it difficult to localize layer-specific computations. We take a different generative approach of synthesizing images that better distinguish layers. We created a single set of artificial stimuli with the objective of decorrelating the image-by-image representational similarity matrix (RSM) of different layers. The resulting 16 images produced a (second-order) layer-by-layer RSM with low or weakly negative similarity, much lower than expected for natural images. This means that the image-by-image RSM for each layer provides a specific hypothesis about the unique computational role of that layer. To test these layer-specific hypotheses in the human brain, we scanned participants with fMRI while they viewed the images repeatedly in a random order. We verified that the images produced reliable neural representations by comparing pattern similarity across repetitions of the same vs. different images, and found that the representations were reliable in V1, V2, LO, IT, fusiform, and parahippocampal regions. We then computed the image-by-image RSM based on voxel activity patterns from the ROIs and across the whole brain (using a searchlight). Model and neural RSMs were compared, resulting in a representational similarity for each ROI/searchlight across layers. We quantified the degree of overlap for each layer's expression in the brain as the ratio of voxels uniquely expressing that layer to voxels additionally expressing other CNN layers. For some but

not all layers, we found stable, non-overlapping correspondences to clusters in the brain. For example, some earlier layers corresponded to clusters in occipital cortex (e.g., occipital pole; LO) whereas some higher layers corresponded to clusters in temporal (e.g., fusiform) and parietal (e.g., superior parietal lobule) cortices. We are developing other ways of more directly relating the model and neural responses to the same images using regression and autoencoder models. This general approach can be applied to any model that can generate inputs and can be used to compare model parameters and evaluate biological plausibility at the representational level.

Disclosures: K. Peng: None. **J. Wammes:** None. **K. Norman:** None. **N. Turk-Browne:** None.

Poster

132. Object Coding and Scene Perception

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 132.08

Topic: D.06. Vision

Support: David and Lucille Packard Foundation
E. Matilda Ziegler Foundation for the Blind
NIH T32 EY013360

Title: Neurons in ventrolateral prefrontal cortex have ventral stream-like visual tuning

Authors: *O. ROSE[1], C. R. PONCE[2];
[1]Neurobio., Harvard Med. Sch., Boston, MA; [2]Neurobio., Harvard Univ., Boston, MA

Abstract: The prefrontal cortex (PFC) is a functionally heterogeneous region that supports complex executive processes, such as decision-making and working memory. Neurons in ventrolateral PFC (vlPFC) also demonstrate spontaneous responses to sensory stimuli, particularly to complex images such as faces. Additionally, vlPFC neurons have been shown to respond to visual stimuli presented at specific spatial locations, and functional neuroimaging has identified retinotopic organization in PFC. However, it is unclear whether visually responsive vlPFC neurons have comparable properties to visual neurons in occipital and temporal cortex. For example, visual vlPFC neurons may preserve the same selectivity and invariant properties of V4/IT neurons in addition to extraretinal functions, or they may "trade away" some visual properties to gain non-visual functions (*e.g.*, sensitivity to gaze position or auditory tuning). Here, we implanted 32-channel chronic microelectrode arrays in vlPFC (anterior to the arcuate sulcus and ventral to the central sulcus) of two rhesus macaques (Monkeys C & D), with a second 32-channel array placed in V4 of Monkey C. We characterized the visual responses of all neurons using briefly presented stimuli (100-ms long) during passive fixation. Of the 32 sampled vlPFC sites per subject, 5.0% (Monkey D) and 9.1% (Monkey C) of vlPFC sites demonstrated significant tuning to stimulus position across days, as compared to 86.4% of V4 sites (Monkey C). Positional tuning by vlPFC was comparable to classic receptive fields (RFs) in visual

neurons of the ventral stream: vlPFC RFs were eccentric, were yoked to retinal position (independent of gaze, unlike gain fields), showed differential responses across photographs, and were able to guide image generators into creating strongly activating images (*prototypes*) (Ponce, Xiao *et al.*, 2019; Rose, Johnson *et al.*, 2021). Prototypes had consistent visual motifs across months, with stability comparable to those of the ventral stream. Stimuli presented concurrently at multiple retinotopic positions reduced the firing rates of vlPFC neurons more so than those of V4 neurons (median reduction in firing rate: 0.31 spikes/s for V4 sites, 4.57 spikes/s for vlPFC sites). Our results suggest visual vlPFC neurons have occipitotemporal-like response properties, acting as concurrent stage of processing for cortical object vision. We theorize that these neurons could arise from direct V4-vlPFC projections that bypass IT, in which subsets of vlPFC neurons perform IT-like computations for the for the rapid integration of visual input with higher-order behavioral processes.

Disclosures: **O. Rose:** A. Employment/Salary (full or part-time):; Polygence Online Research Academy. **C.R. Ponce:** None.

Poster

132. Object Coding and Scene Perception

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 132.09

Topic: D.06. Vision

Support: ARC Fellowship DE200101159
ARC Grant DP160101300
ARC Grant DP200101787

Title: The dynamics of object coding within and across the hemispheres

Authors: *A. K. ROBINSON[1], T. GROOTSWAGERS[2], S. M. SHATEK[3], M. BEHRMANN[4], T. A. CARLSON[3];
[1]Univ. of Queensland, Brisbane, Australia; [2]Western Sydney Univ., Sydney, Australia; [3]Univ. of Sydney, Sydney, Australia; [4]Carnegie Mellon Univ., Pittsburgh, PA

Abstract: The human brain integrates information across the hemispheres to construct a coherent representation of the world. Characterising how visual information from the left and right visual fields is coded in each hemisphere can inform the nature of information transfer in the brain. Here, we investigated information processing within each hemisphere and the distinctiveness or redundancy across hemispheres. We presented participants (N = 20) with images of faces, words and objects in rapid sequences while neural responses were measured using electroencephalography (EEG). To drive distinct responses in each hemisphere, stimuli were presented either centrally or lateralised to the left and right visual fields. Participants performed an orthogonal colour change task on dots that marked possible image positions. Multivariate pattern analyses were applied to the neural data to assess coding of object

information in the brain, separately for electrode clusters over each hemisphere. As expected, stimulus information was more robust and emerged earlier in the contralateral than the ipsilateral hemisphere. Interestingly, the temporal dynamics within the two hemispheres followed different trajectories. The representational structure was consistent across the hemispheres with a delay approximating interhemispheric transmission time. These results provide insights into the dynamics of object perception and the competitive versus cooperative nature of hemispheric processing.

Disclosures: A.K. Robinson: None. **T. Grootswagers:** None. **S.M. Shatek:** None. **M. Behrmann:** None. **T.A. Carlson:** None.

Poster

132. Object Coding and Scene Perception

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 132.10

Topic: D.06. Vision

Support: JSPS KAKENHI 21H05813
JSPS KAKENHI 22K07318

Title: Encoding of optical material properties from photo-realistic rendering images in the monkey inferior temporal cortex

Authors: *R. SUZUKI[1], M. SAWAYAMA[3], T. MATSUO[4], A. IIJIMA[1,2], T. SUZUKI[5], T. OKATANI[6], I. HASEGAWA[2], K. KAWASAKI[2];
[1]Grad. Sch. of Sci. and Technol., [2]Grad. Sch. of Med., Niigata Univ., Niigata, Japan; [3]Inria, Bordeaux, France; [4]Tokyo Metropolitan Neurolog. Hosp., Tokyo, Japan; [5]Ctr. for Information and Neural Networks, Natl. Inst. of Information and Communications Technology., Osaka, Japan; [6]Grad. Sch. of Information Sci., Tohoku Univ., Sendai, Japan

Abstract: Objects in our daily life include various materials. Optical material parameters, such as reflection or scattering, describe physical material properties. Humans perceive object materials according to diagnostic image features correlated with these material properties. Previous neurophysiological studies have shown that the inferior temporal cortex (ITC) plays a pivotal role in both object and material perception. Specifically, ITC activities reflected the perceptual properties of materials. Besides, the response of subpopulations of ITC neurons was modulated by surface specular reflection in terms of gloss strength and sharpness. However, how the ITC encodes and represents a plethora of image features that accompany material transitions remains poorly understood. In the present study, we employed photo-realistic rendering images with multidimensional material properties, specifically rendered three-dimensional computer graphics objects manipulating five material dimensions of gloss strength, gloss sharpness, translucency, change from metal to glass (metal/glass), change from metal to plastic (metal/plastic). While the monkey was engaged in a passive visual fixation task, we conducted

the electrocorticography (ECoG) recording from ITC. A 128-channel ECoG electrode was placed, covering the whole ITC area, including the lower bank of the superior temporal sulcus. Visual evoked response was recorded, and event related spectral perturbations (ERSPs) were calculated. To track the encoding from low-level image features to material properties in ITC, we fitted ERSP at each spatial time-frequency point with lasso linear regression using the image statistics and the optical material parameters. We used the Portilla and Simoncelli image statistics (PS statistics), which include lower-order statistics such as spectral and marginal, and higher-order statistics such as linear and energy cross-feature statistics, material contrasts such as metal/glass, metal/plastic ratio, translucency, gloss strength and sharpness as the material parameters. ERSPs were fitted well with marginal skewness, kurtosis, and material contrasts. In the thirty-five to seventy-seven percentage varying with material dimensions, fitting weight was largest for the material contrasts. Furthermore, fitting performance was better on average in regression with full parameters, including both material parameters and PS statistics, than without material parameters (PS statistics only). These results suggest that ITC ultimately encodes the material properties or features other than PS statistics closer to the material properties.

Disclosures: **R. Suzuki:** None. **M. Sawayama:** None. **T. Matsuo:** None. **A. Iijima:** None. **T. Suzuki:** None. **T. Okatani:** None. **I. Hasegawa:** None. **K. Kawasaki:** None.

Poster

132. Object Coding and Scene Perception

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 132.11

Topic: D.06. Vision

Support: NIH Grant R01MH118847

Title: Impaired feedback signal to foveal cortex for peripheral object recognition in autism

Authors: ***X. FAN**[1], T. KOLODNY[1], K. WOODARD[1], A. TASEVAC[1], W. R. GANZ[2], H. REA[2], E. KURTZ-NELSON[3], S. J. WEBB[2], S. O. MURRAY[1];
[1]Dept. of Psychology, [2]Dept. of Pyschiatry and Behavioral Sci., Univ. of Washington, Seattle, WA; [3]Sch. of Med., Indiana Univ., Indianapolis, IN

Abstract: Previous findings suggested altered feedback modulation of early sensory processing in individuals with autism spectrum disorder (ASD). Yet evidence regarding such an altered feedback modulation is mixed. Recent studies identified a novel form of feedback interaction occurring between higher stages of the visual system and foveal regions in early visual cortex during the analysis of peripheral objects' fine spatial details. In this study, we tested whether the feedback to foveal cortex during peripheral object recognition is impaired in ASD. We presented objects in the periphery and noise at the fovea after different object-noise stimulus onset asynchronies (SOAs) while subjects performed a discrimination task on peripheral objects. In the

neurotypical (NT) group, results were consistent with previous findings, revealing a selective impairment of performance when foveal noise was presented at 150-ms SOA. This delayed effect of foveal noise is consistent with the existence of a foveal feedback processing mechanism. However, discrimination of peripheral objects was not disrupted by foveal noise at any specific SOA in autistic participants. Moreover, participants with autism had decreased task performance compared to NT participants even when there was no noise presented. These results suggest that impaired foveal feedback mechanism results in decreased peripheral spatial details discrimination in ASD.

Disclosures: **X. Fan:** None. **T. Kolodny:** None. **K. Woodard:** None. **A. Tasevac:** None. **W.R. Ganz:** None. **H. Rea:** None. **E. Kurtz-Nelson:** None. **S.J. Webb:** None. **S.O. Murray:** None.

Poster

132. Object Coding and Scene Perception

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 132.12

Topic: D.06. Vision

Support: National Eye Institute Intramural Research Program at the National Institutes of Health (ZIA EY000511)

Title: What does the superior colliculus know about visual objects and when does it know it?

Authors: *G. YU, L. N. KATZ, C. QUAIA, A. MESSINGER, R. J. KRAUZLIS;
Lab. of Sensorimotor Res., Natl. Eye Inst., Bethesda, MD

Abstract: We recently found that inactivation of the macaque superior colliculus (SC) reduces responses to visual objects in temporal cortex neurons, suggesting that visual object processing may be an important component of how the SC contributes to visual attention and orienting. Here, we investigated how SC neurons are modulated by visual object stimuli during a passive viewing task. We recorded the spiking activity of 59 visually responsive neurons in the superficial and intermediate layers of the SC in a fixating macaque monkey during the presentation of object images in the visual receptive field. We used 150 grayscale images of objects belonging to 5 categories that have been extensively used to test visual object representation in the temporal cortex: face, body, hand, fruit/vegetable, and human-made objects. Crucially, the categories were matched in their distributions of low-level features (RMS contrast, size, power in 3 spatial frequency bands) across the 30 images comprising each category, allowing us to assess how both low-level features and object category information contributed to neuronal responses. The contribution of low-level features was evaluated using a multiple linear regression (MLR) model including all the low-level features as regressors. Variance in the initial SC visual response across objects could be largely (27%) accounted for by low-level features (peaking at ~50ms after object onset), in particular by RMS contrast and power in the 'medium' spatial frequency band (0.6 to 2.5 cycles/degree). We then assessed to what degree SC responses

covaried with object category, independently of low-level visual features, by performing an ANOVA on the residuals of the MLR model (i.e., after regressing out the contributions of low-level features). This analysis revealed that the responses of ~85% of neurons were significantly modulated by object category. Unlike the variance explained by low-level features, the variance explained by object category was low during the initial ~80ms of the visual response, and then increased toward a peak ~150ms after object onset. Together, our results show that the visual responses of SC neurons rapidly transition from an initial phase dominated by low-level features, especially those related to visual salience, to a later phase that includes selectivity for at least some categories of visual objects.

Disclosures: G. Yu: None. **L.N. Katz:** None. **C. Quaia:** None. **A. Messinger:** None. **R.J. Krauzlis:** None.

Poster

132. Object Coding and Scene Perception

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 132.13

Topic: D.06. Vision

Support: Human Frontier Science Program (RGP0008/2017)

Title: Identifying the Neural Correlates of Numerosity in Larval Zebrafish

Authors: *P. LUU[1], A. NADTOCHIY[2], M. JONES[3], C. BRENNAN[4], G. VALLORTIGARA[5], S. E. FRASER[3], T. V. TRUONG[3];
[1]Mol. Biol., [2]Quantitative Computat. Biol., [3]Translational Imaging Ctr., USC, Los Angeles, CA; [4]Queen Mary Univ. of London, London, United Kingdom; [5]Univ. of Trento, Trento, Italy

Abstract: Recognition of numerosities (discrete quantities) is a cognitive ability that is widespread among animals and has been demonstrated by diverse behavioral analyses. Here, we leverage the optical transparency of zebrafish (Danio rerio) to study the development and neuronal basis of numerosity perception. The zebrafish expressing a pan-neuronal calcium indicator, H2B-GCaMP6s, are presented with visual number stimuli (2, 3, & 5 dots) varying in pattern, size, timing, and other geometric controls in a pseudorandom order. Simultaneously with the stimuli presentation, we record the calcium activity using a custom-built two-photon light sheet microscope. Data handling, management, and analysis were performed using custom python libraries and scripts (Github: VoDEx and NuMan). We identified the neurons demonstrating a significant rise in activity during the presentation of at least one type of the stimuli. Neurons uniquely responsive to a number stimulus are determined by a significantly higher relative fluorescent level compared to the time point right before the stimuli onset (Bootstrap method, $p<0.05$). The resulting neurons demonstrate a wide range of behavior: responsive to only one number, highest activity for a number, inhibition, etc. We found neurons uniquely responsive to each of the 2, 3, and 5 dot stimuli in the optic tectum and forebrain in 7-9

days post-fertilization (dpf) larvae. These results suggest the development of numerosity-related neurons arise at or before 7 dpf. Interestingly, our data mirrors the results previously reported in the prefrontal cortex neurons in rhesus monkeys (Viswanathan & Nieder 2013): we identified a subset of neurons highly tuned to “2” that shows a higher affinity for “5” than “3”. Future work will explore the brain activity in response to a wider range of number stimuli to map the extent of numerosity recognition. Additionally, we will expand on both younger and older larval zebrafish to detail the development of neurons correlating with numerosity recognition.

Disclosures: **P. Luu:** None. **A. Nadtochiy:** None. **M. Jones:** None. **C. Brennan:** None. **G. Vallortigara:** None. **S.E. Fraser:** None. **T.V. Truong:** None.

Poster

132. Object Coding and Scene Perception

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 132.14

Topic: D.06. Vision

Support: NIH Training Grant 5 R90 DA 033461-08
Allen Institute for Brain Science sponsorship

Title: A biologically inspired architecture with switching units can learn to generalize across backgrounds

Authors: *D. VOINA[1], E. T. SHEA-BROWN[2], S. MIHALAS[3];
[2]Applied Mathematics, [1]Univ. of Washington, Seattle, WA; [3]Allen Inst. For Brain Sci., Seattle, WA

Abstract: Humans and other animals navigate different environments effortlessly, their brains rapidly and accurately generalizing across contexts. Understanding what network architectures and circuit motifs the brain uses to achieve these remarkable feats will bring us a step closer to explaining the computational principles behind our ability to do context-invariant recognition. Inspired by recent studies that characterize the circuit patterns in the primary visual cortex (V1) of mice, we systematically investigate network motifs that enable context generalization for object classification. We show how a bio-inspired network motif can uniquely address the issue of contextual adaptation and generalization when incorporated into a feedforward artificial neural network (ANN) for object classification.
To study context generalization, we use a dataset of MNIST digits of varying transparency, set on one of two backgrounds of different statistics that define two contexts: a pixel-wise noise or a more naturalistic background from the CIFAR-10 dataset. After learning digit classification when both contexts are shown sequentially, we find that both shallow and deep networks have sharply decreased performance when returning to the first background -- an instance of the the catastrophic forgetting phenomenon known from training ANN's in the continual learning framework. To overcome this, we propose the bottleneck-switching network, or switching

network for short. This is a bio-inspired architecture analogous to a well-studied network motif in the visual cortex, with additional "switching" units that are activated in the presence of a new background. Intriguingly, only few of these switching units are sufficient to enable the network to learn the new context without catastrophic forgetting. Moreover, the switching mechanism leads to sparser activation patterns, and we provide intuition for why this helps to solve the task. We also find that -- analogously to the underlying biological network motif -- the switching units must be recurrently connected to network layers for context generalization to succeed. Further, the bottleneck-switching network can generalize to novel contexts similar to contexts it has learned. In sum, our study demonstrates a sparse, bio-inspired motif with few units to inhibit redundant contextual features and achieve generalization across context.

Disclosures: D. Voina: None. **E.T. Shea-Brown:** None. **S. Mihalas:** None.

Poster

132. Object Coding and Scene Perception

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 132.15

Topic: D.06. Vision

Support: NRF-2022R1A2C3008991
NRF-2019M3E5D2A01058328
NRF-2021M3E5D2A01019544
NRF-2021R1C1C2007086

Title: Quantity comparison in untrained deep neural networks

Authors: *H. LEE[1], W. CHOI[1], D. LEE[1], S.-B. PAIK[1,2,3];
[1]Dept. of Bio and Brain Engin., [2]Program of Brain and Cognitive Engin., [3]Dept. of Brain and Cognitive Sci., Korea Advanced Inst. of Sci. and Technol., Daejeon, Korea, Republic of

Abstract: The ability to compare two quantities is considered an essential function for animal survival (McComb 1994, Wilson 2002). Intriguingly, even naïve animals and infants can compare two visual quantities, implying that the ability can arise spontaneously without training (Izard 2009, Rugani 2016). Notably, neuronal responses selectively tuned to a specific proportion between two quantities are observed both in monkeys and humans (Vallentin 2008, Jacob 2009), suggesting that such neuronal tuning provides the basis of the functional circuits for quantity comparison. Nonetheless, how the brain can develop this tuning in the absence of learning remains unclear. Here, we found that neuronal units selectively tuned to proportion or to differences between two quantities can arise spontaneously in an untrained hierarchical deep neural network. Using a randomly initialized AlexNet model, we found that units selectively respond to proportion or difference with regard to the number of white and black dots in each stimulus trial. We confirmed that the observed neuronal tunings are invariant to the total number of dots or to various image features. We also found that the network can compare two quantities,

reproducing the behavioral and neuronal characteristics observed in the brain (Vallentin 2008). Next, to examine the mechanism of how this tuning can emerge without learning, we adopt a model of summation coding (Kim 2021) in which neuronal responses tuned to either proportion or difference can arise from the weighted sum of increasing and decreasing responses in the preceding layer. We confirmed that increasing/decreasing units in a preceding layer provide a biased synaptic input to the proportion/difference unit, but not to non-selective units, as predicted from the proposed model. In addition, an ablation test revealed that the number of proportion/difference units decreases significantly when increasing/decreasing units are silenced, confirming that these are essential components of comparison tuning. Lastly, we found that a slight difference in the nonlinearity of monotonic responses can determine the types of tuning of connected units such that a unit receiving power-like responses generates proportion selectivity while a unit receiving exponential-like responses develops the difference selectivity. We found that the ablation of power-like responses suppressed the emergence of proportion units, and vice versa, as expected. Taken together, our results suggest that various cognitive functions can emerge from biased feedforward projections even in random networks, providing insight into the developmental mechanisms of innate cognitive functions.

Disclosures: **H. Lee:** None. **W. Choi:** None. **D. Lee:** None. **S. Paik:** None.

Poster

132. Object Coding and Scene Perception

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 132.16

Topic: D.06. Vision

Support: NIH Grant ZIA-MH002588

Title: The left dorsal mid-insula represents the inferred taste quality of visually depicted foods

Authors: *J. A. AVERY, M. CARRINGTON, A. MARTIN;
Lab. of Brain and Cognition, Natl. Inst. of Mental Hlth., Bethesda, MD

Abstract: Our everyday experience of food is a broadly multisensory experience involving not just taste, but other sensory modalities as well. According to grounded cognition models of the brain, our representation of food would thus be distributed across the various sensory and motor brain regions involved in the experience of food. In a previous study from our lab, we used multivoxel pattern analysis (MVPA) to decode the taste quality of sweet, salty, and sour tastant solutions delivered during (fMRI), as well as the taste category of food pictures (sweet, salty and sour) viewed during scanning, within the gustatory dorsal mid-insular cortex (Avery et al., PNAS, 2021). This previous finding suggests that this region represents the inferred taste quality of food pictures. However, this mid-insula region has been associated with other food properties such as flavor, oral texture, or the post-ingestive response to food. Thus, the inferred response to food pictures within this region could reflect any one of these properties individually, or some

combination of all of them. To explore this question further, we examined subjects as they performed explicit taste-related mental imagery while undergoing ultra-high resolution functional magnetic resonance imaging (fMRI) at high magnetic field strength (7-Tesla). During scanning, 20 healthy participants actively imagined basic tastes (sugar, salt, lemon juice) and the taste of water. During separate scanning runs, subjects passively viewed pictures of a variety of sweet, salty, and sour foods, as well as non-food objects, while performing an image repetition-detection task. Imagined tastes (vs. imagined water) activated the bilateral dorsal mid-insular cortex, which was also activated when subjects viewed pictures of food vs. non-food objects. Using MVPA, we were able to reliably classify both imagined tastes and the taste category of food pictures within the left dorsal mid-insula, left orbitofrontal cortex (BA11l), and ventral occipito-temporal cortex (whole-brain searchlight, $p < 0.05$, FWE-corrected). Importantly, within the left dorsal mid-insular cortex, we were able to cross-decode the taste category of food pictures by training our model on imagined basic tastes (and vice versa). This suggests that the evoked response to food pictures within this region does indeed contain information about the basic taste properties of the depicted foods.

Disclosures: **J.A. Avery:** None. **M. Carrington:** None. **A. Martin:** None.

Poster

132. Object Coding and Scene Perception

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 132.17

Topic: D.06. Vision

Support: International NIH funding

Title: Predicting Category Similarity and Grasping Behavior from Deep-CNN Layers: Is one Visual Hierarchy Enough?

Authors: *A. ZOROUFI[1], A. MIREBRAHIMI TAFRESHI[2], C. I. BAKER[3], M. VAZIRI-PASHKAM[4];
[1]K.N.TOOSI Univ. of Technol., K.N.TOOSI Univ. of Technol., Tehran, Iran, Islamic Republic of; [2]Univ. of Western Ontorio, London, ON, Canada; [3]Lab. Brain and Cognition, [4]NIH, Bethesda, MD

Abstract: Looking at objects in the visual environment, we can immediately categorize them and judge their similarity. Just as readily, we know how to shape our hands to grasp those objects. Both these tasks require visual processing. Can the same visual process support both tasks? To investigate this, we collected a large database of 3D-printed objects and collected two different behaviors on these objects: 1) a grasping task and 2) a similarity judgment task. For the grasping task, we recorded participants' finger positions when they grasped the objects. For the similarity judgment task, we asked participants to perform an odd-one-out task on triplets of objects and obtained a similarity matrix based on these judgments. Comparing these matrices

across the two tasks suggests distinct features of objects are used for each. We next explored if the features extracted in different layers of state-of-the-art deep convolutional neural networks (Deep-CNNs, e.g., AlexNet, VGG11, Resnet18, CorNet & VOneNet) could be used for predicting the two behaviors. For similarity judgments, the accuracy of the predictions increased from low to higher layers of the networks, while those for grasping behavior increased from low to mid-layers and then dropped again at higher layers. In other words, the higher layers of a network trained for object categorization were suitable for predicting category similarity judgment while failing to predict grasping. These results suggest that for building a system that could perform these two tasks, the hierarchy may need to be split starting at the mid-layers. These results could inform future computational models that can perform a broader set of tasks on natural images.

Disclosures: A. Zoroufi: None. **A. Mirebrahimi Tafreshi:** None. **C.I. Baker:** None. **M. Vaziri-Pashkam:** None.

Poster

132. Object Coding and Scene Perception

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 132.18

Topic: D.06. Vision

Title: Using the common marmoset to study visual processing of object three-dimensionality and lighting in a scene.

Authors: *A. DAS, M. BEZLEPKINA, E. B. ISSA;
Columbia Univ. Dept of Neurosci., New York, NY

Abstract: When interpreting a scene, both the three-dimensionality of objects present and the lighting direction are likely treated as primitives or elementary visual features. Human observers as well as non-human primates (macaques) appear to process these visual features particularly rapidly and accurately even in flat two-dimensional (2D) representations of three-dimensional (3D) scenes. In visual search tasks for an oddball in a 2D test image, both human and macaque observers perform consistently better when search items can be interpreted as 3D objects rather than 2D patterns (Enns and Rensink Science 1990; Lee et al Nat. Neuro. 2002). Performance is particularly good when the oddball 3D target appears lit from below surrounded by 3D distractors lit “naturally” from above. However, despite pioneering neurophysiological studies in the macaque visual cortex, brain mechanisms underlying visual processing of three-dimensionality and lighting cues are as yet poorly understood. That is likely because the mechanisms involve interactions across multiple brain areas that need to be recorded simultaneously (Lee et al Nat. Neuro. 2002).
The common marmoset (callithrix jacchus) with its lissencephalic visual cortex and growing armamentarium of tools including genetically encoded optical drivers and reporters is an appealing model organism to recruit for this study. However, it is important to first establish that

marmosets can gauge object three-dimensionality and lighting direction in a manner that parallels human behavior.
Here we report initial results from a visual search / oddball detection task designed to probe marmoset visual perception of object dimensionality and scene lighting. Visual targets and distractors presented in 2D test images consisted of cubes in isometric projection, either lit from above or from below. The two animals tested were consistently faster and more accurate when picking out an oddball target lit from below surrounded by distractors lit from above, than vice versa. These results suggest, first, that marmosets can process cues of three-dimensionality in 2D images like humans and macaques. In addition they suggest that marmosets also have a prior bias for "natural" lighting from above. The marmoset visual system is thus a valuable model to understand human brain mechanisms for interpreting three-dimensionality and lighting of objects in a visual scene. We are currently proceeding to establish the neural responses to these features in marmoset visual cortex, as a first step to using the marmoset as a model to broadly study visual processing of complex scenes.

Disclosures: **A. Das:** None. **M. Bezlepkina:** None. **E.B. Issa:** None.

Poster

132. Object Coding and Scene Perception

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 132.19

Topic: D.06. Vision

Support: HHMI
NIH Grant R01 EY030650-01
Simons Foundation
ONR

Title: Ambiguity is resolved during a second wave of activity in IT cortex

Authors: *Y. SHI[1], J. K. HESSE[2], F. A. M. LANFRANCHI[1], D. Y. TSAO[2,3];
[1]Div. of Biol. and Biol. Engin., CALTECH, Pasadena, CA; [2]Dept of Mol. and Cell Biol., UC Berkeley, Berkeley, CA; [3]Howard Hughes Med. Inst., Chevy Chase, MD

Abstract: Humans are able to infer the big picture from small pieces of evidence ("以小见大") - we can recognize someone's face immediately even if it is strongly occluded, and effortlessly detect an object in clutter. Hierarchical inference has been proposed as a framework for resolving ambiguous visual scenes by incorporating higher-level information through feedback. Yet clear evidence for this function of feedback is currently lacking. To understand the mechanisms of hierarchical inference, we take advantage of high-throughput recordings from several brain regions simultaneously, allowing us to monitor the dynamics of information flow across the cortical hierarchy. We developed a system for recording with two Neuropixels probes in primates at the same time, yielding over a thousand units in a single session. We recorded from

posterior face patch MF and anterior face patch AL while monkeys passively viewed face images rendered ambiguous in different ways: noisy, blurry, occluded, etc. Our recordings reveal distinct waves of activity that are coordinated across cells and areas in response to face stimuli. The latency of these waves shows striking variability across trials in response to the exact same stimulus, in particular for degraded faces. Intriguingly, on many trials, there is a distinct second response wave within the stimulus duration. During these second waves, the neural representation of the face becomes more invariant to different degradations of the same face. Response latencies between patches follow a feedforward hierarchy during the first wave of information flow but not during the second wave. To our knowledge, this is the first case of clear evidence for a second wave of neural activity which may serve the function of filling-in incomplete information through feedback. Overall, these results suggest that the visual system may function as a generative model that constantly feeds back higher-level information to resolve ambiguity.

Disclosures: **Y. Shi:** None. **J.K. Hesse:** None. **F.A.M. Lanfranchi:** None. **D.Y. Tsao:** None.

Poster

132. Object Coding and Scene Perception

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 132.20

Topic: D.06. Vision

Support: Howard Hughes Medical Institute
Simons Foundation
ONR

Title: Neural representation of continuous visual experience in the primate hippocampus

Authors: *J. LU, K. MOHAN, D. Y. TSAO;
Mol. and Cell Biol., Univ. of California, Berkeley, CA

Abstract: The mammalian brain is remarkably efficient at building memories of our conscious experience. We effortlessly reconstruct experienced events, and we can establish and maintain detailed episodic memories even after single, one-shot episodes. This ability to rapidly record events under a coherent internal model of the world is thought to rely on the hippocampus and its interactions with the cortex. Decades of experimental work have emphasized the role of the rodent hippocampus in constructing a spatial map of the environment, but the underlying hippocampal code for representing visual experience, beyond simple awareness of spatial location, remains unknown. To tackle the question of how the primate hippocampus represents rich, naturalistic visual experience, we recorded neural population activity in the hippocampus (N=247) with V Probes. During recordings, animals navigated 3D immersive virtual reality (VR) environments tiled with visual objects at distinct spatial locations. Using custom-made VR headsets, animals received juice rewards as they actively explored the environments with a two-

axis joystick. In addition to active experience during exploration, the same visual objects were presented passively to compare neural responses of the same cells to the same objects during active versus passive experience. We characterized the selectivity of individual hippocampal neurons to environmental variables (such as object identity, spatial location of animal, spatial location of currently viewed object, etc.), behavioral variables (such as joystick position, gaze position, reward, etc.), as well as interactions between these variables. Single neurons showed selective activity around salient events in virtual space, such as entering and leaving the virtual arena, and approach towards objects in the arena, suggesting that hippocampal cells encode key events in continuous experience. We test the hypothesis that the hippocampus represents the ingredients of a visual scene - multiple objects and their spatial locations - through an abstract, compositional representation. Overall, our results provide an understanding of visual representations in the hippocampus during exploration of object-rich environments.

Disclosures: **J. Lu:** None. **K. Mohan:** None. **D.Y. Tsao:** None.

Poster

132. Object Coding and Scene Perception

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 132.21

Topic: D.06. Vision

Support: HHMI
R01 EY030650-01
Simons Foundation
ONR

Title: Probing feedforward and feedback contributions on perception using a novel microstimulation technique

Authors: *F. A. M. LANFRANCHI[1,2], J. K. HESSE[2,1], Y. SHI[1,2], D. Y. TSAO[2,3];
[1]Div. of Biol. and Biol. Engin., CALTECH, Pasadena, CA; [2]Dept of Mol. and Cell Biol., UC Berkeley, Berkeley, CA; [3]Howard Hughes Med. Inst., Chevy Chase, MD

Abstract: Gaining insight into how conscious experience is shaped by different projection pathways in the brain, both feedforward and feedback, is a central puzzle in system neuroscience. A powerful approach to identify specific projection pathways and assess the causal effect of perturbation of specific nodes on brain activity is electrical microstimulation coupled with electrophysiological recording. To maximize the efficacy of this approach, we introduce a new technique coupling large-scale Neuropixels recording with a novel microstimulation protocol that allows recording with extremely short electrical artifacts. We combine novel hardware and software to analyze and eliminate electrical artifacts in real time, enabling us to establish optimal parameters for electrical stimulation across experiments. This shortens artifacts to a millisecond or shorter, enabling identification of antidromic spikes even for adjacent brain

areas. We use this technique to study perceptual function across different species (macaques, tree shrews, zebra finch, rodents) and brain areas using two approaches. First, we antidromically identified projection neurons, allowing us to distinguish between feedforward and feedback neurons and characterize their respective roles in encoding visual perception. Second, we electrically microstimulated higher-level regions while recording from lower-level regions to generate perceptual representations in the absence of any feedforward input. Together, these two approaches give us an unprecedented view of how feedback shapes perception.

Disclosures: F.A.M. Lanfranchi: None. **J.K. Hesse:** None. **Y. Shi:** None. **D.Y. Tsao:** None.

Poster

132. Object Coding and Scene Perception

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 132.22

Topic: D.06. Vision

Support: HHMI
ONR
Simons Foundation

Title: Characterizing visual Imagery at single cell resolution in human inferotemporal cortex

Authors: *V. WADIA[1,2], C. REED[3], J. CHUNG[3], A. N. MAMELAK[2], U. RUTISHAUSER[1,2,4], D. Y. TSAO[5,6];
[1]Dept. of Biol. and Bioengineering, Caltech, Pasadena, CA; [2]Dept. of Neurosurg., [3]Dept. of Neurol., [4]Ctr. for Neural Sci. and Medicine, Dept. of Biomed. Sci., Cedars-Sinai Med. Ctr., Los Angeles, CA; [5]Dept. of Mol. and Cell Biology, Helen Wills Neurosci. Inst., Univ. of California Berkeley, Berkeley, CA; [6]Howard Hughes Med. Inst., Ashburn, VA

Abstract: The ability to internally generate percepts in the absence of external stimuli is a remarkable phenomenon that allows us to remember previous experiences, imagine new ones, make plans, and solve problems. In the visual domain, animal studies have yielded rich insight into bottom-up processing of objects from the first discovery of face patches to determining the precise code for general objects in macaque inferotemporal (IT) cortex. However, the neural mechanisms of internally generated top-down processing have been much more elusive. Here we record 169 visually responsive single neurons in IT cortex of 7 epilepsy patients as they view and subsequently visualize from memory carefully parametrized visual objects. The feedforward computational scheme for encoding visual objects is similar in humans and macaques: the firing rate of single neurons in human IT cortex to a given stimulus is proportional to the projection of said stimulus onto specific preferred axes in feature space, and that these responses are well explained by deep convolutional neural network models. We further show that on average this projection value of an object onto a neuron's preferred axis predicts the neuron's firing rate when that object is being visualized. Together these findings demonstrate that neurons in human IT

cortex encode visual objects using an axis code during bottom-up viewing and top-down visualization. We therefore hypothesize that these neurons support visual imagery by internally generating similar network activity to viewing.

Disclosures: V. Wadia: None. **C. Reed:** None. **J. Chung:** None. **A.N. Mamelak:** None. **U. Rutishauser:** None. **D.Y. Tsao:** None.

Poster

132. Object Coding and Scene Perception

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 132.23

Topic: D.06. Vision

Support: HHMI
Simons Foundation
NIH Grant EY030650-01
ONR

Title: The role of recurrent feedback during conscious perception in binocular rivalry

Authors: *J. K. HESSE[1], F. A. M. LANFRANCHI[1], Y. SHI[1], D. Y. TSAO[1,2];
[1]Univ. of California, Berkeley, Berkeley, CA; [2]Howard Hughes Med. Inst., Chevy Chase, MD

Abstract: Consciousness is arguably the most important reason why it matters to us whether we are dead or alive. Yet, the neural mechanisms of conscious perception remain unknown. Here, we investigate the hypothesis that conscious perception is due to top-down feedback interpreting and recreating incoming sensory inputs. To reveal the mechanisms of how new conscious percepts are generated and coordinated across different nodes of the cortical hierarchy, we use newly developed primate Neuropixels probes to simultaneously record from thousands of neurons across different face patches in macaque IT cortex during a binocular rivalry paradigm. In binocular rivalry, a constant visual input evokes spontaneous changes of conscious perception, allowing to dissociate neural representations of conscious percept and physical input. We employed a novel no-report binocular rivalry paradigm that allowed us to infer conscious percept from eye movements. We find that neural activity during spontaneous perceptual switching in rivalry differs dramatically from activity when physically alternating the stimulus. First, in contrast to physical alternation, where an unambiguous consciously perceived stimulus is encoded, during rivalry cells in face patches encoded not only the consciously perceived but also the suppressed stimulus. Second, response latencies across different levels of the hierarchy during rivalry did not follow the feedforward hierarchy of latencies observed during physically alternated stimuli. Taken together, our results suggest that switches of conscious percept are generated by a recurrent or feedback mechanism and may provide an approach for pinpointing where in the brain a new conscious percept arises first.

Disclosures: J.K. Hesse: None. **F.A.M. Lanfranchi:** None. **Y. Shi:** None. **D.Y. Tsao:** None.

Poster

133. Spatial and Feature Attention in Visual Systems

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 133.01

Topic: D.06. Vision

Title: Spatial Information Encoded by the Time Domain in a Pigeon Model

Authors: *C. KIRKMAN[1], A. P. BLAISDELL[2];
[1]UCLA Psychology, [2]UCLA, UCLA, Los Angeles, CA

Abstract: Vision is critical to the way that humans and other visually dominant animals navigate through space. In most animals, spatial navigation requires rapid and efficient transformations between egocentric and allocentric perspectives. Semantic information, such as landmarks, must be embedded into an allocentric mental map. However, the neural mechanisms that enable anchoring of semantic information into mental maps is unknown. Arisaka (2022) has proposed a novel model and neural mechanism for this process. The Neural Holographic Tomography (NHT) model suggests that two-dimensional retinotopic information is compressed into one-dimensional temporal information by a process of alpha phase procession. This time-code compression allows for complex object information to be efficiently bound, transferred, and integrated into allocentric mental maps. The neural circuit responsible for this process has been isolated to the Holographic Ring Attractor Lattice (HAL; Arisaka, 2022). A number of human psychophysical studies have confirmed support for these concepts. The current research is a cross-species exploratory replication utilizing visually dominant pigeon models to explore the evolutionary validity of the NHT and HAL concepts. In our psychophysical experimental task, we measured reaction time (RT) to either semantic or non-semantic stimuli presented at various degrees of eccentricity in the visual field. We have replicated effects shown in humans, suggesting cross-species validity of the NHT and HAL concepts and exciting cross-disciplinary growth between neurophysics and neuroscience.

Disclosures: C. Kirkman: None. **A.P. Blaisdell:** None.

Poster

133. Spatial and Feature Attention in Visual Systems

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 133.02

Topic: D.06. Vision

Title: Inferring trial-by-trial changes in the state of visual spatial attention

Authors: *C. A. HENRY[1], J. MAYO[2];
[1]Albert Einstein Col. of Med., Bronx, NY; [2]Dept. of Ophthalmology, Univ. of Pittsburgh, Pittsburgh, PA

Abstract: During natural behavior, internal cognitive state and behavioral performance are in flux, dynamically shifting across a range of time scales. Even in well-controlled perceptual tasks, observers' cognitive state likely varies across trials, in a manner hidden from experimenters' view. While slower changes over minutes in the brain states that support cognition are increasingly better understood (Cowley et al., 2020), the impact of moment-by-moment changes in cognitive fluctuations—and their effects on behavior—are less well studied. To better understand the relationship between trial-by-trial changes in behavior and the underlying activity of neuronal populations, we developed a generalizable analytical approach to measure nonstationary changes in observers' detection strategies from perceptual response data, based on a reasonable assumption that changes smoothly varied across trials. We used this novel approach to link variation in change detection performance to attention-related changes in V4 neuronal activity in a cued spatial attention task (Mayo and Maunsell, 2016). In this task, two monkeys maintained central fixation while two continuous, sinusoidally modulated Gabor patches were presented peripherally in each hemifield. The monkeys were rewarded for making a saccade to one of the Gabors if it changed orientation. During instruction trials at the beginning of "cued" blocks, a cue was presented at the location where the orientation change would occur on 80% of the trials (80% cue validity). These blocks were interleaved with "neutral" blocks of trials where a cue was presented during instruction trials at both stimulus locations (50% cue validity). The neutral blocks of trials encouraged switching/dividing attention between locations on each trial, more akin to everyday behavior. Nonstationary analysis of behavior that was blind to the cueing condition and blocking of the trials correctly inferred that detection thresholds were higher in neutral trials compared to cued trials, as expected during switching/dividing attention. Further, inferred observer parameters from the nonstationary models better explained performance on held out trials than static observer models fit to each cueing condition. Performance in all neutral blocks was better explained by the nonstationary models. Also, in many cued conditions, nonstationary models performed better, indicating meaningful changes in observer state across trials despite consistent cueing. Finally, we used this approach to design targeted trial-by-trial analyses of V4 population responses and better understand the neuronal correlates of attention changes during the task.

Disclosures: C.A. Henry: None. **J. Mayo:** None.

Poster

133. Spatial and Feature Attention in Visual Systems

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 133.03

Topic: D.06. Vision

Support: Fondecyt # 1210169
Fondecyt # 1151432

Title: A blinking, re-entrant "spotlight" scans the tectum for vision in the avian tectofugal pathway

Authors: B. REYNAERT, C. MORALES, J. MPODOZIS, J. LETELIER, ***G. MARÍN**; Facultad de Ciencias, Univ. de Chile, Santiago, Chile

Abstract: Re-entrant connections are inherent to nervous system organization; however, a comprehensive understanding of their operation is still lacking. In birds, topographically organized re-entrant signals, carried by axons from the nucleus-isthmi-parvocellularis (Ipc), are distinctly recorded as bursting discharges across the optic tectum (TeO). Here, we used up to 48 microelectrodes regularly spaced on the superficial tectal layers of anesthetized pigeons to characterize the spatial-temporal pattern of this axonal re-entrant activity in response to different visual stimulation. We found that a brief luminous spot triggered repetitive waves of bursting discharges that, appearing from initial sources, propagated horizontally to areas representing up to 28 deg of visual space, widely exceeding the area activated by the retinal fibers. In response to visual motion, successive burst-waves started along and around the stimulated tectal path, tracking the stimulus in discontinuous steps. When two stimuli were presented, the burst-wave sources alternated between the activated tectal loci, as if only one source could be active at any given time. Because these re-entrant signals boost the retinal input to higher visual areas, their peculiar dynamics mimics a blinking "spotlight", just as the classic metaphor alluded to explain spatial attention. Tectal re-entry from Ipc is thus highly structured and intrinsically discontinuous, and higher tectofugal areas, which lack retinotopic organization, will thus receive incoming visual activity in a sequential and piecemeal fashion. We anticipate that analogous re-entrant patterns, perhaps hidden in less bi-dimensionally organized topographies, may organize the flow of neural activity in other parts of the brain as well.

Disclosures: B. Reynaert: None. **C. Morales:** None. **J. Mpodozis:** None. **J. Letelier:** None. **G. Marín:** None.

Poster

133. Spatial and Feature Attention in Visual Systems

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 133.04

Topic: D.06. Vision

Support: Department of Biotechnology/Wellcome Trust India Alliance Senior Fellowship IA/S/18/2/504003
Tata Trusts
DBT-IISc Partnership Programme
Indian Institute of Science Ph.D. Research Fellowship

Title: Effect of visual attention on different neural measures in human EEG

Authors: *A. DAS, N. NANDI, S. RAY;
Ctr. for Neurosci., Indian Inst. of Sci., Bangalore, India

Abstract: The effect of attention on neural signals has been extensively studied using various techniques such as macaque neurophysiology and human electro/magneto encephalogram (EEG/MEG). In EEG studies, attention-mediated modulation has been observed in evoked responses as well as in alpha (8-12 Hz) and gamma (>30 Hz) bands in response to static stimuli. In addition, EEG studies often use flickering stimuli that produce a specific neural measure called steady-state visually evoked potentials (SSVEPs), which is also modulated by attention. However, since the stimuli and task paradigms vary widely across these studies, a thorough comparison of the effectiveness of these various neural measures in capturing attentional modulation has not been done. In a recent macaque neurophysiology experiment in which flickering stimuli were used, we found that the effect of attention was more salient in the gamma band and beyond of the local field potential (LFP) as compared to alpha or SSVEP. To test this in EEG recordings, we designed an orientation change detection task where we presented both static and counterphase flickering stimuli of matched difficulty levels, which allowed us to compare the attentional modulation of various measures under similar stimulus and behavioral conditions in human EEG. We first performed a series of preliminary experiments to find stimulus parameters like spatial frequency, orientation, size and eccentricity that produced maximal gamma and SSVEP amplitude. Then we found appropriate orientation changes for static and flickering stimuli such that performance was comparable. These stimuli were finally used in an orientation change detection task. We performed the attention task on 26 human participants and analyzed alpha and gamma band powers for both static and flickering stimuli, and SSVEP power for flickering stimuli. We report three main results. First, for single trial analyses (where we computed power for each trial and subsequently averaged), alpha showed a much stronger attentional modulation than SSVEPs. Second, when we calculated power for the trial-averaged signal, attentional modulation was comparable for SSVEP and alpha, implying that for SSVEP calculation, the power estimation method plays a significant part. Finally, we found that non-foveal stimuli produced weak gamma in spite of various stimulus optimizations, and therefore showed a negligible effect on attention, although the same participants showed robust gamma activity for full-screen gratings. This study highlights the usefulness of different neural measures in studying attentional modulation.

Disclosures: **A. Das:** None. **N. Nandi:** None. **S. Ray:** None.

Poster

133. Spatial and Feature Attention in Visual Systems

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 133.05

Topic: D.06. Vision

Support: NIH EY014924
NIH NS116623

Title: Coding of Selected Visual Targets and Visually Guided Eye Movements by Populations of Primate Visual Cortical Neurons

Authors: *R. XIA, T. MOORE;
Neurobio., Howard Hughes Med. Inst. - Stanford Univ., Stanford, CA

Abstract: How does goal-directed top-down signal modulate the coding of information in primate visual cortex? To answer this question with a broader view of neuronal population dynamics, we performed high-density, high-channel count recordings in primate extrastriate areas MT/MST using recently developed Neuropixels NHP long (46 mm) probes (IMEC, inc.). In a typical session, hundreds of well-isolated neurons were simultaneously recorded, and receptive fields (RFs) covering both foveal and peripheral regions were found distributed along the probe shank. This allowed us to explore the patterns of population activity during visuomotor tasks that involve information integrated between neurons with different RFs. In the present study, two drifting grating stimuli were shown simultaneously at two fixed locations on opposite sides of a fixation spot. A monkey was trained to remain fixated until the fixation spot disappeared, and then to make a saccade to one of the gratings for a reward. A larger reward was more likely if the monkey selected the target that was less chosen in recent trials, encouraging frequent choice switches. Our preliminary analyses showed that the choice of target can be decoded from population activity prior to target choice, similar to previous observations of choice probability signals in MT/MST. Strikingly, the decoding score largely increased immediately prior to saccadic onset. Moreover, decoding of target feature (direction of motion) showed that the population activity contained more information about the chosen target than the unchosen one, consistent with the well-known effects of attention. This modulation was observed in both foveal and peripheral-preferred neurons, and among both narrow-spiking and broad-spiking neuronal populations. Lastly, we measured the influence of visual motion contained within the choice stimuli on the metrics of targeting saccades and examined its relationship to the activity of ensembles of MT/MST neurons. As previously described, the endpoints of saccades made to drifting gratings are biased in the drifting direction within the grating (Schafer and Moore, 2009). We found that on single trials, the confidence in the decoding of visual motion from ensemble activity was correlated with the amplitude of the motion-induced bias of targeting saccades. This correlation depended critically on target choice: the correlation was observed only when the coded stimulus was selected as the target. Thus far, our results suggest that attentional selection not only modulates the coding of visual stimuli, but also influences the integration of selected sensory information into the metrics of visually guided movements.

Disclosures: R. Xia: None. **T. Moore:** None.

Poster

133. Spatial and Feature Attention in Visual Systems

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 133.06

Topic: D.06. Vision

Support: DFG CRC 1436/B05

Title: A common cortical mechanism underlies covert focus shifts and the spatial resolution of attention

Authors: M. V. BARTSCH[1], C. MERKEL[2], M. A. SCHOENFELD[3], **J.-M. HOPF**[2]; [1]Leibniz Inst. for Neurobio., Leibniz Inst. for Neurobio., Magdeburg, Germany; [3]Univ. of Magdeburg, [2]Univ. of Magdeburg, Magdeburg, Germany

Abstract: Despite a wealth of knowledge about local cortical mechanisms and control structures involved in covert spatial focusing, there is still little understanding of the dynamic of involved processes across the hierarchy of visual areas as a whole. Here, we investigate this dynamic using MEG-based source localization of the N2pc component, which is a reliable index of attentional focusing in visual search. Specifically, we analyze the spatiotemporal progression of N2pc source activity in human male and female observers performing various versions of a cued visual search task. In three experiments (Exp 1: n=23, 8 females, mean age 26.8; Exp 2: n=20, 10 females, mean age 27.2; Exp 3: n=20, 9 females, mean age 26.8), we vary the size and the number of attention shifts required for target selection. We find (1) that covert shifts of attention are associated with activity modulations progressing in reverse hierarchical direction from highest (IT) through mid-level (V4) to lowest levels (V1) of representation in visual cortex. (2) Pre-cuing a narrower target region causes those modulations to start at lower levels in the visual hierarchy - an observation that extends previous work showing that the locus of N2pc sources reflects the spatial resolution required for target discrimination. (3) Cued successive focus shifts involve repeated reverse progressions through the hierarchy, which are indistinguishable from cortical modulations previously shown to underlie the increase of spatial resolution. These observations together suggest that covert shifts of the focus of attention are inherently linked to the operation of increasing the resolution of discrimination, with both being accomplished by the same coarse-to-fine selection process propagating in reverse hierarchical direction in visual cortex.

Disclosures: **M.V. Bartsch:** None. **C. Merkel:** None. **M.A. Schoenfeld:** None. **J. Hopf:** None.

Poster

133. Spatial and Feature Attention in Visual Systems

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 133.07

Topic: D.06. Vision

Support: NIMH DIRP

Title: Dynamic interplay between covertly attended events and saccade targets in macaque prefrontal cortex

Authors: *A. MESSINGER[1], F. DI BELLO[2], A. GENOVESIO[2];
[1]NIH, Bethesda, MD; [2]Dept. di Fisiologia e Farmacologia, Sapienza Univ., Roma, Italy

Abstract: To assess the role of prefrontal cortex in covert attention and saccadic planning, we recorded from monkeys performing a task that spatially dissociated these variables. The monkey covertly attended one of four possible locations to detect a subtle brightening (the Go signal) that indicated it was time to saccade to another of these locations. Where to attend and where to look were simultaneously and symbolically specified on each trial by a two-colored central cue. Previously we showed (Messinger et al., 2021) that prefrontal neurons (including frontal eye fields neurons) with tuned delay period activity mostly represented either the attended location (30%) or saccade target (53%), with a minority representing both (17%). Here we assess how attention and motor targets are encoded in prefrontal multiunit activity across the trial as a function of behavior and trial type. On correct trials, the decoding accuracy for both the attended location and the saccade target increased from chance level (25% correct) following cue onset and remained above chance through the variable delay period. After the Go signal, decoding of the attended location increased, peaking ~300 ms after this peripheral brightening event (N=97 multi-units, 300 ms sliding window). Decoding of the saccade target also increased, peaking 750 ms following the Go signal, which was after saccade execution and thus reflected the new gaze location. Decoding after the Go signal was markedly different on error trials when the monkey failed to detect the brightening (i.e. misses) and hence made no saccade. Decoding of the attention location on such miss trials was at near chance level at the time of the Go signal and did not improve following the undetected brightening event. Saccade target decoding on miss trials was above chance but, in the absence of a saccadic response to the Go signal, accuracy gradually diminished to chance level. We also assessed decoding on a subset of trials where the saccade target was specified but the location of the Go signal was not. As expected, decoding of the attended location on these uncued trials was at chance prior to the Go signal (N=214 multi-units). Decoding improved on both cued and uncued correct trials after the Go signal but was more accurate when covert attention was already directed to the location that would brighten. The saccade target was accurately decoded on cued and uncued trials, as the saccade target was specified for both. However, decoding of the saccade target was impacted by whether covert attention was directed (cued trials) or unconstrained (uncued trials), suggesting that covert attention can influence the fidelity of saccade planning signals.

Disclosures: **A. Messinger:** None. **F. Di Bello:** None. **A. Genovesio:** None.

Poster

133. Spatial and Feature Attention in Visual Systems

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 133.08

Topic: D.06. Vision

Support: SFB 1372

Title: Neural encoding of space in the pigeon hippocampus

Authors: *M. INDA, G. H. GADEA, C. S. SEVINCIK, R. PUSCH, O. GUNTURKUN;
Ruhr Univ. Bochum, Dept. of Biopsychology, Bochum, Germany

Abstract: The neural encoding of spatial cognition is established in mammals such as rats and bats by place cells, grid cells, head directional cells, and several more. Some of these cell types have also been found in avian species like titmice and quails. Pigeons are capable of short and medium-distance navigation and command excellent spatial cognition. We, therefore, investigate the neural encoding of spatial cognition in the pigeon hippocampus. One potential problem with this research has been the challenge of restricting the bird's movement due to the cable-connected electrodes, but the advance in wireless electrodes has made it possible to acquire neural activities from freely moving pigeons. We designed an arena with 5m x 2m x 2m as a space in which the pigeons could move around. 18 food feeders were placed on the ceiling that drop food on the floor according to a quasi-random sequence, thereby keeping the birds walking. The behavior of pigeons during the experiment is recorded using eight monochrome cameras. Multiple camera recordings and triangulation make it possible to detect the animal’s trajectory in space and reconstruct the pigeon’s pose using markerless machine learning systems. A head-mounted device for wireless electrodes was implanted on the pigeon's head, and neural responses in the freely moving pigeon's hippocampus were acquired from multi-channel electrodes. Using the above dedicated experimental system, we investigated the relationship between the pigeon's neural response data and location data to understand the spatial encoding system in the pigeon hippocampus.

Disclosures: M. Inda: None. **G.H. Gadea:** None. **C.S. Sevincik:** None. **R. Pusch:** None. **O. Gunturkun:** None.

Poster

133. Spatial and Feature Attention in Visual Systems

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 133.09

Topic: D.06. Vision

Support: NIH Grant EY028626

Title: Testing for correlates of salience to naturalistic textures in macaque V1 and V2

Authors: *A. DAVILA, A. KOHN;
Neurosci., Albert Einstein Col. of Med., Bronx, NY

Abstract: Salience theories propose that visual attention is guided by a priority map, defined using differences in low-level features within a visual scene. Surround suppression in primary

visual cortex (V1) is thought to act as a mechanism that determines feature differences, with responses to homogenous arrays of features being suppressed relative to responses to heterogeneous arrays. Differences in responsivity between these two conditions have been referred to as a neural correlate of salience.We tested whether there are neural correlates of salience for more complex stimuli, for which selectivity does not arise until after V1. Specifically, we measured responses to arrays of naturalistic textures: whereas V1 responses are determined by the spectral content of textures, V2 responses are also affected by their higher-order statistics. We recorded responses from populations of V1 and V2 neurons in anesthetized macaque monkeys to homogeneous and heterogeneous arrays of textures. The heterogeneous array consisted of either a texture or spectrally-matched noise stimulus centered on the receptive fields (RF) of the recorded units and surrounded by either spectrally-matched noise or texture stimuli, respectively. The homogenous display contained the same stimuli within and outside the RF. If salience signals are dependent on selectivity, salience signals should be higher in V2 than V1, since V1 is "blind" to the feature differences between target and distractors. In single units, responses in V2 but not V1 differed between homogeneous and heterogeneous arrays. The strength of these differences were correlated, across neurons, with the magnitude of surround suppression. To assess the strength of population salience signals, we trained a linear classifier to distinguish between homogenous and heterogenous displays using V1 and V2 population responses. Classifiers could readily distinguish between displays, though this was texture dependent, with discriminability for some displays being higher in V1 and for others in V2. We conclude that priority maps are calculated for more complex features like texture statistics and are not limited to low-level feature differences. This process is likely guided by surround suppression mechanisms in higher visual cortex.

Disclosures: **A. Davila:** None. **A. Kohn:** None.

Poster

133. Spatial and Feature Attention in Visual Systems

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 133.10

Topic: D.06. Vision

Support: Wellcome Grant 219627/Z/19/Z
Gatsby Charitable Foundation GAT3755

Title: Neural implementation of time-based visual attention switching

Authors: *M. HAMADA, T. MRSIC-FLOGEL;
Sainsbury Wellcome Ctr., Univ. Col. London, London, United Kingdom

Abstract: Selective attention to specific features in the sensory environment is critical for animals to behave efficiently in a complex and dynamic world. Moreover, animals must often change which aspects of the sensory inputs they attend to in different contexts.

To study how the brain flexibly prioritizes the processing of particular sensory stimuli to guide behaviour, we developed an uncued visual attention task in which mice respond to different aspects of a visual stimulus depending only on their internal sense of elapsed time. Specifically, we trained mice to report a sustained increase or decrease in average temporal frequency (TF) of a drifting grating stimulus that fluctuates stochastically around a mean speed of 2Hz. Although the exact time of this sustained change in TF is randomized on each trial, we paired the direction of TF change with time in the trial: increases in TF are more likely to happen soon after trial onset, while decreases are more likely to happen later in the trial (or vice versa). Mice learned to respond selectively to a particular direction of TF change depending on time in the trial, indicating that they use an internal judgment of time elapsed in a trial to guide visual attention. We recorded neural activity with Neuropixels probes across multiple brain regions from mice performing this task. Whilst cortical and subcortical visual areas quite faithfully represented the TF of the visual input, neurons in secondary motor cortex and dorsal striatum exhibited ramping activity throughout the duration of the trial, with responses to fluctuations in TF riding on top of these ramps. Interestingly, the direction of ramping in individual neurons was correlated with their preferred direction of TF change, such that the baseline activity levels of neurons preferring a fast or slow TF change were highest when mice were paying attention to the corresponding TF change direction.
This alignment between time-dependent and stimulus-dependent neuronal activity was sufficient to explain the animals' behaviour, suggesting that this may be a simple mechanism allowing mice to respond selectively to particular features in the visual input depending on their internal sense of time.

Disclosures: **M. Hamada:** None. **T. Mrsic-Flogel:** None.

Poster

133. Spatial and Feature Attention in Visual Systems

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 133.11

Topic: D.06. Vision

Support: DAAD Grant 57449728
JSPS KAKENHI 20H04487
RIEC Grant R04/A14

Title: Gamma activity spindles in V4 LFPs are modulated by stimulus dynamics and attentional demand

Authors: M. SHISHIKURA[1], U. A. ERNST[2], I. GROTHE[3], A. K. KREITER[3], *K. SAKAI[1]; [1]Dept Computer Sci., Univ. Tsukuba, Tsukuba, Japan; [2]Dept Theoretical Physics/Computational Neurophysics, [3]Brain Res. Institute/Cognitive Neurophysiol. Group, Univ. Bremen, Bremen, Germany

Abstract: Stimulus processing in the visual system is typically accompanied by oscillatory activity in the gamma range (50-90 Hz). Interestingly, gamma activity is not stationary, but seems to be organized into characteristic ‘spindles‘ of high-amplitude oscillations, separated by periods of more stochastic activation. Currently it is neither clear how these spindles emerge, nor what functional role they might play.
For addressing these questions, we re-analyzed data from an experiment where macaques had to perform a demanding shape-tracking task requiring sustained attention. Stimuli consisted of two sequences of morphing shapes, one of which had to be attended. The animal’s task was to memorize the initial shape, and to indicate its reappearance in the attended morphing sequence. While performing the task, local field potentials were recorded from neurons in area V4 whose receptive fields covered the two stimuli. For detecting spindles, we first filtered the LFPs in the gamma band, computed the LFP’s time-varying amplitude from the analytic signal, and extracted periods of high-amplitude gamma activity by applying a high (onset)-threshold and low (offset)-threshold to the data. Next, we compared spindle statistics for characteristic periods during a trial, i.e. the blank period (no stimulus, attention has been allocated), static period (memorize shape), 1st morph cycle (dynamic stimulus, but no attention needed because target cannot reappear), and 2nd to last morph cycles (dynamic, attention needed, because target might appear).
Consistently for the two animals, we find that spindle duration increases monotonously from 55 to 80ms over trial progression, while frequency-of-occurrence (FOO) first decreases, reaching a minimum during the 1st morph cycle, and then increases again. For interpreting these results, we performed model simulations with a recurrent excitatory-inhibitory spiking network capable to generate gamma oscillations. In order to also exhibit spindle dynamics, the couplings were adjusted as such that the circuit was at a transition point between stochastic and oscillatory activity. By first increasing the constant external input and then making it time-varying, we simulated the stimulus transitions “blank” to “static” to “morphing”, and found a monotonous increase in spindle duration consistent with the experiment. However, at the same time FOO decreased monotonously, thus failing to reproduce its observed increase in the behaviorally most relevant period after the 1st morph cycle. We thus conclude that spindle statistics are not explained by stimulus variations alone, but in fact are strongly driven by attention increasing their FOO.

Disclosures: **M. Shishikura:** None. **U.A. Ernst:** None. **I. Grothe:** None. **A.K. Kreiter:** None. **K. Sakai:** None.

Poster

133. Spatial and Feature Attention in Visual Systems

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 133.12

Topic: D.06. Vision

Support: NHMRC Investigator Award 1196855

Title: Neural circuits for prey selection in larval zebrafish

Authors: *S. I. ZHU[1,2], Z. PUJIC[2], B. SUN[2], G. J. GOODHILL[1,2];
[1]Washington Univ. in St. Louis, Saint Louis, MO; [2]The Univ. of Queensland, Brisbane, Australia

Abstract: Zebrafish develop complex hunting behaviors from a very early age. During hunting, selecting the most accessible prey from distractors including other prey and debris in the environment is a challenging problem. The neural circuit mechanisms underlying prey selection in zebrafish remain unclear. Here, we used 2-photon calcium imaging in a tail-free preparation to study both neural activity and behavior in response to competing prey-like stimuli of equal or unequal priority (i.e., order of appearance). Neural imaging included the optic tectum, pretectum, habenula, and pallium. We found that behavioral responses were related to stimuli priority. In the optic tectum, neural responses to unilateral competing stimuli were determined by receptive field properties, and responses to bilateral competing stimuli scaled with stimuli priority confirming the existence of a saliency map in this region. However, these neurons decoded competing stimuli less accurately than single stimuli. In contrast, in the habenula we found a subpopulation of neurons which preferentially encoded competing stimuli. Together, these results suggest that, while the optic tectum contains information about stimuli priority, the habenula may play a critical role in the computation of prey selection.

Disclosures: **S.I. Zhu:** None. **Z. Pujic:** None. **B. Sun:** None. **G.J. Goodhill:** None.

Poster

134. Basal Ganglia: Stimulation and Disease Models

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 134.01

Topic: E.03. Basal Ganglia

Title: Analysis of correlated modulation of neural activity in subcortical nucleus with active movement

Authors: *S. JAVADZADEH NO[1], J. NATARAJ[2], Y. SUN[2], S. A. SEYYED MOUSAVI[2], T. D. SANGER[2,3];
[1]BME, [2]EECS, Univ. of California Irvine, Irvine, CA; [3]Children's Hosp. of Orange County, Orange, CA

Abstract: Brain activity at both the single neuron and population level have been studied extensively in the motor cortex. However, there have been less opportunities to thoroughly investigate circuitry in deep structures such as basal ganglia and thalamus.Current basal ganglia (BG) models suggest some circuitries within BG should have decreased neural activity during movement. However, we hypothesize that all basal ganglia regions have increased power during activity comparing to rest. Our goal here is to examine this hypothesis and investigate the correlation between limb movement and neural activity in deep motor regions.The use of Deep Brain Stimulation (DBS) as a treatment for movement disorders such as childhood dystonia

provides us with the rare opportunity to study the modulation of BG and thalamic neurons by movement. During the DBS procedure, several stereoelectroencephalography (sEEG) depth electrodes are implanted in various BG and thalamic nuclei. Recorded electrical activity from these temporary stimulation/recording electrodes can be utilized to understand the underlying dynamics of dystonia and motor control in general. DBS surgery is followed by one week of tests and recordings in an inpatient neuromodulation unit (NMU) to find optimal DBS targets.For the purpose of this study, while recording the intracranial data, we asked the patient to perform an experiment that included 24 trials (i.e., 6 trials per each arm and leg) of 60 seconds of voluntary reaching task. Each trial was followed by 30 seconds of rest. We employed a custom spike sorting pipeline in order to acquire neural activity from BG and thalamic regions on both the multi-unit and population scales. This pipeline was tailored for our data recorded from lower impedance electrodes compared to single-unit recording electrodes. Identification and clustering of spikes using this pipeline has allowed us to investigate the relationships between limb movement and ipsilateral and contralateral brain activity. Our results demonstrate that movement increases the power of neural population activity of all recorded basal ganglia regions in comparison to rest. This modulation can be quantified by measuring changes in spike rates that have the largest variances in a given brain region. However, the change in power of neural activity does not always correlate with changes in movement intensity. These findings substantiate our hypothesis, indicating that there is increased activity in BG circuits during movement. Additionally, the relationship between neural activity in deep motor control structures and limb movement is more complex than that of cortical motor control structures.

Disclosures: S. Javadzadeh No: None. **J. Nataraj:** None. **Y. Sun:** None. **S.A. Seyyed Mousavi:** None. **T.D. Sanger:** None.

Poster

134. Basal Ganglia: Stimulation and Disease Models

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 134.02

Topic: E.03. Basal Ganglia

Title: Increased task-unrelated frequency content in the affected side of a hemidystonic child during a continuous motor task

Authors: *J. NATARAJ[1], R. SOROUSHMOJDEHI[1], S. A. SEYYED MOUSAVI[1], T. D. SANGER[2];
[1]Electrical Engin. and Computer Sci., Univ. of California, Irvine, Irvine, CA; [2]Children's Hosp. of Orange County, Orange, CA

Abstract: Childhood dystonia is a movement disorder that presents with clinical features of involuntary intermittent or sustained muscle contractions causing abnormal postures, repetitive and twisting movements, or both. Dystonia can be further classified as hemidystonia if it affects only one half of the body. The motor features of childhood dystonia may involve reduced

suppression of involuntary muscle activity, resulting in the superposition of extraneous motor components on desired movements. In this case study, we aim to characterize differences in the affected and unaffected sides of a left hemidystonic child performing a continuous figure-eight writing task. We expect that in a continuous writing task, muscle activity will occur at "task-related" frequencies that match the frequencies of motion. Therefore, we hypothesize that upper limb muscles and intracranial motor control structures such as basal ganglia and thalamus will contain task-related frequency content in both the affected and unaffected sides, and that there will be increased "task-unrelated" frequency content in both muscle and intracranial signals during movement of the affected side. The figure-eight writing task was performed while the subject was participating in an inpatient Neuromodulation Monitoring Unit (NMU). During the NMU, four temporary depth electrodes were placed in the left basal ganglia and thalamus. The subject was asked to perform five trials of the continuous writing task with both left (affected) and right (unaffected) hands on an iPad while kinematic trajectories, intracranial data, and electromyographic signals were recorded. Individual repetitions of the task were scaled to matching durations offline, and power spectra of all signals were used to compare the frequency content of the affected and unaffected sides. When the motor task was performed by the affected side, the corresponding upper limb muscles and ipsilateral intracranial recordings contain more task-unrelated frequency content. Additionally, the task-related components are not well-resolved on the affected side compared to performance on the unaffected side, presenting as more wideband activation around task-related frequencies. Our findings are consistent with the hypothesis that motor task performance by the affected side of a hemidystonic child would present with changes in task-related frequency content and increased task-unrelated frequency content both in muscles and intracranially when compared to performance by the unaffected side. This affirms that childhood dystonia is associated with poorly suppressed components of motion that are not related to desired motor outcomes.

Disclosures: J. Nataraj: None. **R. Soroushmojdehi:** None. **S.A. Seyyed Mousavi:** None. **T.D. Sanger:** None.

Poster

134. Basal Ganglia: Stimulation and Disease Models

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 134.03

Topic: E.03. Basal Ganglia

Title: Deep brain stimulation decreases task-unrelated frequencies of deep brain signals in a dystonic patient while performing a continuous task: a case study

Authors: *R. SOROUSHMOJDEHI[1], J. NATARAJ[1], S. A. SEYYED MOUSAVI[1], T. D. SANGER[1,2];
[1]EECS, Univ. of California Irvine, Irvine, CA; [2]Children's Hosp. of Orange County, Orange, CA

Abstract: In patients with neurological or movement disorders such as dystonia, abnormal inputs from deep brain regions can correspond to difficulty in preventing involuntary muscle activities that are not associated with the desired motor task. One of the effective surgical interventions that improves quality of life in patients with movement disorders such as dystonia is Deep Brain Stimulation (DBS). Despite recent advancements in clinical applications of DBS, the underlying mechanism of DBS is not yet well understood. In this case study, our goal is to investigate: i) frequency components of signals from basal ganglia and thalamus recorded from a patient who was participating in an inpatient Neuromodulation Monitoring Unit (NMU) while performing a continuous drawing task, and ii) the effects of deep brain stimulation on brain activity using frequency-domain analysis. We hypothesize that the frequency content of signals acquired from intracranial recordings during the continuous task consist of two distinct components that correspond to voluntary movements, referred to as task-related frequencies, and involuntary movements, referred to as task-unrelated frequencies. We also hypothesize that DBS can reduce or modify abnormal signals in deep brain regions before they result in abnormal muscle activation.To test our hypotheses, we recorded stimulated and non-stimulated brain activity through depth electrodes in a patient with dystonia while they were performing multiple trials of a continuous Figure-Eight drawing task on an iPad. We implanted up to 10 temporary AdTech MM16C depth leads, each consisting of 10 recording microcontacts, into potential DBS targets. While performing the drawing task, electromyography (EMG) signals of 8 upper limb muscles, brain activity signals from implanted DBS electrodes, and kinematic data were recorded. We calculate Power Spectral Density (PSD) of each trial in order to study the frequency content of the acquired signals and to better understand the underlying mechanism of DBS.Results demonstrate the presence of task-related frequencies in power spectra of kinematics, muscle EMGs, and intracranial recordings that are consistent with the pattern of hand motion while performing the task. Furthermore, we provide evidence of the presence of task-unrelated frequencies that can be associated with abnormal motions caused by dystonia.Moreover, results show that the power of task-unrelated frequencies decreases during DBS compared to that of the non-stimulated frequencies. This suggests that DBS has the potential to reduce or modify abnormal signals in deep brain regions before they result in abnormal muscle activation.

Disclosures: **R. Soroushmojdehi:** None. **J. Nataraj:** None. **S.A. Seyyed Mousavi:** None. **T.D. Sanger:** None.

Poster

134. Basal Ganglia: Stimulation and Disease Models

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 134.04

Topic: E.03. Basal Ganglia

Support: Cerebral Palsy Alliance Research Foundation Inc. Grant PG02518
Crowley-Carter Foundation

Title: An Algorithm for Automated Detection of Deep Brain Stimulation Evoked Potentials (ADDEP)

Authors: *J. S. L. VIDMARK[1], S. A. SEYYED MOUSAVI[2], T. D. SANGER[1,2];
[1]Biomed. Engin., [2]Electrical Engin. and Computer Sci., Univ. of California, Irvine, Irvine, CA

Abstract: Deep brain stimulation (DBS) is a common treatment of movement disorders. When used in combination with externalized depth electrodes, which can both stimulate and record, valuable insight can be obtained into the brain's neural responses to electrical stimulation (referred to as evoked potentials or EPs). With the numerous combinations of possible stimulation and recording locations, and other stimulation parameters, thousands of different conditions can be studied—the recordings of all of which must be searched for EPs. While manual labeling is time consuming for the researcher and also inserts bias, automated EP detection methods often struggle to distinguish between artifacts and the highly varying shapes of the neural responses. To resolve this, we developed a novel algorithm for automated detection of DBS EPs (ADDEP). ADDEP evaluates stimulus-triggered averages of neural recordings during polarity-reversed bipolar stimulations. Polarity reversal refers to the flipping of cathodic & anodic stimulation contacts, which reverses the sign of the stimulus artifact, but not the neural response. As such, neural responses are expected to positively correlate between the pair of polarity-reversed stimulation recordings, while artifactual components correlate negatively, or not at all. The ADDEP algorithm makes use of this experimental approach to distinguish neural responses from artifacts, through the following steps: 1) Remove decay artifacts from the pair of polarity-reversed stimulation recordings. 2) Measure correlation between the resulting artifact-free recordings over the expected EP region. 3) If a significant positive correlation is found, obtain the average between the two recordings. 4) Determine the ratio of the peak-to-peak amplitude in the EP region to the baseline standard deviation. 5) If this ratio meets an empirically chosen threshold, label the average recording as an EP. Else, if 3 & 5 are not both met, label as non-EP. The ADDEP algorithm does not require a predefined EP shape; hence, it does not discriminate towards or against any shapes. Another benefit is its user-defined amplitude threshold, which can be lowered or raised to reduce the false negative or false positive rates, respectively, to match the preference of the researcher or project. Initial results from testing ADDEP on recordings from pediatric patients with movement disorders have proven our ability to distinguish EPs of varying shapes and sizes from stimulus artifacts and other noise. Improvements to the algorithm, such as the removal of complex decay artifacts and establishment of ideal thresholds, are in progress to further improve the algorithm's accuracy.

Disclosures: J.S.L. Vidmark: None. **S.A. Seyyed Mousavi:** None. **T.D. Sanger:** None.

Poster

134. Basal Ganglia: Stimulation and Disease Models

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 134.05

Topic: E.03. Basal Ganglia

Title: A neural hashcode model of basal ganglia function

Authors: *T. D. SANGER;
EECS, UCI, Irvine, CA

Abstract: The hypothesis that dopaminergic neurons in the ventral tegmentum and substantia nigra could encode predicted future reward has led computational neuroscientists to propose that the basal ganglia could be part of a network that implements Reinforcement Learning (RL). However, RL requires a network that represents the relationship between state, state change, and predicted future reward, and such networks have not been found. I propose a new model based on known basal ganglia anatomy that implements a form of RL related to Q-learning. Current state is mapped to action through direct and indirect pathways that place rewarded or non-rewarded state-action pairs into separate "buckets" with excitatory or inverting outputs. "Bucket Q-learning" provides a biologically plausible network structure without the need for explicit representation of future predicted reward. Efficient implementation is based on neural hash coding, a new learning algorithm that permits one-shot learning by using random representations of state to eliminate overlap between training examples. While this structure requires generalization to be implemented elsewhere (for example, in the input representation), in return it gives very rapid and reliable learning, reminiscent of human behavior in which a single rewarded or punished example is often sufficient to modify future action. Finally, in this model the output of basal ganglia modulates thalamo-cortical loops, thereby allowing basal ganglia to select state-dependent cortical dynamics for movement, accentuating or inhibiting dynamic components based on prior experience of reward. The model thus combines three elements: (1) bucket Q-learning, (2) neural hash codes, (3) modulation of dynamics. I show that not only does this provide stable rapid learning of dynamics from reward, but specific injuries can provide models for hypertonic dystonia, hyperkinetic dystonia, and chorea.

Disclosures: T.D. Sanger: None.

Poster

134. Basal Ganglia: Stimulation and Disease Models

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 134.06

Topic: E.03. Basal Ganglia

Support: Cerebral Palsy Alliance Research Foundation Inc. (PG02518)

Title: Low frequency thalamic and pallidal local field potential correlation with voluntary movement in children with dystonia

Authors: *M. KASIRI[1], T. D. SANGER[2,3];
[1]Biomed. Engin., [2]Electrical Engin. and Computer Sci., Univ. of California, Irvine, Irvine, CA;
[3]Div. of Neurol., Children's Health, Orange County, Orange, CA

Abstract: Understanding the relationship between neural activity and voluntary movement provides new insights into the motor control mechanism. In three children receiving clinical implantation of deep brain stimulation (DBS) leads, we were able to investigate the relationship between deep brain oscillations and voluntary movement. 10 temporary AdTech MM16C leads, each containing 10 microwire electrodes, were implanted bilaterally into globus pallidus interna (GPi), ventralis oralis anterior/posterior (VoaVop), subthalamic nucleus (STN), ventral intermediate nucleus (VIM), pedunculopontine nucleus (PPN), and ventral anterior (VA). After the surgery, the participants were asked to perform a voluntary reaching task for 90 seconds followed by a resting period of 30s, for four trials with their upper limb; while we recorded electromyogram (EMG) from the corresponding muscles and the local field potential (LFP) through all 10 micro contacts on DBS leads. After removing the 60 Hz noise from the recordings, the LFP signals were high pass filtered and transformed into bipolar montage (voltage difference between each two pairs of adjacent micro-contacts) and the EMG recordings were filtered using a Bayesian nonlinear filter to highlight the changes in muscle activity as well as the activation itself. We then performed a time-frequency analysis on the LFP and explored the correlation between the subnuclei activation power in five frequency bands up to 1000 Hz with either the EMG or derivative of the EMG which is a measure of movement onset and offset or torque. The preliminary results demonstrate that there exists higher correlation (p-value < 0.05) between the EMG and the motor-subnuclei of the deep brain regions (GPi, VoaVop, VA, and STN) compared to other regions (VIM and PPN), regardless of the frequency band. Moreover, despite the presence of both excitatory and inhibitory connections between regions, all regions are active during movement, consistent with modulation of patterns of activity within each region, rather than modulation of the overall activity of the regions. This could be a biomarker of dystonia or a pattern in the healthy brain and it requires further study. This study has never been done in human subjects before and the findings suggest that the low frequency deep brain recordings can potentially be a predictor of movement for neural control of prosthetics.

Disclosures: **M. Kasiri:** None. **T.D. Sanger:** None.

Poster

134. Basal Ganglia: Stimulation and Disease Models

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 134.07

Topic: E.03. Basal Ganglia

Support: NINDS K08
NINDS R01

Title: The role of striatal dopamine in a mouse model of impulse control disorder in Parkinson's disease

Authors: *J. LEMAK[1], X. ZHUANG[3], A. B. NELSON[2];
[2]Neurol., [1]Univ. of California San Francisco, San Francisco, CA; [3]UCSF, San Francisco, CA

Abstract: Impulsive decision-making is common across many different neuropsychiatric disorders. One notable example is in Parkinson's disease (PD), in which a subset of patients develop impulse control disorder (ICD) during dopamine replacement therapy, in particular with dopamine D2/D3 receptor agonists such as pramipexole (PPX). ICD can include compulsive gambling, binge eating and hypersexuality. The cellular and circuit mechanisms of ICD are unknown, but imaging studies and the expression patterns of D2/3 receptors suggest the striatum and dopamine signaling are critical components. ICD has been studied in patients using a behavioral test called delay discounting. In the delay discounting task, subjects choose whether to receive a small reward immediately, or a larger reward later. Parkinson's patients experiencing ICD show a preference for immediate rewards, which correlates with higher impulsivity. We adapted a delay discounting task in a mouse model of Parkinson's Disease utilizing local infusions of the toxin 6-OHDA. In this model, loss of midbrain dopamine neurons and striatal dopaminergic axons correlated with motor symptoms. We found these moderately parkinsonian mice had increased impulsivity following PPX administration. To study the role of striatal dopamine in ICD, we utilized the fluorescent dopamine sensor dLight. We measured dLight fluorescence with fiber photometry during the delay discounting task. In healthy animals, we found that greater dopamine signals at the time of large versus small rewards. In dopamine depleted animals treated with PPX, we suspect there is reduced ability to differentiate small versus large rewards, leading to greater overall impulsivity. We hope these findings help us to better understand the physiological underpinnings of ICD and improve treatment of PD.

Disclosures: J. Lemak: None. **X. Zhuang:** None. **A.B. Nelson:** None.

Poster

134. Basal Ganglia: Stimulation and Disease Models

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 134.08

Topic: E.03. Basal Ganglia

Support: NINDS R01
NINDS K08
Parkinson's Foundation Postdoctoral fellowship

Title: Aberrant striatal activity in a rodent model of impulse control disorder in Parkinson's disease

Authors: *X. ZHUANG[1], J. LEMAK[2], A. B. NELSON[1];
[1]Neurol., [2]Univ. of California, San Francisco, San Francisco, CA

Abstract: Impulsive decision-making is common across multiple neuropsychiatric disorders. One notable instance is in Parkinson's disease (PD), where impulsive decision-making occurs in

the context of dopamine replacement therapy for motor symptoms. Impulse control disorder (ICD) can manifest as compulsive gambling, binge eating, or hypersexuality, and is identified in about 14-40% of PD patients taking dopamine D2/3-type receptor (D2/3R) agonists. Evidence in PD patients suggests the basal ganglia, the striatum, is a critical site of circuit dysfunction in ICD. Within striatum, D2Rs are densely expressed on indirect pathway medium spiny neurons (iMSNs). In the context of decision making, excitatory medial prefrontal cortex (mPFC) inputs onto striatal neurons are another circuit substrate of ICD. However, few studies have modeled ICD in PD in animals, and none have assayed the role of striatal activity in causing this disorder. To model ICD in PD, we adapted a delay discounting task, in which the value of a reward decreases according to the time needed to wait for it. We combined this model with cell-type specific optogenetics and in vivo striatal single-unit recordings or ex vivo electrophysiology to examine how parkinsonism and D2/3R agonist (pramipexole, PPX) treatment alter striatal activity and PFC-striatal synaptic connectivity. We found that parkinsonian mice showed greater impulsivity following the administration of PPX. In pilot cohorts from healthy mice, we have found that direct pathway medium spiny neurons (dMSNs) increased firing around reward delivery and iMSNs ramped their activity during delay periods, suggesting encoding key aspects of delay discounting. Interestingly, direct and indirect pathway neurons from parkinsonian mice showed abnormal PPX evoked firing rates, and this could disrupt task-related signals and cause impulsivity. Furthermore, cortico-striatal excitatory synaptic inputs were reduced by acute PPX bath application, suggesting the potential role in driving aberrant striatal activity in vivo. These findings shed light on striatal mechanisms of impulsivity in PD patients, but also inform the use of dopamine replacement therapy with a goal of ameliorating ICD.

Disclosures: X. Zhuang: None. **J. Lemak:** None. **A.B. Nelson:** None.

Poster

134. Basal Ganglia: Stimulation and Disease Models

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 134.09

Topic: E.03. Basal Ganglia

Title: Neural spectral features capture severity of dyskinesia in Parkinson's Disease

Authors: *M. OLARU[1], W.-J. NEUMANN[2], S. LITTLE[1], R. ABBASI-ASL[1], P. A. STARR[1]; [1]Univ. of California, San Francisco, San Francisco, CA; [2]Movement Disorder and Neuromodulation Unit, Charité - Universitätsmedizin Berlin, Berlin, Germany

Abstract: Objective: Determine whether neural spectral features correspond to severity of motor signs in patients with Parkinson's Disease.Background: For Parkinson’s Disease, narrow-band gamma oscillations (60-90Hz) are correlated with dyskinesia [1]. However, these correlates mainly correspond to the presence or absence of dyskinesia, versus the severity of dyskinesia [1]. Here, we examine whether linear combinations of neural spectral features weighted by variance correlate to severity of dyskinesia.

Methods: We've conducted over 4000 hours of multisite recordings in 21 hemispheres of 13 patients with Parkinson's disease implanted with the investigational Medtronic RC+S device prior to the onset of stimulation. Each hemisphere contains 2 lead arrays, 1 in sensorimotor cortex, and 1 in the basal ganglia (globus pallidus n=8, subthalamic nucleus n=15), with each array providing two bipolar recording channels. During this time, wrist-wearable accelerometers have recorded continuous measures of dyskinesia. On a single-patient level, we computed power spectra in 60s intervals for each channel. Then, we correlated motor scores to spectral power in 1 Hz-wide frequency bins. Next, we generated principal component (PC) loadings of neural data across pooled time. Lastly, we projected these PCs across frequency onto a 2D plane with dyskinesia scores.

Results: For initial analyses in a single patient, we first confirmed classical neural correlates, with narrow-band gamma oscillations at 78Hz across all channels correlating to dyskinesia (Fig 1a). The top 2 PC loadings also contain gamma oscillations, with PC1 containing broadband gamma (60-90Hz) and PC2 containing narrow-band gamma (78Hz). Additionally, both PCs captured anti-correlated gamma and beta-band (13-30Hz) activity (Fig 1b). Projecting these PCs onto a 2D plane captured severity of dyskinesia scores (Fig 1c).

Conclusion: Physiomarkers containing correlations between gamma-band and beta-band activity may be necessary to characterize the severity of dyskinesia symptoms.

Fig 1A: Individual Spectral feature correlates

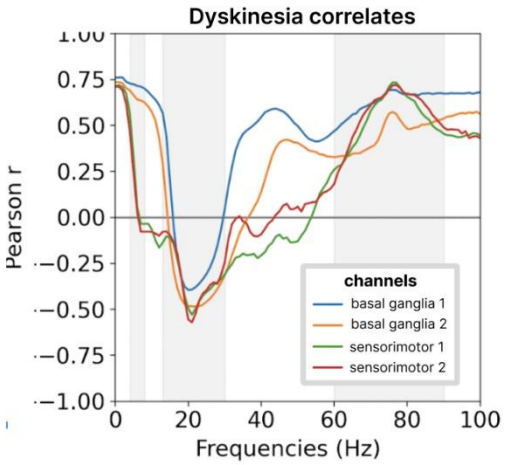


Fig 1B: Neural PC loadings

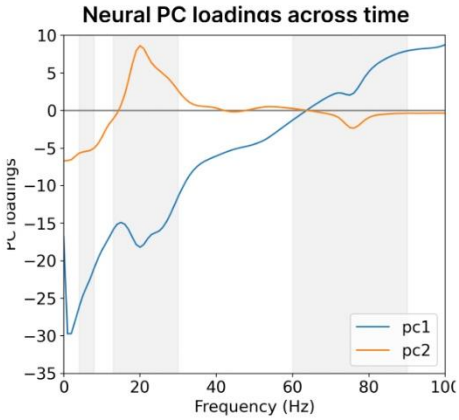
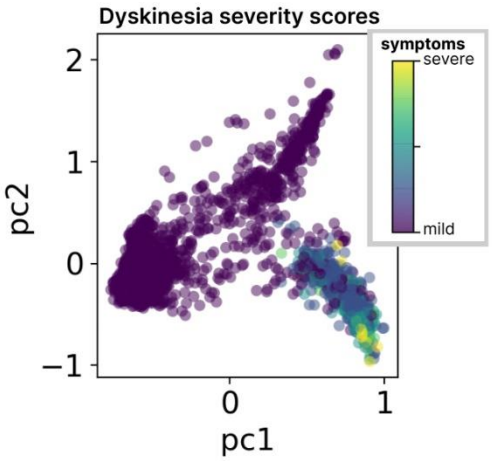


Fig 1C: 2D PC projection



Disclosures: **M. Olaru:** None. **W. Neumann:** None. **S. Little:** None. **R. Abbasi-Asl:** None. **P.A. Starr:** None.

Poster

134. Basal Ganglia: Stimulation and Disease Models

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 134.10

Topic: E.03. Basal Ganglia

Support: NIH grant P50NS098685
NIH grant P50NS123103
NIH grant P51OD011132
Aligning Science Across Parkinson's grant ASAP-020572

Title: Basal Ganglia Neurons in Healthy and Parkinsonian Primates Generate Recurring Sequences of Spikes

Authors: A. GALVAN, ***T. WICHMANN**;
Emory Natl. Primate Res. Center, Udall Ctr. of Excellence in Parkinson's Dis. Res., Emory Univ., Atlanta, GA

Abstract: Basal ganglia spiking activity can be described by statistical steady-state measures such as the average firing rate, or the coefficient of variation of inter-spike intervals (ISIs), or by quantifying the occurrence of non-stationary spike groupings, such as burst discharges. Many of these parameters are altered in the parkinsonian state. In this study, we examined another feature of neuronal discharge that may describe basal ganglia firing, i.e., the occurrence of precisely replicating sequences of inter-spike intervals, comparing data from normal and parkinsonian Rhesus monkeys.

The study utilized an algorithm which identified recurring sequences of ISIs in which each ISI differed by less than 1% from the corresponding ISI of the reference sequence. The analysis was performed on existing ISI series, each 5000 ISIs in length, that had been recorded in the external and internal pallidal segment of the globus pallidus (GPe and GPi, respectively) or the subthalamic nucleus (STN) of two Rhesus monkeys, before (GPe: 38 neurons, STN: 13 neurons, GPi: 33 neurons) and after they were rendered parkinsonian by treatment with 1-methyl-4-phyl-1,2,3,6-tetrahydropyridine (MPTP; GPe: 40 neurons, STN: 27 neurons, GPi: 34 neurons). For each cell, the results were statistically compared to randomly shuffled representations of the original ISI series.

Neurons in all three nuclei nucleus tended to fire in repeating sequences, typically 2 ISIs long (i.e., involving three spikes). In these recordings, 20-40% of spikes participated in sequences. Compared to similar analyses in shuffled representations of the same data, sequences were more common in the original representation of ISIs in the STN and the GPe. Induction of parkinsonism reduced the proportion of sequence spikes in GPe, but increased it in the STN. We found no relation between the sequence generation and the firing rate of neurons, and, at most, a weak correlation between sequence generation and the incidence of bursts. We conclude that basal ganglia neurons fire in recognizable sequences of ISIs, whose incidence is influenced by the induction of parkinsonism.

Disclosures: **A. Galvan:** None. **T. Wichmann:** None.

Poster

134. Basal Ganglia: Stimulation and Disease Models

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 134.11

Topic: E.03. Basal Ganglia

Support: Vetenskapsrådet
Olle Engkvist foundation
Magnus Bergvall foundation
Åhléns stiftelse

Title: Midbrain plasticity in Parkinson's Disease: experimental studies on the synaptic microcircuit.

Authors: *M. MOLINARI, E. SANTINI, A. BORGKVIST;
Neurosci., Karolinska Inst., Solna, Sweden

Abstract: Parkinson´s Disease (PD) is characterized by a progressive cell-death of the dopaminergic (DA) neurons of the Substantia nigra pars compacta (SNc). The loss of SNc neurons and the subsequent reduction in DA signaling within the basal ganglia causes the cardinal PD motor symptoms such as bradykinesia and hypokinesia.
The Substantia nigra reticulata (SNr) is an important output nucleus of the basal ganglia motor system and its firing activity controls motor behavior: SNr firing causes reduction of motor activity, while inhibition of the SNr allows movement initiation. Studies on animals have revealed that aberrant firing activity in the SNr correlates with experimental Parkinsonism. However, the mechanisms involved in the establishment of dysregulated basal ganglia output by loss of DA have not been characterized.
To better understand how synaptic changes in the SNr microcircuitry contributes to motor symptoms in PD, we have performed electrophysiological studies on acute brain slices from mice with hemi-parkinsonism induced by the neurotoxin 6-OHDA.
Optogenetic activation of GABAergic synaptic inputs from the Striatum, comprising the direct pathway, caused a reliable inhibition of SNr in DA intact animals. In contrast, SNr cells recorded in slices from DA depleted mice were significantly less sensitive to striatonigral inhibition. The reduction of inhibition in DA depleted animals was not accompanied by change in the amplitude of spontaneous inhibitory currents, indicating normal levels of $GABA_A$ receptor expression in DA depleted animals.
Immunohistological analysis of midbrain tissue from DA depleted animals revealed a significant reduction of the potassium and chloride symporter, KCC2, in the membrane of SNr neurons. Striatonigral activation was ineffective in slices of DA intact animals in the presence of the KCC2 inhibitor VU0463271 (10µM), confirming that KCC2 is essential for synaptic inhibition in SNr cells.

In DA intact animals, both VU-sensitive outward and VU-insensitive inward spontaneous currents were present when SNr cells were clamped at membrane potentials close to the equilibrium potential for chloride. In contrast, SNr cells in DA depleted animals had primarily inward currents because of loss of KCC2 function.
In conclusion, we describe a new ionic mechanism underlying motor symptoms in PD and propose a therapeutic potential for KCC2-modifying drugs.

Disclosures: **M. Molinari:** None. **E. Santini:** None. **A. Borgkvist:** None.

Poster

134. Basal Ganglia: Stimulation and Disease Models

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 134.12

Topic: E.03. Basal Ganglia

Support: NSF Grant No. 2038436

Title: Modulation of striatal lateral inhibition in levodopa-induced dyskinesia

Authors: *E. TWEDELL[1,3,4], A. B. NELSON[2,3,4];
[1]Neurosci. Program, [2]Neurol., UCSF, San Francisco, CA; [3]Kavli Inst. for Fundamental Neurosci., San francisco, CA; [4]Weill Inst. for Neurosci., San francisco, CA

Abstract: The balance between selecting appropriate movements and suppressing alternative motor commands is disrupted in multiple movement disorders, including levodopa-induced dyskinesia (LID). LID is characterized by abnormal, involuntary movements that arise as a complication of long-term Parkinson's disease treatment with the dopamine precursor, levodopa. While the cellular and circuit mechanisms underlying LID are not fully understood, convergent evidence suggests that hyperactivity of the movement-promoting direct pathway is a central mechanism. One possible explanation for elevated firing rates of direct-pathway medium spiny neurons (dMSNs) is a loss of inhibition. While dMSNs receive inhibition from multiple sources, local lateral inhibitory connections between medium spiny neurons are well-positioned to shape striatal output. Furthermore, while it is known that lateral connections from indirect-pathway medium spiny neurons (iMSNs) to dMSNs are reduced in parkinsonian mice, the role of lateral inhibition in LID remains virtually unexplored. Here, we use *ex vivo* electrophysiology and optogenetic activation to probe changes in striatal lateral inhibition in a mouse model of LID. We find a decrease in iMSN-dMSN oIPSC amplitude in parkinsonian animals relative to healthy controls. Surprisingly, in parkinsonian animals chronically treated with levodopa, our data suggest there may be a partial restoration of oIPSC amplitude towards control levels. These experiments will elucidate the role of lateral inhibition in basal ganglia function and dysfunction, thus expanding the framework on the role of striatal microcircuitry in action selection.

Disclosures: **E. Twedell:** None. **A.B. Nelson:** None.

Poster

135. Basal Ganglia: Physiology and Function II

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 135.01

Topic: E.03. Basal Ganglia

Support: NIH Grant R01NS107599

Title: Dorsolateral striatum, not frontal cortex, is a bottleneck for sensory selection in a whisker detection task in mice

Authors: *A. LAM, B. ZAREIAN, E. ZAGHA;
Univ. of California, Riverside, Riverside, CA

Abstract: A learned sensory-motor behavior engages multiple brain regions, including the neocortex and the basal ganglia. How these brain regions coordinate to select target stimuli remains poorly understood. Here, we performed electrophysiological recordings and pharmacological inactivations of frontal cortex and dorsolateral striatum to determine the representations within and functions of each region during performance of a selective whisker detection task. From the recording experiments, in deep layers of frontal cortex and dorsolateral striatum we observed robust post-stimulus sensory encoding and pre-response activity. Peak pre-response activity and significant choice probability emerges in the frontal cortex before the dorsolateral striatum, suggesting a sensory-to-motor transformation in which the striatum is downstream of frontal cortex. We performed pharmacological inactivation studies to determine the necessity of these brain regions for this task. We found that suppressing the dorsolateral striatum, but not frontal cortex, severely disrupts responding to task-relevant stimuli, without disrupting the ability to respond. Together these data support the dorsolateral striatum, and not frontal cortex, as an essential node in the sensory-to-motor transformation of this whisker detection task.

Disclosures: A. Lam: None. **B. Zareian:** None. **E. Zagha:** None.

Poster

135. Basal Ganglia: Physiology and Function II

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 135.02

Topic: E.03. Basal Ganglia

Title: Coordinated Cortex-striatum activity dynamics throughout motor learning

Authors: O. JAIDAR*[1], T. KIM*[2], Y. ZHANG[2], E. ALBARRAN[1], M. J. SCHNITZER[2], J. B. DING[1];
[1]Neurosurg., Stanford Univ. Sch. of Med., Stanford, CA; [2]Dept. of Biol., Stanford Univ., Palo Alto, CA

Abstract: The motor cortex and the striatum are critically involved in the acquisition and execution of motor skills. Previous studies have shown that motor cortical neurons and striatal spiny projection neurons both develop stable sequential firing patterns during motor learning. However, the relationship between activity in the motor cortex and striatum to motor behavior, and how the interactions of these two brain regions evolve during the acquisition and learning of a new motor task remain unclear. Here we expressed GCaMP7f in both presynaptic cortico-striatal projection neurons and postsynaptic striatal neurons and simultaneously imaged the activities of the motor cortex and dorsolateral striatum (DLS) using a dual-axis two-photon microscope in awake behaving mice. We repeatedly imaged the same populations of neurons with single cell resolution over weeks while mice learned a wheel running task. This approach allowed us to evaluate changes in activity patterns and in the interactions between motor cortex and DLS during the acquisition and the performance of the motor task. Furthermore, we analyzed each brain region's contribution to motor performance throughout the learning process.

Disclosures: O. Jaidar*: None. **T. Kim*:** None. **Y. Zhang:** None. **E. Albarran:** None. **M.J. Schnitzer:** None. **J.B. Ding:** None.

Poster

135. Basal Ganglia: Physiology and Function II

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 135.03

Topic: E.03. Basal Ganglia

Support: ZIA AG000928

Title: Sex-specific behavioral role of glutamatergic input to aldehyde dehydrogenase 1A1-positive nigrostriatal dopaminergic neurons in mice

Authors: *K. F. CARMICHAEL, H. CAI;
Transgenic Section, Lab. of Neurogenetics, Natl. Inst. on Aging, NIH, Bethesda, MD

Abstract: A subpopulation of dopaminergic neurons (DANs) that selectively express aldehyde dehydrogenase 1A1 (ALDH1A1) are preferentially degenerated in the ventrolateral *substantia nigra pars compacta* (SNc) of patients with Parkinson's disease (PD). Despite research supporting a role of these neurons in regulating locomotor skill acquisition in mice, how their activity is regulated by presynaptic inputs remains elusive. By knocking out *Grin1*, a gene coding for a critical N-methyl-D-aspartate receptor (NMDAR) subunit, in ALDH1A1-positive (ALDH1A1+) midbrain DANs in adult mice (*Aldh1a1*$^{+/P2A\text{-}CreERT2}$/*Grin1*$^{fl/fl}$), we investigated the contribution of NMDAR-mediated glutamatergic input during open field locomotion, rotarod

motor learning, and a cost-benefit operant task. Relative to *Grin1*$^{fl/fl}$ controls, both female and male 3-4 month-old *Aldh1a1*$^{+/P2A\text{-}CreERT2}$/*Grin1*$^{fl/fl}$ mice displayed no difference in an initial investigation of open field locomotion (n=35) or rotarod motor learning (n=37). Because aging is associated with changes in nigrostriatal dopaminergic neurons, performance in a different cohort of ~1 year-old mice during open field (n=18) and rotarod (n=20) was also assessed. Again, impaired NMDAR-mediated glutamatergic input had no effect on performance during either behavior. Conversely, performance in both fixed and progressive ratio operant tasks suggests a sex-specific effect associated with impaired NMDAR-mediated glutamatergic input to ALDH1A1+ midbrain DANs in 3-4 month-old mice (n=35). While disrupting NMDAR-mediated glutamatergic input had no effect on performance in males, *Aldh1a1*$^{+/P2A\text{-}CreERT2}$/*Grin1*$^{fl/fl}$ female mice earned more rewards during both fixed and progressive ratio schedules relative to female controls. These results suggest that while impaired NMDAR-mediated glutamatergic regulation of ALDH1A1+ midbrain DANs may not comprehensively impact spontaneous locomotion or rotarod motor learning, it is associated with a female-specific increase in motivation to work for a reward. The presence of sex-specific effects on behavior highlights the importance of considering the role of sex in neurodegenerative diseases like PD.

Disclosures: K.F. Carmichael: None. **H. Cai:** None.

Poster

135. Basal Ganglia: Physiology and Function II

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 135.04

Topic: E.03. Basal Ganglia

Support: NIH R37 NS040894

Title: Deep brain stimulation (DBS) is robust to stimulation gaps of 50 ms when treating bradykinesia, but not tremor, in Parkinson's disease (PD)

Authors: *K. PALOPOLI-TROJANI[1], S. L. SCHMIDT[1], J. J. PETERS[1], D. A. TURNER[2], W. M. GRILL[1];
[1]Biomed. Engin., Duke Univ., Durham, NC; [2]Neurosurg., Med. Ctr., Durham, NC

Abstract: Constant rate DBS (ie, > 100Hz) is effective in treating motor symptoms of PD, including tremor and bradykinesia. However, the temporal pattern of stimulation remains a novel parameter space that may increase the efficiency and / or efficacy of DBS. Moreover, temporal patterns of stimulation can elucidate the mechanism of action of DBS. In intraoperative experiments, we measured the effects of two temporally non-regular patterns of stimulation on both local field potentials (LFP) in the subthalamic nucleus (STN) and motor symptoms in participants with PD (n = 20). The Institutional Review Boards at Duke University and Emory University approved the study protocol and participants gave written informed consent. Motor symptoms were monitored according to each participant's dominant symptom. Tremor (n = 7)

was measured with a hand-mounted accelerometer or bradykinesia (n = 13) was evaluated using an alternating finger tapping task (FTT). We tested five conditions: *Off*, *Low* (10 Hz), *High* (185 Hz), and two temporally non-regular stimulation patterns with geometric mean of 185 Hz (characterized by the *Absence* and *Presence* of short bursts of pulses). Analysis consisted of paired signed rank tests between *Off* and *On*. In the tremor cohort, *High* ($p = 0.0156$) and *Presence* ($p = 0.0156$) reduced tremor power compared to *Off*, while *Absence* ($p = 0.0625$) showed a trend and *Low* ($p = 0.844$) did not. No stimulation pattern had a significant effect on theta-, alpha-, or beta-band LFP power in the STN in the tremor cohort. In the bradykinesia cohort, *High* ($p = 0.000977$), *Absence* ($p = 0.000244$) and *Presence* ($p = 0.00977$) showed improved FTT performance compared to *Off*, while *Low* ($p = 0.0625$) did not. Additionally, *High* ($p = 0.00977$), *Absence* ($p = 0.0061$) and *Presence* ($p = 0.0195$) reduced beta power in the LFP compared to *Off*, while *Low* ($p = 0.438$) did not, but the reduction in bradykinesia was not correlated with a reduction in beta power ($p = 0.215$). These data suggest that DBS efficacy is maintained during stimulation gaps of up to 50 ms for bradykinesia-dominant PD. This finding can help reduce the total electrical energy delivered (TEED) during DBS while preserving clinical efficacy for bradykinesia-dominant PD, thus prolonging battery life. Conversely, DBS efficacy was not sustained during stimulation gaps of up to 50 ms for tremor-dominant PD. A previously published study (Birdno 2012) found similar results when treating essential tremor (ET) with ventral intermediate (VIM) thalamus DBS. Together, these data suggest that gaps in the stimulation pattern consistently reduce DBS efficacy when treating tremor, whether in ET with VIM thalamus target, or in PD with STN target.

Disclosures: K. Palopoli-Trojani: None. **S.L. Schmidt:** None. **J.J. Peters:** None. **D.A. Turner:** None. **W.M. Grill:** Other; Cofounder, Director and CSO of Deep Brain Innovations LLC. WMG is Director and CSO of NDI Healthcare Fund. These relationships are reported to the Conflict of Interest Committee at Duke University.

Poster

135. Basal Ganglia: Physiology and Function II

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 135.05

Topic: E.03. Basal Ganglia

Support: CRC 1451 / DFG

Title: On-off and off-on responses in dopamine substantia nigra neurons related to self-paced movement initiation and termination during open-field locomotion in mice

Authors: *D. SCHENKEL[1], M. KUHN[2], N. HAMMER[1], P. VOGEL[1], S. BETZ[1], G. SCHNEIDER[2], J. ROEPER[1];
[1]Inst. of Neurophysiol., [2]Inst. of Mathematics, Johann Wolfgang Goethe-University Frankfurt, Frankfurt, Germany

Abstract: Dopamine substantia nigra (DA SN) neurons are a major target of Parkinson disease (PD) and their loss is thought to contribute to the motor impairments in PD. Da Silva et al. (2018) demonstrated that subpopulations of DA SN neurons either increased or decreased their firing rates shortly before movement initiations. However, the functional topography of this diversity among DA neurons across the SN has not been fully characterized. We performed chronic multi-electrode recordings of pharmacologically identified DA SN neurons in awake freely-moving male C57Bl/6N mice, aged 8 - 16 weeks, while simultaneously tracking their head and body movements. Overall, our data set of n=59 (N=16) DA SN neurons was in accordance with the results by Da Silva and colleagues (2018) with about 30% of DA SN neurons (n=17/59) transiently increasing their firing rate (baseline to maximum: +5.3 ± 4.8Hz, mean ± SD) shortly before initiation of self-paced movements and also about 30% of DA SN neurons (n=18/59) transiently decreasing their firing rate (baseline to minimum: -3.6 ± 1.2Hz, mean ± SD) shortly after initiation of self-paced movement in the open field. Additionally, about one third of those DA SN neurons with transient rate increases before movement initiation (n=6/17) also showed a rate reduction with termination of these movements (baseline to minimum: -1.9 ± 1.5Hz, mean ± SD). In contrast, two thirds of DA SN neurons with transient rate reductions before movement initiation (n=13/18) significantly increased their firing rate shortly before movement termination (baseline to maximum: +3.4 ± 1.5Hz, mean ± SD). A more fine-grained topographical analysis revealed that DA neurons with transient rate reductions before movement initiation were predominantly found in the medial SN (n=11/22) compared to central SN (n=7/30). These responses were absent in the lateral SN (n=0/7). In contrast, the proportion of DA neurons with transient rate increases prior to movement initiation were more prominent in central SN (n=13/30) compared to medial SN (n=3/22) and lateral SN (n=1/7). In light of the functional topography of axonal projections of DA SN neurons (Farassat et al., 2019), our data suggest a differential involvement of distinct nigrostriatal projections in self-paced movement initiation and termination. However, definitive experiments require selective molecular tagging of distinct DA SN projections. In order to define clear behavioral phenotypes and explore their correlation to different nigrostriatal projections, we are currently establishing more detailed analyses of self-paced locomotion in the open field.

Disclosures: D. Schenkel: None. **M. Kuhn:** None. **N. Hammer:** None. **P. Vogel:** None. **S. Betz:** None. **G. Schneider:** None. **J. Roeper:** None.

Poster

135. Basal Ganglia: Physiology and Function II

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 135.06

Topic: E.03. Basal Ganglia

Support: HFSP LT000838/2020
5U19NS113201

Title: Tracing life’s arc through behavior

Authors: *D. R. LEVY, R. ANYOHA, N. HUNTER, S. R. DATTA;
Neurobio., Harvard Med. Sch., Boston, MA

Abstract: Animals exhibit age-specific motor patterns. However, whether behavioral trajectories continuously change across lifespan or crystalize during specific developmental time points remains unknown. Here we provide the first systematic characterization of the ontogeny of vertebrate behavior from weaning till death. We find, using an ethologically inspired behavioral characterization algorithm, that behavior changes continuously and systematically throughout life. Mice exhibit a stereotypical behavioral signature that can predict age within days-to-weeks. However, the rate of behavioral evolution is dynamic: the motor repertoire of juvenile mice is similar across individuals but changes rapidly over time until puberty when the rate of change significantly drops. In late adulthood the change rate drops further and age decodability decreases while the ability to predict individual identity significantly rises. When mice age, motor repertoires consolidate into consistent patterns characteristic of groups of individuals. Male and female behavior followed distinct trajectories, as female behavior remained unstable until adulthood, and exhibited a higher degree of inter-individual similarity. These results provide a unique platform for understanding the arc of species-, sex- , and individual-specific behavior and introduces a framework for studying the dynamic organization of motor circuits supporting action selection.

Disclosures: D.R. Levy: None. **R. Anyoha:** None. **N. Hunter:** None. **S.R. Datta:** None.

Poster

135. Basal Ganglia: Physiology and Function II

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 135.07

Topic: E.03. Basal Ganglia

Support: NIH NS094754
NIH MH112883

Title: Selective activation of subthalamic nucleus output quantitatively scales movements

Authors: *A. D. FRIEDMAN, H. H. YIN;
Duke Univ., Durham, NC

Abstract: The subthalamic nucleus (STN) is a diencephalic nucleus strongly connected with the basal ganglia. It is thought to suppress movement by enhancing inhibitory basal ganglia output via the indirect pathway, and disruption of STN output by deep brain stimulation (DBS) can restore movement in Parkinson's patients. However, experimental evidence for the STN's role in movement suppression is mixed, and studies of STN DBS usually rely on electrical stimulation, which cannot selectively target STN output neurons. Moreover, most studies did not measure behavior precisely during STN manipulations. Here we selectively stimulated STN projection neurons by expressing channelrhodopsin in vesicular glutamate transporter 2-positive (VGlut2+)

projection neurons in the STN. We also quantified behavior in freely moving male mice with high spatial and temporal resolution using 3D motion capture at 200 frames per second. We found that STN stimulation resulted in movements with very short latencies (10-15 ms). Unilateral stimulation quantitatively determines orientation, head yaw, and head roll in the direction ipsiversive to the stimulated STN, while stimulation of either STN quantitatively increases head pitch. Bilateral stimulation causes movement consistent with the sum of the movements caused by unilateral stimulation of each STN. Strikingly, a single pulse of light was sufficient to generate movement, and there was a highly linear relationship between stimulation frequency and movement kinematics. Elements of these effects were also caused by stimulation of mesencephalic locomotor region projecting VGlut2+ STN terminals. These results question the common assumption that STN suppresses movement; instead, they suggest that STN output can precisely specify action parameters via direct projections to brainstem regions.

Disclosures: A.D. Friedman: None. **H.H. Yin:** None.

Poster

135. Basal Ganglia: Physiology and Function II

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 135.08

Topic: E.03. Basal Ganglia

Support: R01 NS113817
P01 NS044393

Title: Differential encoding of random movement sequences in the primate globus pallidus and primary motor cortex

Authors: *D. R. HARSCH[1], W. J. LIPSKY[1], P. RICE[2], R. S. TURNER[1];
[1]Dept. of Neurobio., Univ. of Pittsburgh, Pittsburgh, PA; [2]Univ. of Washington, Seattle, WA

Abstract: Efficient execution of a motor skill often requires the concatenation of discrete movements into a sequence performed in quick succession. Prior work suggests that neurons in basal ganglia (BG) areas such as the striatum and globus pallidus (GP) are selectively active at the boundaries (i.e., beginning and end) of movement sequences. Most previous studies, however, considered over-learned sequences in which the order of component movements is fixed and known beforehand. Furthermore, animal studies typically deliver rewards only at the end of the whole sequence, thereby adding reward contingency as a factor that may account for boundary-selective activity. To advance our understanding of the BG's role in sequence production, it is necessary to use a motor sequence task that disassociates these factors.
Our task required 2 rhesus macaques to control a cursor on a screen using a joystick. The animals followed visual cues to execute 5 out-and-back motions between a center position and 1 of 8 peripheral targets, selected at random. Reward was delivered following each movement. We recorded extracellular single unit activity in arm-related regions of GP and motor cortex (M1, n=

178 and 99, respectively) while the animal performed the task.
We analyzed how well the direction and ordinal position of movements in the sequence accounted for changes in firing for each neuron using a 2-factor ANOVA. We found that 21% of recorded GP neurons showed a main effect of direction, 11% showed a main effect of sequence order, 24% showed both, and 38% did not show significant modulation by these factors. We contrast this with M1, where 57% of recorded neurons showed a main effect of direction, 7% showed a main effect of sequence position, 16% showed both, and 20% showed neither. These proportions differed significantly between GP and M1 ($p<.01$, χ^2). In GP, more neurons modulated their activity in response to both direction and sequence order than expected if the two factors were independent (43%, $p<.01$, permutation test). M1 neurons' likelihood of encoding both factors were consistent with these factors being independent. 11% of GP neurons and 23% of M1 neurons showed an interaction between direction and sequence encoding, suggesting that direction tuning is modulated by sequence encoding. Surprisingly, we found that neurons in both GP and M1 modulate their responses more during the first sequence element (Tukey test, $p<.01$). Our findings corroborate prior studies linking the BG to sequence production but also suggest roughly equal involvement of M1. Selective activation at the initiation of a random series of movements suggests that this effect is not only an effect of overlearned fixed sequences.

Disclosures: **D.R. Harsch:** None. **W.J. Lipsky:** None. **P. Rice:** None. **R.S. Turner:** None.

Poster

135. Basal Ganglia: Physiology and Function II

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 135.09

Topic: E.03. Basal Ganglia

Support: ISF 297/18

Title: Revealing neuronal encoding in the striatum using kinematic sensors

Authors: *Y. EL-HANANY[1], O. TAHARY[1], K. BELELOVSKY[1], K. LÖFFLER[2], I. BAR-GAD[1];
[1]Bar Ilan Univ., Ramat Gan, Israel; [2]Karlsruhe Inst. of Technol., Karlsruhe, Germany

Abstract: The cortico-basal ganglia-thalamic (CBGT) pathway is involved in compositing basic behaviours into complex behaviours. Thus, neuronal activity along this pathway is expected to correlate with both individual elements of behaviour and their composition. Animal Activity Recognition is a field of classifying the continuous behavioural dynamics to discrete activities which may be hierarchically aggregated. This classification is currently a major bottleneck in the analysis of animals experiments during free behaviour. Annotation of different activities is resource intensive and often biased by the annotator experience and training. Creating a common language for these activities is hindered by mixing terms relating to different levels of activity,

such as (high level) exploration and (low level) limb movement. The annotation is further complicated by the multifaceted aspects of activities, e.g. simultaneous walking and sniffing. The goal of this study is to create an automated pipeline that classifies the activities objectively with minimal human annotator involvement, thus enabling large scale detection of CBGT neuronal activity related to these activities.
We recorded neuronal activity from different parts of the CBGT pathway of freely behaving rats with concurrent recording from kinematic sensors (accelerometers, gyroscopes and magnetometers) mounted on the rat's head. We recorded from rats displaying motor tics and hyperactive behaviour following striatal disinhibition invoked by local microinjections of bicuculine and from normal controls.We used unsupervised learning to map the high-dimensional kinematic data into a low-dimensional latent space created using autoencoder. Distance metrics over the latent space reflect a similarity metric between individual activity patterns. The projected activities are subsequently clustered and assessed by randomly sampling the clusters and annotating activities.
The results display high correlation of the clusters to video observable behaviour patterns such as exploration, sniffing, head grooming, belly grooming as well as mutifaceted behaviours. Neuronal data from the dorsal and ventral striatum, recorded concurrently with the kinematic sensors, was correlated to the clustered data and the rat behaviour patterns. Kinematic sensors are widely available and thus provide important insights into behaviour and enable its breakdown into discrete activities. These activities may be used to identify neuronal patterns of behaviour and can serve as the basis for decoding the neuronal population activity in the CBGT pathway.

Disclosures: Y. El-Hanany: None. **O. Tahary:** None. **K. Belelovsky:** None. **K. Löffler:** None. **I. Bar-Gad:** None.

Poster

135. Basal Ganglia: Physiology and Function II

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 135.10

Topic: E.03. Basal Ganglia

Support: CONACYT fellowship CVU 808903
Ciencia Básica CONACyT grant 220412
Fronteras de la Ciencia CONACyT grant 2022
Fronteras de la Ciencia CONACyT grant 154039
DGAPA-PAPIIT-UNAM grant IA200815
DGAPA-PAPIIT-UNAM grant IN226517
DGAPA-PAPIIT-UNAM grant IN203420

Title: Investigating the entopeduncular nucleus contribution to ipsi/contralateral goal directed movements

Authors: *A. K. VERMA RODRIGUEZ[1], J. O. RAMIREZ-JARQUIN[2], F. TECUAPETLA[3];
[1]Insituto de Fisiología Celular, Univ. Nacional Autónoma de México, Ciudad de Mexico, Mexico; [2]Insituto de Fisiología Celular, Univ. Nacional Autónoma de México, Mexico City, Mexico; [3]Dept. de Neuropatologia, Insituto de Fisiología Celular, Univ. Nacional Autónoma de México, Mexico city, Mexico

Abstract: The entopeduncular nucleus (EPN, rodent analog of the Globus Pallidus internal segment, GPi) is one of the main outputs of the basal ganglia. It has been implicated in action evaluation via reward-related signals. As well, movement correlated activity under certain memory-dependent contexts has been suggested. Furthermore, the basal ganglia have been shown to differentially contribute to ipsilateral and contralateral decisions and movement-related variables (such as speed) in freely moving rodents. Given that studies focusing on the GPi have mostly been done in head-fixed tasks, this study intends to analyze the contribution of this nucleus to movement and decision in a freely behaving animal.
We trained mice in an auditory two-alternative forced-choice task that involved turning right or left and moving towards the reward port. The auditory stimuli were graded in difficulty such that a psychophysical curve could be obtained. The increased uncertainty in the decision increased the reaction time and decreased the speed of their movement. Preliminary analyses of recordings from the entopeduncular nucleus show activity correlated with the turn direction and angular velocity. Furthermore, there is correlation between the distance to the goal and the firing rate of certain neurons. Additionally, reward related neurons are modulated according to the difficulty of the stimulus. Finally, some neurons show correlation with the gait phase.

Disclosures: A.K. Verma Rodriguez: None. **J.O. Ramirez-Jarquin:** None. **F. Tecuapetla:** None.

Poster

135. Basal Ganglia: Physiology and Function II

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 135.11

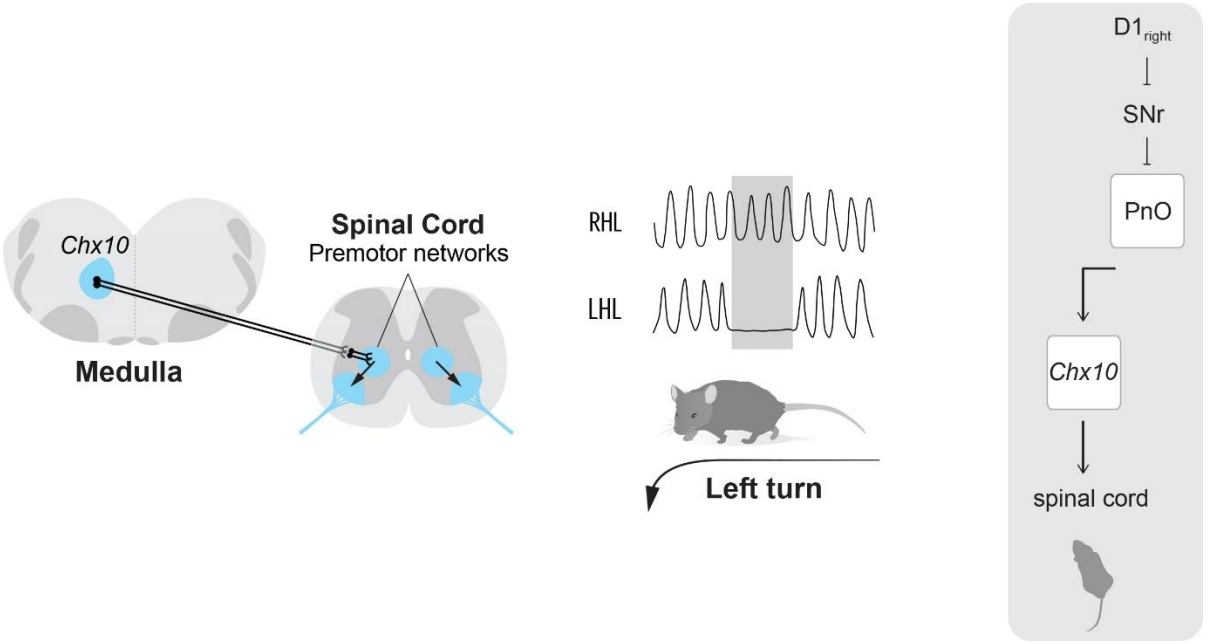
Topic: E.03. Basal Ganglia

Support: Lundbeck Foundation Postdoc Fellowship (R347-2020-2393 to J.M.C)
European Union's Horizon 2020 Research and Innovation Program (REP-SCI-693038 to O.K.)
Novo Nordisk Laureate Program (NNF15OC0014186 to O.K.)
Lundbeck Foundation Professorship (R276-2018-183 and R345-2020-1769 to O.K.)

Title: Basal ganglia-spinal cord pathway that commands locomotor asymmetries

Authors: *J. M. CREGG, S. K. SIDHU, I. ALLODI, R. LEIRAS, O. KIEHN;
Dept. of Neurosci., Univ. of Copenhagen, Copenhagen, Denmark

Abstract: Motor impairments in Parkinson's disease are caused by loss of dopamine input to basal ganglia circuits. Although the basal ganglia are important for locomotion in particular, mechanisms underlying basal ganglia control over spinal locomotor networks remain unclear. One hallmark feature of human Parkinsonism is exacerbated turning deficits which are often accompanied by falls. Chx10 gigantocellular (Gi) neurons are required for turning gait asymmetries (Cregg et al., 2020; Usseglio et al., 2020), suggesting that turning deficits in Parkinson's disease may arise via this spinal projection pathway. Using deep brainstem calcium recording in mice, we found that D1 and D2 striatal projection neurons initiate turning gait asymmetries via a dominant crossed pathway to Chx10 Gi neurons on the contralateral side. Leveraging Chx10 Gi neurons as an entry point, we used a reverse dissection approach to uncover the prinicipal basal ganglia-spinal cord pathway for locomotor asymmetries in mammals: striatal projection neurons -> substantia nigra pars reticulata (SNr) -> pontine nucleus oralis (PnO) -> Chx10 Gi neurons -> spinal locomotor networks. PnO was identified using an intersectional viral screening strategy, where a subset of PnO neurons defined by Vglut2 expression and commissural projection proved to act as the critical link between basal ganglia output and Chx10 Gi neurons. Finally, we took advantage of this pathway information to restore contralateral turning in hemi-Parkinsonian mice. Our results reveal the circuit logic underlying a critical motor program, from action commitment in the basal ganglia to execution by spinal locomotor networks.



Disclosures: **J.M. Cregg:** None. **S.K. Sidhu:** None. **I. Allodi:** None. **R. Leiras:** None. **O. Kiehn:** None.

Poster

135. Basal Ganglia: Physiology and Function II

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 135.12

Topic: E.03. Basal Ganglia

Support: Foundation for OCD Research
R01MH118369 NIMH

Title: Dopaminergic encoding of task completion in dorsal striatum

Authors: *E. DIAZ-HERNANDEZ[1], J. GALANAUGH[1], A. SANCHEZ-FUENTES[3], F. TECUAPETLA[4], M. V. FUCCILLO[2];
[2]Neurosci., [1]Univ. of Pennsylvania Neurosci. Grad. Group, Philadelphia, PA; [3]UCLA, LA, CA; [4]Dept. de Neuropatologia, Inst. De Fisiologia Celular-UNAM, Mexico city, Mexico

Abstract: The ability to complete actions is essential to life. Perturbations to the neural encoding of task completion may contribute to the manifestation of compulsive and impulsive behaviors seen in multiple neuropsychiatric disorders. The dorsal striatum has been implicated in action selection and initiation; however less is known about how this region contributes to the completion of motor sequences. Dopaminergic signaling within the basal ganglia has been implicated broadly in action initiation, and sensory and motor learning. Here we test the potential contributions of this dopaminergic signaling to the encoding of task completion in lateral and medial regions of dorsal striatum (DLS & DMS) using 2 approaches: recording DA via GRAB-DA and evaluating DA contribution using optogenetic terminal inhibition. We sought to investigate these signals in these regions with an adapted sequence completion task in mice. In this task, mice are presented with 2 levers on different walls of an operant box and are expected to complete a sequence of 4 presses on the first "sequence-lever" and report completion of this sequence on the second "report-lever" to receive reward. Preliminary results show distinct DA patterns during the sequence of lever presses, showing higher levels when the animal completes the "sequence lever" in DLS, and high levels of dopamine before the "report lever" in DMS. To test whether those signals contribute to mouse estimates of proper task completion, we used DAT-Cre mice to perform optogenetic terminal inhibition. Preliminary results show perturbations in the number of "sequence lever" presses with DLS DA-terminal inhibition but no changes for DMS DA-terminal inhibition. This work will broaden our understanding of striatal dopamine signals in guiding the completion of motor sequences.

Disclosures: E. Diaz-Hernandez: None. **J. Galanaugh:** None. **A. Sanchez-Fuentes:** None. **F. Tecuapetla:** None. **M.V. Fuccillo:** None.

Poster

135. Basal Ganglia: Physiology and Function II

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 135.13

Topic: E.03. Basal Ganglia

Support: NIH Grant U01AA025932
NIH Grant R01AA021505
NIH Grant R01AA027768

Title: Extinction depotentiates corticostriatal plasticity in dMSN ensembles to reduce relapse to alcohol seeking behavior

Authors: *X. XIE[1], T. TAN[1], J. LU[1], X. WANG[1], Y. ZHOU[2], J. WANG[1];
[1]Texas A&M Hlth. Sci. Ctr., Bryan, TX; [2]Texas A&M Hlth. Sci. Ctr., Houston, TX

Abstract: Instrumental learning requires the constant shaping of neuronal ensembles, which are groups of coactive neurons encoding memories for specific behaviors. Corticostriatal plasticity between the medial prefrontal cortex (mPFC) and the dorsomedial striatum (DMS) is known to control alcohol-seeking behavior. However, whether learning of alcohol-seeking recruits striatal dMSN ensembles ($dMSN^{ens}$) and how extinction training (Ext) affects $dMSN^{ens}$ and corticostriatal plasticity to modulate relapse are unclear. To address this, FosTRAP;Ai140;D1-tdT mice were trained to self-administer alcohol in operant chambers. $dMSN^{ens}$ were TRAPed during the acquisition or maintenance phase of operant self-administration (OSA). We observed that the maintenance phase of OSA recruited more $dMSN^{ens}$ in DMS than that during the acquisition phase. Chemogenetic inhibition of $dMSN^{ens}$ TRAPed during the maintenance phase acutely suppressed alcohol-seeking behavior. Electrophysiological recordings revealed that alcohol intake preferentially potentiates corticostriatal transmission from mPFC to $dMSN^{ens}$. Second, we employed optogenetic induction of corticostriatal LTP or LTD and assessed how such plasticity regulates operant reinforcement and memory. Intracranial self-induction of corticostriatal LTP reinforced instrumental learning. Importantly, the cue paired with such stimulation induced strong reinstatement of seeking behavior, suggesting the lasting memory formed by this LTP. Conversely, corticostriatal LTD persistently suppressed alcohol-seeking behavior and reduced the number of striatal $dMSN^{ens}$. Lastly, we examined how Ext suppressed relapse by regulating corticostriatal plasticity. Corticostriatal LTP was induced after 9-d Ext or LTD was induced after 9-d abstinence (Abs). Post-Ext LTP or post-Abs LTD enhanced or suppressed reinstatement of alcohol-seeking, respectively, suggesting that Ext depotentiates corticostriatal plasticity. As reduced plasticity may decrease activation of ensembles, we tested how Ext affects the re-activation of OSA-recruited $dMSN^{ens}$. $dMSN^{ens}$ were captured during OSA in FosTRAP mice. Animals went through 9-d Abs or Ext. Reinstatement was tested on day 10, followed by cFos staining. $dMSN^{ens}$ that were captured during the OSA were reactivated during the reinstatement, and Ext training decreased the reactivation of these $dMSN^{ens}$. These findings provide critical cellular and circuit mechanisms of striatal ensembles in alcohol use disorder, and how extinction training can reduce the relapse by affecting striatal ensembles, which provides insight for this behavioral treatment and future improvements.

Disclosures: **X. Xie:** None. **T. Tan:** None. **J. Lu:** None. **X. Wang:** None. **Y. Zhou:** None. **J. Wang:** None.

Poster

135. Basal Ganglia: Physiology and Function II

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 135.14

Topic: E.03. Basal Ganglia

Title: Effects of the optogenetic maipulation of the Striatum on the Secondary Motor Cortex activity in the working memory task

Authors: *A. STETSENKO, T. Z. KOOS;
Rutgers Univ., Newark, NJ

Abstract: The research about the interactions between different brain regions is providing more insights into how the cognitive functions such as working memory are substantiated. In particular, there is an ample body of research about the influence of the cortex on the activity of the Basal Ganglia. However, a lot of questions remain about the effects of the Basal Ganglia processing on the cortical activity. For example, the question about the known involvement of the Striatum in the working memory tasks. How does the activity of the Striatum influence the activity in the Antero Lateral Motor cortex (ALM)? In the current research, we optogenetically manipulate the Striatum and discover the effects on both the behavior and the activity of the ALM of the mouse in the context of the cued dual-choice working memory task.

Disclosures: A. Stetsenko: None. **T.Z. Koos:** None.

Poster

135. Basal Ganglia: Physiology and Function II

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 135.15

Topic: E.03. Basal Ganglia

Support: NIH Grant 2R01NS094667-06

Title: Dopaminergic reward and performance error signals are gated during courtship

Authors: *A. C. ROESER[1], V. GADAGKAR[3], P. A. PUZEREY[1], A. DAS[2], B. KARDON[2], J. H. GOLDBERG[2];
[1]Cornell Univ., [2]Cornell Univ., Ithaca, NY; [3]Columbia Univ., Columbia Univ., New York, NY

Abstract: How do social interactions affect dopaminergic (DA) responses to rewards and performance outcomes? We used electrophysiology and fiber photometry to record DA signals in two mesostriatal pathways as male songbirds sang alone and to females. When alone, singing-related performance error signals were restricted to a song-specialized mesostriatal pathway; reward prediction error signals were observed globally. When singing to a female, DA responses

to both water reward predicting cues and song performance outcomes diminished and were instead driven by female calls that occurred specifically during the male's song. Together, we discover that reward and performance error signals are differentially routed through distinct DA pathways, that DA signals dynamically change their tuning during courtship, and that an affiliative social interaction, when precisely timed, activates distinct mesostriatal DA systems.

Disclosures: **A.C. Roeser:** None. **V. Gadagkar:** None. **P.A. Puzerey:** None. **A. Das:** None. **B. Kardon:** None. **J.H. Goldberg:** None.

Poster

135. Basal Ganglia: Physiology and Function II

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 135.16

Topic: E.03. Basal Ganglia

Support: Weill Institute Innovation Award
NSF GRFP Grant
NIH Grant 5R01NS101354

Title: Alterations in striatal activity in a mouse model of tardive dyskinesia

Authors: *J. A. STANSIL, M. M. MCGREGOR, J. S. SCHOR, A. B. NELSON;
Univ. of California San Francisco, San Francisco, CA

Abstract: Antipsychotic drugs (neuroleptics) are widely used to treat psychosis and mania, as well as other conditions like Tourette's syndrome, nausea, and migraine. Chronic use of neuroleptics is limited by their tendency to induce tardive dyskinesia (TD), a movement disorder characterized by involuntary movements of the face, mouth, and upper extremities. Disruptions in dopamine signaling and striatal activity are thought to play a role in the development of TD, but it is currently unknown what alterations causally mediate the motor symptoms of TD. In this study, we investigate how changes in dopamine signaling and striatal activity contribute to the involuntary movements of TD. We used a mouse model of TD, based on chronic treatment with the neuroleptic haloperidol. This model produced robust orofacial movements during treatment, which persisted for months after treatment. To monitor striatal dopamine release *in vivo*, we expressed the fluorescent dopamine sensor, dLight1.1, and recorded activity using fiber photometry. We found that haloperidol treatment caused an increase in dopamine transient frequency that persisted for months after drug washout. To determine if this change in dopamine signaling is linked to alterations in striatal output, we then used GCaMP6s to measure cell-type specific calcium activity in striatal medium spiny neurons of either the direct (dMSN) or indirect (iMSN) pathway. Acutely, haloperidol markedly decreased dMSN activity while having a variable effect on iMSN activity. Over time, however, chronic haloperidol treatment resulted in modest increases in both dMSN and iMSN activity. To correlate neural spiking with orofacial movements on a fine timescale, we are now combining optically labeled single-unit recordings

with a head-mounted “selfie cam” in freely moving mice. Current work suggests increased activity around chewing movements in both cell types in control animals. These results show how elevated dopamine levels due to chronic haloperidol treatment leads to cell-specific changes in striatal activity, strengthening our understanding of striatal microcircuit dysfunction in TD. Together, these findings open up new avenues for circuit-based prevention and intervention.

Disclosures: **J.A. Stansil:** None. **M.M. McGregor:** None. **J.S. Schor:** None. **A.B. Nelson:** None.

Poster

135. Basal Ganglia: Physiology and Function II

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 135.17

Topic: E.03. Basal Ganglia

Support: NIH grant 1R01NS115797
NSF grant CBET-1848029
NSF grant CIF-1955981

Title: Locomotor state-dependent sensory shaping of striatal networks

Authors: *S. SRIDHAR[1], H. GRITTON[2], J. FREIRE[1], C. ZHOU[1], F. LIANG[1], X. HAN[1]; [1]Boston Univ., Boston, MA; [2]Univ. of Illinois at Urbana-Champaign, Univ. of Illinois, Urbana, IL

Abstract: The striatum receives broad cortical and subcortical inputs and is well positioned to integrate sensory and motor information during behavior. While recent studies have highlighted the intricate anatomical connections of different brain regions with the striatum, it remains largely unclear how the striatum integrates locomotion and sensory information at the network level during voluntary movement. We performed large-scale wide-field calcium imaging from individual neurons expressing the genetically encoded calcium sensor GCaMP7f in the dorsal striatum of awake mice during voluntary movement, occasionally presented with audio-visual sensory stimulation at either 10Hz or 145Hz. We found that sensory stimulation at both frequencies promoted locomotion, leading to a significant increase in the percentage of time the mice spent in movement. Individual striatal neurons exhibited large variations in their responses during locomotion, but as a population, striatal activity was strongly correlated to movement speed with bulk neural activity proceeding movement by about 300ms, confirming a causal role of the striatum in promoting movement. Striatal neurons exhibit heterogeneous responses to sensory stimulation, locomotion, or both. Interestingly, we found that movement responsive neurons were largely suppressed by sensory stimulation during locomotion, but activated during resting, highlighting a behavioral state-dependent sensory shaping of locomotor encoding at the single neuron level. Furthermore, sensory stimulation enhanced neuronal pairwise correlation selectively during resting, but not during movement. Together, these results demonstrate

locomotor state-dependent sensory modulation of striatal motor output by engaging distinct network connectivity patterns via recruitment of heterogenous neuron populations.

Disclosures: **S. Sridhar:** None. **H. Gritton:** None. **J. Freire:** None. **C. Zhou:** None. **F. Liang:** None. **X. Han:** None.

Poster

135. Basal Ganglia: Physiology and Function II

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 135.18

Title: WITHDRAWN

Poster

135. Basal Ganglia: Physiology and Function II

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 135.19

Topic: E.03. Basal Ganglia

Support: NIH Grant R21NS114816A

Title: Neural correlates of impaired interlimb coordination in Parkinson's disease

Authors: *J. CHUNG[1], I. MALIK[2], A. E. BOWER[1], C. A. KNIGHT[1,3], J. J. JEKA[1,3], J. P. MARTELLO[4], R. G. BURCIU[1,3];
[1]Dept. of Kinesiology and Applied Physiol., [2]Ctr. for Biol. & Brain Imaging, [3]Interdisciplinary Neurosci. Grad. Program, Univ. of Delaware, Newark, DE; [4]Dept. of Neurosciences, Christiana Care Hlth. Syst., Newark, DE

Abstract: Numerous functional MRI studies of Parkinson's disease (PD) have used single-limb movements as a testing paradigm to gain insight into the brain mechanisms underlying some of the main motor symptoms in PD such as bradykinesia and rest tremor. While the effect of PD on the performance of single-limb movements and associated brain activity is well documented, little is known about the neural correlates of impaired coordination in PD. Coordinated control of multi-limb movements is essential to many activities of daily living, and is impaired in PD compared to healthy, older adults. Here we present preliminary results from a study that employs a force control paradigm to study brain changes in PD during an interlimb coordination task involving non-homologous limbs (i.e., hand and foot). Study participants included 18 PD and 17 controls that were age- and gender-matched. PD patients were tested following a 12-h withdrawal from antiparkinsonian medication and on the more affected side. Motor symptoms

were assessed with the motor section of the MDS-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS-III). The tested side for controls was randomized. Inside the MRI scanner, participants performed a visually cued force production task that involved using the hand and foot to produce force simultaneously. Force demands were set at 15% of maximum voluntary contraction (MVC). While both groups were able to produce 15% of MVC, PD had a slower rate of force development and force relaxation than controls. The fMRI analysis revealed that compared to controls, PD had reduced brain activity during the interlimb coordination task in the contralateral M1 foot area and globus pallidus, and increased brain activity in the contralateral superior frontal gyrus as well as ipsilateral cerebellar lobules Crus II and VIIb. Our preliminary findings suggest that force control deficits during interlimb coordination in PD are associated with extensive functional changes that span both the basal ganglia- and cerebellar-cortical motor loops. In the context of a complex task that presents participants with an increased motor and cognitive load, it is possible that the increased prefrontal and cerebellar activity in PD may reflect a compensatory effect facilitating task performance.

Disclosures: **J. Chung:** None. **I. Malik:** None. **A.E. Bower:** None. **C.A. Knight:** None. **J.J. Jeka:** None. **J.P. Martello:** None. **R.G. Burciu:** None.

Poster

135. Basal Ganglia: Physiology and Function II

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 135.20

Topic: E.03. Basal Ganglia

Support: Swedish Medical Research Council VR-M-2019-01854
EU/Horizon 2020 no.945539 (HBP SGA3)
We acknowledge PRACE for awarding us access to Dardel hosted by the PDC Center for High Performance Computing, KTH Royal Institute of Technology, Sweden
The computations were enabled by resources provided by the Swedish National Infrastructure for Computing (SNIC) at the PDC Center for High Performance Computing, KTH Royal Institute of Technology
We acknowledge PRACE for awarding us access to Piz Daint, at the Swiss National Supercomputing Centre (CSCS), Switzerland.

Title: The impact of surround inhibition in striatum in silico

Authors: *J. FROST NYLEN[1], J. HJORTH[2], A. KOZLOV[2], I. CARANNANTE[2], W. THUNBERG[1], J. HELLGREN KOTALESKI[2], S. GRILLNER[1];
[1]Neurosci., Karolinska Inst., Stockholm, Sweden; [2]Sci. for Life Laboratory, Sch. of Electrical Engin. and Computer Sci., Stockholm, Sweden

Abstract: The striatum is the input structure of the basal ganglia, involved in motor learning, action selection and habit formation. The striatum consists of 95% striatal projection neurons (dSPNs and iSPNs) with sparse inhibitory connectivity targeting distal dendrites. The remaining 5 %, consists of mainly GABAergic interneurons, including fast spiking (FS) and low threshold spiking interneurons (LTS), which target SPNs and cholinergic interneurons which release acetylcholine. Ensembles of SPNs and interneurons are active during movement. Little is known about the importance of the intrastriatal lateral inhibition and the local inhibition on the population level. Using a large-scale network simulation up to 40k neurons (Hjorth et al 2020), we constructed networks of the striatum with biologically realistic neuron models, synaptic connectivity and appropriate cellular density and investigated the impact of dopaminergic modulation. We simulated the response of cortical and dynamic activation of striatal subpopulations and investigated the inhibitory interaction between SPNs and interneurons by ablation of connections and selective activation of ensembles of cells. We recorded the membrane potential in both somatic and dendritic compartments of dSPNs and iSPNs within the network. The effect of an activation of small spatially clustered ensembles (350 neurons) on surround inhibition was investigated including the spatial interaction between two of these ensembles. We increased the size of the spatially clustered populations to investigate the effect of larger ensembles of 40k neurons. The ablation of connections showed that the inhibitory effect within a module modified the activity of dSPN and iSPNs, which could vary markedly both in timing and strength. The inhibitory inputs onto distal dendrites of SPN modify the corticostriatal input and on a single cell level can modify plateau potentials. The inhibition from a small population decreases with distance up to 400 microns, which would mean that lateral inhibition can play a role within a module of striatum for instance the fore- or hindlimb areas. Hence, the inhibitory connections within striatum can modify both spiking activity and dendritic integration. This effect is dependent on the relative activity of the populations and the connectivity between these populations. Dopamine further modifies the relationship between these populations.

Disclosures: **J. Frost Nylen:** None. **J. Hjorth:** None. **A. Kozlov:** None. **I. Carannante:** None. **W. Thunberg:** None. **J. Hellgren Kotaleski:** None. **S. Grillner:** None.

Poster

135. Basal Ganglia: Physiology and Function II

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 135.21

Topic: E.03. Basal Ganglia

Support: NIH R01MH115030
Tourette Association of America

Title: Investigating the neural dynamics involved in action modulation

Authors: S. M. FERRIGNO[1], E. DIAZ-HERNANDEZ[2], M. F. DAVATOLHAGH[2], M. V. FUCCILLO[2];
[1]Neurosci. Grad. Group, [2]Dept. of Neurosci., Univ. of Pennsylvania, Philadelphia, PA

Abstract: One understudied endophenotype of multiple neuropsychiatric and neurodevelopmental disorders is abnormalities in the regulation of actions. The processes that regulate actions can be segregated into different aspects including action selection, initiation, and suppression, all of which have received substantial attention. However, one relatively understudied feature of action regulation includes the modulation of ongoing actions. The cortico-basal-thalamic pathway has long been implicated in the control of these distinct processes. However, it is not well understood how these circuits function to regulate ongoing action modulation. As prefrontal projections to dorsal striatum are known to be heavily involved in action planning and execution, we hypothesize that these circuits may support action modulation towards specific goals. To investigate how internal estimations guide action modulation, we have developed a novel treadmill-based operant task for head-fixed mice. The behavior requires mice to decelerate their velocity after reaching a randomized target distance, which must be estimated based on a sequence of ascending tones signifying relative progress through the task. Furthermore, using dual-site *in vivo* electrophysiological techniques, we were able to concurrently obtain single and multiunit activity from prefrontal cortical areas along with activity from dorsal striatum during these behavioral assays. Preliminary analysis has identified cortico-striatal populations selectively activated during this modulation of ongoing action. Our findings will provide valuable insight into the neural dynamics involved in the modulation of ongoing actions, which ultimately will aid in understanding the processes involved in regulating action.

Disclosures: S.M. Ferrigno: None. **E. Diaz-Hernandez:** None. **M.F. Davatolhagh:** None. **M.V. Fuccillo:** None.

Poster

135. Basal Ganglia: Physiology and Function II

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 135.22

Topic: E.03. Basal Ganglia

Support: R01 NS126391-01
DFG Walter Benjamin Fellowship

Title: Striatal Control of Spontaneous versus Sensory Evoked Movement

Authors: *J. L. KLEE, T. SIPPY;
New York Univ., New York Univ., New York, NY

Abstract: The classical model of striatal function assumes that the initiation of movements is controlled through the antagonistic action of dSPNs and iSPNs. However, accumulating

evidence from freely moving mice indicates that dSPNs and iSPNs instead act cooperatively to initiate and suppress movements. Importantly, studies showing cooperative dSPN/iSPN activity have almost exclusively focused on spontaneous, internally motivated behavior and have largely ignored situations in which movements are triggered in response to external sensory cues. Given that motor cortical areas almost exclusively project to the anterior lateral parts of the striatum (ALS) and sensory cortical areas almost exclusively project to the tail of the striatum (TS), we hypothesized that these two striatal subregions might be differentially involved in the generation of spontaneous vs sensory-evoked movements, with ALS controlling spontaneous and TS controlling sensory-evoked movements. In addition, we hypothesized that spontaneous and sensory-evoked movements might rely on differential recruitment of dSPNs and iSPNs. To test this, we developed a lever-pressing task for mice that allows us to compare activity in the ALS and TS while animals perform either spontaneous lever presses or perform lever-presses in response to auditory cues. We combined this task with cell-type-specific optogenetics and two-photon calcium imaging of dSPNS and iSPNs in the ALS and TS. We found that optogenetic activation of dSPNs in the ALS, which receives input from the forepaw area of motor cortex, increased lever-pressing during both the spontaneous, as well as the auditory-cued task phase. In contrast, we found that activation of dSPNs in the TS, which receives input from auditory cortex, only resulted in increased lever-pressing during the auditory phase of the task. iSPN activation of either the ALS or the TS had no effect on spontaneous lever-pressing, but reduced lever-pressing during the auditory phase of the task. To better understand this apparent triple dissociation between cell-type, sub-area, and task phase on movement control in the striatum, we subsequently established simultaneous two-photon calcium imaging of dSPNs and iSPNs in either ALS or TS while mice engaged in the task. Our initial results reveal a plethora of sound, movement, and reward-related responses in both striatal subregions as well as substantial changes in single-cell activity between task phases. In full, this data set will help us to comprehensively describe the function of dSPNs and iSPNs in movement control and may contribute to a significantly updated general model of striatal function.

Disclosures: **J.L. Klee:** None. **T. Sippy:** None.

Poster

135. Basal Ganglia: Physiology and Function II

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 135.23

Topic: E.03. Basal Ganglia

Support: NIH R01NS118424

Title: The Role of Dopamine and Its Target Song Basal Ganglia in Vocal Learning

Authors: ***J. QI**[1], M. MARTINEZ[2], S. N. BRUDNER[3], J. M. PEARSON[4], R. D. MOONEY[5]; [1]Duke Univ., Durham, NC; [2]Duke Univ., DURHAM, NC; [3]Neurobio., [4]Biostatistics and Bioinformatics, Duke Univ., Durham, NC; [5]Med. Ctr., Durham, NC

Abstract: The Role of Dopamine and Its Target Song Basal Ganglia in Vocal Learning Jiaxuan Qi[1], Miles Martinez[2], Samuel Brudner[1], John Pearson[1,3], Richard Mooney[1]1 Department of Neurobiology, Duke University, Durham, NC 277102 Department of Electrical & Computer Engineering, Duke University, Durham, NC 277103 Department of Biostatistics & Bioinformatics, Duke University, Durham, NC 27710Some complex motor skills, such as human speech and musical performance, are learned without external reward or punishment. The neural mechanisms that enable such internally guided forms of learning are poorly understood, partly due to the scarcity of well-documented forms of internally guided learning in animals. With special relevance to human speech learning, juvenile male zebra finches copy an adult male (tutor) song during development. Previous work has implicated dopamine (DA) release in a song-specific part of basal ganglia (the sBG), in this process of sensorimotor learning. We sought to better understand how sBG activity and, more specifically, DA signaling in the sBG affect juvenile song copying. We reversibly dialyzed either the $GABA_A$ antagonist muscimol or the D1 receptor antagonist SCH-23390 into the sBG of previously tutored juvenile male zebra finches engaged in song copying. After song copying was complete, we used an unsupervised machine learning method variational autoencoder (VAE) and an artificial neural network to relate each song rendition produced by a juvenile during sensorimotor learning to its overall song learning trajectory. Through this combination of approaches, we established that blocking sBG activity entirely prevents daily learning-related improvements in song, while blocking D1 receptors in the sBG strongly reduces these daily improvements. In ongoing experiments, we are using miniature microscopes and virally-expressed GCaMP to image singing-related activity of sBG neurons in freely behaving juvenile finches during song copying. These studies are beginning to elucidate the mechanisms by which DA signaling regulates sBG activity to drive vocal learning, thus offering insight into the role of DA and BG activity in forms of internally guided complex skill learning.

Disclosures: J. Qi: None. **M. Martinez:** None. **S.N. Brudner:** None. **J.M. Pearson:** None. **R.D. Mooney:** None.

Poster

135. Basal Ganglia: Physiology and Function II

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 135.24

Topic: E.03. Basal Ganglia

Support: NIH Grant 1RF1NS118424-01

Title: Expression of recent learning requires basal ganglia activity during juvenile song copying

Authors: *D. C. SCHREINER[1], S. N. BRUDNER[1], J. M. PEARSON[1,2,3], R. D. MOONEY[1]; [1]Neurobio., [2]Biostatistics and Bioinformatics, [3]Electrical and Computer Engin., Duke Univ., Durham, NC

Abstract: Many of our most impressive skills, from speech to musical performance, require intense practice to master, and are learned without primary reinforcement. While cortico-basal ganglia circuits are crucial for learning externally reinforced skills, their role in the learning of intrinsically motivated and sequentially organized skills is less well understood. Juvenile songbirds naturally learn to copy their tutor's song without external reinforcement. Importantly, songbirds possess a song-specialized basal ganglia nucleus (the sBG) that is necessary for song copying. However, evidence for sBG's necessity comes from relatively blunt manipulations in the juvenile or from manipulations made during adult pitch learning, which effectively reduces song learning into an externally reinforced "vocal lever pressing." We sought to test the influential, though not yet rigorously tested in the juvenile, hypothesis that *sBG activity is acutely necessary to express recently learned changes* during song copying.

A major challenge to uncovering the role of the sBG in juvenile song copying is that birdsong is high dimensional, and the juvenile can vary many song features in parallel as it learns to copy its tutor's song. To address this challenge, we apply a novel Variational Autoencoder method to render the analysis of this high dimensional song data tractable. In concert, we developed a feed forward neural network to quantify song maturity, providing an unbiased measure of song learning.

We combine these computational analyses with closed-loop optogenetic inhibition of sBG activity to uncover its role in juvenile song learning. We expressed the inhibitory opsin ArchT (or fluorophore control) in the sBG of juvenile zebra finches (20-30 days post hatch) and subsequently verified ArchT-mediated inhibition of sBG activity in vivo. Then, during song learning (~60-90 days post hatch), we optogenetically suppressed sBG activity on a random subset (~10%) of song renditions on alternating days.

In ArchT-expressing, but not control birds, we observed a significant reduction in song maturity on laser-targeted vs. control syllable renditions (-0.35±0.11 days (mean±sem) across 19 syllables/4 ArchT birds vs. +0.02±0.04 days across 6 syllables/1 control bird). This suggests that sBG activity is necessary - on a rendition-to-rendition basis - to express recently acquired learning and provides empirical support for the hypothesized contribution of sBG to juvenile song copying.

Disclosures: D.C. Schreiner: None. **S.N. Brudner:** None. **J.M. Pearson:** None. **R.D. Mooney:** None.

Poster

135. Basal Ganglia: Physiology and Function II

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 135.25

Topic: E.03. Basal Ganglia

Support: Tourette Association of America

Title: Functional anatomy of the urge to blink

Authors: *C. L. DRIGGS[1], C. A. RICHARDS[2], E. C. BIHUN[1], J. M. KOLLER[3], K. J. BLACK[4];
[1]Dept. of Psychiatry, [2]Departments of Psychiatry and Intrnl. Med., [4]Departments of Psychiatry, Neurology, Radiology and Neurosci., [3]Washington Univ. in St. Louis Sch. of Med., St. Louis, MO

Abstract: The premonitory urge to tic is an important feature of Tourette syndrome (TS), but cannot be studied directly in people without tics. Previous studies examined the urge to blink during voluntary blink suppression as a similar natural urge that can be studied in those without tics. Most prior studies assumed a shape for the time-urge curve, but we showed that self-reported urge to blink followed none of those models. Online self-reported urge severity ratings during fMRI acquisition would be a reasonable approach, but changes the nature of the task from experiencing the urge to blink to experiencing the urge while attending to and rating it. We previously validated two methods for estimating the urge to blink during one blink suppression trial based on subject-specific self-report data from other trials. Here we apply one of those methods to fMRI data acquired during a blink suppression task in 13 adults with TS and 15 control participants without tics. Based on previous literature, we hypothesized that increased urge to blink would be associated with brain activity in the insula and amygdala.
Individual participant urge predictions were derived from 10 trials of blink suppression alternating with free-to-blink periods out of the scanner, during which participants continuously rated the severity of discomfort experienced or effort required not to blink. BOLD-sensitive images were acquired during two runs each containing 4 don't-blink blocks alternating with OK-to-blink blocks. After excluding frames with excessive head motion, for each subject a general linear model computed the correlation of BOLD signal with predicted urge to blink at the same time points. The resulting beta (coefficient) images, one per person, were submitted to a second-level analysis using SPM12 to identify regions with activity correlating to the urge to blink across all participants, controlling for diagnosis, age, sex and handedness.
After false discovery rate correction for multiple comparisons, regions significantly associated with the urge to blink included R lateral and medial premotor/SMA (BA6) extending into R insula, L temporal pole (BA38), R BA 7, R putamen, L frontal eye fields (BA8), and L and R V2 (BA18). Activity in bilateral V1 was negatively correlated with the urge to blink.
Using a novel method to estimate individual-specific urge to blink during a blink suppression task in the MRI scanner, the urge to blink corresponded to signal in prefrontal cortex, including premotor cortex and supplementary motor area, and in insula. The next step will be to compare these responses between those with and without a chronic tic disorder.

Disclosures: C.L. Driggs: None. **C.A. Richards:** None. **E.C. Bihun:** None. **J.M. Koller:** None. **K.J. Black:** None.

Poster

136. Voluntary Movements: Cortex

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 136.01

Topic: E.04. Voluntary Movements

Support: Dutch Science Foundation SGW-406-18-GO-086
Dutch Technology Foundation UGT7685
ERC Advanced Grant 320708

Title: Sound over sight: Neural activity in the sensorimotor cortex during audiovisual speech perception is driven by audio rather than visual information

Authors: *A. SCHIPPERS, Z. V. FREUDENBURG, M. J. VANSTEENSEL, N. F. RAMSEY; UMC Utrecht Brain Ctr., Utrecht, Netherlands

Abstract: During communication, both the produced sounds and the visually observable movements of the speakers' mouth provide information that helps the observer to accurately perceive speech. While some studies have found increased activity in the sensorimotor cortex (SMC) during speech perception, it is not known whether this activity is driven by the audio, the visuals, or both types of information. Therefore, we investigated which aspect of speech perception may be the driving force behind the SMC activity changes. We recorded electrocorticography (ECoG) data from subdurally placed electrode grids over the SMC in three patients who were subchronically implanted prior to epilepsy surgery. ECoG electrodes had a center-to-center distance of 10 mm in one patient, and 3 mm in the two others. Patients performed a speech perception task, which included visual, auditive, and audiovisual stimuli (each repeated ten times, in random order). In each trial, a female produced the sounds Do, Re, Mi, Fa, So, La, and Ti at 1.75 second intervals. In the video condition, a video of the lower half of the female's face was shown on a computer screen, but no sound was played. In the audio condition, sound was played, but no video (a picture of the mouth in rest position was shown throughout the trial), while in the audiovisual condition both sound and video were played. We analyzed the high frequency band (HFB, 65-95 Hz) power change in the 350 milliseconds after sound and/or video onset of each stimulus. First, we identified the SMC electrodes that showed a response to speech perception by identifying the set of SMC electrodes that showed significant increases in HFB power during the audiovisual condition compared to rest. Second, to determine whether the responses of each of these electrodes were driven by either audio, visual, or both types of information, we compared HFB power during audiovisual trials to that of video-only, or audio-only trials. We found that for most electrodes the increased HFB response during audiovisual perception is primarily driven by the sound, rather than the video. However, for some electrodes both the sound and the video were found to be related to the HFB increases during audiovisual perception. While more in-depth research is needed, these results suggest that the SMC is more involved in auditive than visual aspects of speech perception.

Disclosures: A. Schippers: None. **Z.V. Freudenburg:** None. **M.J. Vansteensel:** None. **N.F. Ramsey:** None.

Poster

136. Voluntary Movements: Cortex

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 136.02

Topic: E.04. Voluntary Movements

Support: NIH R01 DC016270
NIH T32 DC013017

Title: Cortical responses to jaw and larynx perturbations during speech production in Parkinson's disease: A preliminary fMRI analysis

Authors: *J. L. MANES, J. A. TOURVILLE, E. KEARNEY, A. NIETO-CASTANON, B. G. HOLLAND, J. S. KIM, F. H. GUENTHER;
Boston Univ., Boston, MA

Abstract: During speech production, online somatosensory feedback of speech effectors can be used to detect and correct movement errors. For individuals with Parkinson's disease (PD), impaired somatosensory feedback of the jaw and larynx may interfere with the detection of online sensory errors during speech production. Prior fMRI research in healthy adults demonstrated that jaw somatosensory feedback errors are processed in bilateral ventral postcentral gyrus (PostCG) and supramarginal gyrus (SMG). However, somatosensory perturbations of the larynx have not yet been studied using fMRI. In the present study, we investigated BOLD responses to both jaw and larynx somatosensory speech perturbations in individuals with PD (n=5) and age-matched healthy controls (HC; n=6). Participants read aloud words ('bed', 'bet', 'beck', 'beg', or 'ben'), prolonging the /ɛ/ vowel for ~1.5s. On a subset of trials, we unexpectedly displaced the position of either the jaw (inflating a balloon between the teeth) or larynx (inflating a balloon against the laryngeal prominence) during vowel production. Speech-shaped noise was played simultaneously over headphones at 85 dbA to mask auditory feedback and increase reliance on somatosensory feedback. Participants completed 50 trials each of a) unperturbed speech, b) jaw-perturbed speech, and c) larynx-perturbed speech. To test the prediction that somatosensory perturbations of the jaw and larynx lead to increased BOLD activation in the ventral PostCG/SMG, we first performed pooled analyses of PD and HC groups comparing jaw-perturbed vs. unperturbed speech and larynx-perturbed vs. unperturbed speech (two-tailed t-test; voxel $p<0.001$; cluster $pFDR<0.05$). The results of our pooled analyses showed that: 1) jaw-perturbed speech led to increased cortical activation bilaterally in ventral PostCG, and 2) larynx-perturbed speech led to increased cortical activation in the right parietal operculum and left dorsal PostCG. To test whether individuals in the PD group had attenuated BOLD responses to jaw and larynx perturbations, we then compared group effect sizes within each significant cluster (two-sample t-test, $\alpha=0.05$). The effect sizes for perturbed vs. unperturbed speech contrasts were slightly lower in the PD group across all clusters; however, no statistically significant group differences were found. Preliminary results of our pooled analyses are in line with prior fMRI data of jaw perturbations and provide the first look at BOLD responses to laryngeal perturbations during speech. Further analysis with a larger sample size will shed light on potential group differences.

Disclosures: **J.L. Manes:** None. **J.A. Tourville:** None. **E. Kearney:** None. **A. Nieto-Castanon:** None. **B.G. Holland:** None. **J.S. Kim:** None. **F.H. Guenther:** None.

Poster

136. Voluntary Movements: Cortex

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 136.03

Topic: E.04. Voluntary Movements

Support: University of Toronto
Ontario Research Fund
Canadian Foundation for Innovation
National Sciences and Engineering Research Council

Title: From mouth to hand: how preparing to say particular syllables can delay hand grip reaction time

Authors: *J. HAJJ, L. TREMBLAY;
Univ. of Toronto, Univ. of Toronto, Toronto, ON, Canada

Abstract: Given the neurophysiological relationships between mouth and hand movements (e.g., Babkin reflex) an overlap between neural representations of processes that plan the movement of phonation organs (e.g., tongue) and hand grips is said to exist. If mouth-hand facilitation mechanisms exist, they could have important ramifications for the design of upper-limb (and speech) training and rehabilitation approaches. Vainio et al. (2013) suggested that planning the syllable /ti/ in comparison to /ka/ can facilitate the initiation of a compatible hand grip (i.e., a precision grip) and interfere with the initiation of an incompatible hand grip (i.e., a power grip). As well, they suggested that planning the syllable /ka/ in comparison to /ti/ can facilitate and interfere with the initiation of a power and precision grip, respectively. However, hand grip initiation facilitation could only be confirmed if the planning of said syllables on the initiation of hand grips yields shorter reaction times than when hand grips are performed alone (i.e., without planning a syllable). Further, it was deemed important to delineate effects of syllable planning vs. execution on the initiation of hand grips. Thus, in the current study, participants underwent three separate conditions. In the Silent Reading condition, participants read the syllable /ti/ or /ka/ before initiating a precision or power grip. In the Verbalization condition, participants verbalized the syllable /ti/ or /ka/ while concurrently initiating a precision or power grip. In the Grip Alone condition, participants initiated a precision or power grip (without planning to produce a syllable). For both the Verbalization and Silent Reading conditions, it was found that the syllable /ti/ interfered with the initiation of a power grip relative to when the power grip was performed alone, while the syllable /ka/ did not produce such interference. In contrast, the syllable /ka/ interfered with the initiation of a precision grip relative to when the precision grip was performed alone, while the syllable /ti/ did not produce such interference. Critically, while these findings can corroborate the idea that the syllable /ti/ and /ka/ are compatible with precision and power grips, respectively, they do not facilitate hand grip initiation. Overall, producing verbalizations/sounds during actions (e.g., tennis) could either interfere or not with upper-limb movements, but will unlikely facilitate the initiation of such actions.

Disclosures: J. Hajj: None. **L. Tremblay:** None.

Poster

136. Voluntary Movements: Cortex

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 136.04

Topic: E.04. Voluntary Movements

Title: Hd-tdcs of right prefrontal cortex differently modulates p3 for speech vs. limb movement inhibition

Authors: *K. JOHARI[1], J. I. BERGER[2];
[1]Louisiana State Univ., Louisiana State Univ., Baton Rouge, LA; [2]Univ. of Iowa, Iowa city, IA

Abstract: Adaptive control of speech and limb movements is a crucial aspect of many activities in daily life, which is often affected in neurological conditions. There is some evidence to suggest that speech production and limb movement are subserved by common neural substrates. However, less is known about whether they are supported by a common inhibitory network. Studies probing spatiotemporal dynamics of motor inhibition using electroencephalography (EEG) suggest that the P3 event-related potential (ERP) recorded from frontal electrodes is a neural marker of motor inhibition. In addition, multiple brain networks have been identified as possible sources of the P3, including right prefrontal cortex and bilateral cingulate. It is unknown whether there are differences in the contribution of these regions for speech compared to limb movement inhibition. To address these gaps, we stimulated right dorsolateral prefrontal cortex using high-definition transcranial direct current stimulation (HD-tDCS) in 21 healthy subjects, and subsequently recorded ERPs from high-density EEG while they were performing two different Go/No-Go tasks. Subjects were instructed to either vocalize a speech sound or press a button in response to a Go cue and withhold their responses following No-Go cues (thus requiring inhibitory control). Experimental data were collected in two counterbalanced sessions (cathodal or sham). Results showed both speech and limb No-Go tasks elicited prominent P3 responses over frontocentral and central electrodes. Across subjects, cathodal HD-tDCS significantly increased the amplitude of P3 for speech vs. limb inhibition over frontocentral electrodes, whereas there was no significant difference between P3 ERPs following sham stimulation. Spatiotemporal clustering of source-localized EEG data recorded during the tasks following cathodal HD-tDCS showed remarkably stronger activation over bilateral anterior cingulate and right prefrontal cortex, for speech inhibition compared to limb movement inhibition at the time of the P3, an effect which was not present for sham. These findings suggest that the right prefrontal cortex and anterior cingulate are part of an amodal network for motor inhibition, and the larger response for speech vs. limb movement inhibition indicates that cathodal HD-tDCS facilitates the allocation of more neural resources to suppress motor plans in more cognitively demanding tasks, such as in speech compared to limb movement. These findings have translational implications for conditions such as Parkinson's disease, wherein control of speech and limb is often highly impaired.

Disclosures: K. Johari: None. **J.I. Berger:** None.

Poster

136. Voluntary Movements: Cortex

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 136.05

Topic: E.04. Voluntary Movements

Title: Beta Band Auditory Stimulation Affects Speech Production Processes in Healthy Subjects

Authors: F. NEVISIZADEH[1], ***M. AHMADI PAJOUH**[1], A. DALIRI[2];
[1]Biomed. Eng, Amirkabir Univ. of Technol., Tehran, Iran, Islamic Republic of; [2]Speech and Hearing Science, Col. of Hlth. Solutions, Arizona State Univ., Tempe, AZ

Abstract: Binaural Beets Stimulation (BBS) is a non-invasive brain stimulation technique. This technique applies auditory stimuli with different frequencies to the left and right ears to induce brain entrainment at a frequency equivalent to the difference between the frequencies of the auditory stimuli. We recently showed that BBS at the Theta band (4–8 Hz) changes functional connectivity in temporal and parietal cortices, suggesting that BBS can induce lasting effects on neural processes. In the present study, we examined the impact of BBS at the Beta band (12–30 Hz) on neural processes underlying speech planning and production. A large body of literature suggests that oscillations at the Beta band are neural correlates of speech movement planning and production. We recruited 28 healthy adults: 14 subjects (7 males, age: 21.9±2.1 years) received Beta BBS (i.e., stimulation group), and 14 subjects (8 males, age: 21.1 ±0.9 years) received sham BBS (i.e., control group). The stimulation group received 9-minutes long Beta BBS, and the control group received 9-minutes long sham stimulation (silence). For examining the effects of stimulation on speech production, all subjects completed a speaking task in the context of a reaction time paradigm. Subjects completed two blocks of the speaking task before and after the BBS or sham stimulation. The speaking task consisted of 70 words (35 1-syllable and 35 3-syllable words). We collected EEG and EMG signals during the experiment. We used the EEG signals to calculate Event-Related Potentials (ERPs) time-locked to the onset of the presentation of words. Examining the reaction time data, we found that the reaction time of the stimulation group was statistically significantly decreased after receiving the Beta BBS ($p = 0.014$); however, this was not the case for the control group. We also found that the extent of the effect was the largest for 3-syllable words ($p = 0.008$). We used the ERP data to calculate the amplitude of two ERP components: N100 and P200. We found that N100 ($p = 0.045$) and P200 ($p = 0.04$) amplitudes changed after the Beta BBS and the change was the largest for the 3-syllable words ($p = 0.004$). Overall, these preliminary results indicated that the Beta BBS has lasting behavioral and neural effects on speech planning and production. These findings may be used to develop novel therapeutic techniques to improve neural processing of speech production in individuals with acquired or developmental speech disorders.

Disclosures: F. Nevisizadeh: None. **M. Ahmadi Pajouh:** None. **A. Daliri:** None.

Poster

136. Voluntary Movements: Cortex

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 136.06

Topic: E.04. Voluntary Movements

Support: NIDCD Grant R01DC017439

Title: Somatosensory cortex causally contributes to speech motor learning

Authors: *M. K. FRANKEN[1], T. F. MANNING[1], A. WILLIAMS[1], D. J. OSTRY[1,2];
[1]McGill Univ., Montreal, QC, Canada; [2]Haskins Labs., New Haven, CT

Abstract: Speakers readily adapt their articulation to perturbations of auditory feedback. It is thought that this sensorimotor adaptation relies on the discrepancy between actual sensory feedback and the movement's sensory objective. However, the neural mechanisms that support speech motor learning are poorly understood. There is accumulating evidence that the somatosensory system participates in motor learning. For example, facial skin stretch can alter speech motor learning. The current study tests whether the somatosensory cortex plays a causal role in speech motor learning. The hypothesis is that if a brain area participates in speech motor learning, then disruption of its activity prior to a learning task will either reduce learning or eliminate it altogether. Participants uttered words like 'head', containing the vowel /ɛ/. During speech production, participants received real-time auditory feedback through headphones. After baseline productions, auditory feedback was manipulated such that the first formant frequency was shifted up by 30%, thus shifting /ɛ/ towards /æ/ (e.g., 'had'). Typically, speakers compensate for altered feedback by changing their articulation in the opposite direction. Participants performed this adaptation task after continuous theta burst stimulation, which was used to disrupt activity in tongue area primary somatosensory cortex or primary motor cortex. Results to date show that while participants showed speech motor learning after vertex stimulation, stimulation of somatosensory cortex blocked motor learning, suggesting that tongue area somatosensory cortex causally contributes to speech motor learning. Adaptation was unaffected after stimulation of primary motor cortex, suggesting that the disruption of learning after stimulation of somatosensory cortex was not mediated by current spread to motor cortex. This pattern of results was replicated in a separate experiment, where participants produced fricative sounds that involved lip movements. Participants in a control group showed adaptation, but stimulation of lip area primary somatosensory cortex blocked speech motor learning. Together, these results show that somatosensory cortex causally contributes to speech motor learning, in line with recent evidence that motor learning is at least partially driven by the somatosensory system. In addition, this pattern of results holds across articulators. The current results show that for learning driven by altered auditory feedback, the somatosensory system may be crucial for updating the memory of the adaptive motor commands and their associated somatosensory representations.

Disclosures: M.K. Franken: None. **T.F. Manning:** None. **A. Williams:** None. **D.J. Ostry:** None.

Poster

136. Voluntary Movements: Cortex

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 136.07

Topic: E.04. Voluntary Movements

Support: R01 DC019354
R01 DC015260
Simons Collaboration on the Global Brain

Title: Transient speech planning deficits resulting from perturbations to specific cortical sites

Authors: *G. A. CASTELLUCCI[1], C. K. KOVACH[2], J. D. GREENLEE[2], M. A. LONG[1]; [1]Neurosci. Inst., NYU Sch. of Med., New York, NY; [2]Neurosurg., Univ. of Iowa, Iowa City, IA

Abstract: The neural circuitry underlying spoken language planning is poorly understood. Using primarily noninvasive recording methodologies, several structures in frontal, temporal, and parietal cortices have been associated with the preparation of speech; however, whether these candidate structures are required for such planning remains unclear. In previous work using intracranial electrocorticography, we identified a spatially and functionally segregated cortical network centered on caudal inferior and middle frontal gyri which was active during the planning of spoken responses in conversational turn-taking (Castellucci *et al.*, 2022). To test whether these regions are critical to language planning, we used intracranial direct cortical stimulation to perturb neural activity in neurosurgical patients performing an interactive speech task. In multiple patients, we observed that stimulation of the planning network resulted in protracted planning times and speech errors. Furthermore, we found that these putative planning-critical loci were anatomically distinct from speech arrest sites and speech motor sites - where stimulation instead results in a failure to initiate speech or properly move the vocal tract, respectively. In sum, these results suggest that we have isolated cortical circuitry that is 1) selectively and causally related to language planning and 2) distinct from other classes of speech-critical sites that have been previously identified using neural perturbation techniques.

Disclosures: G.A. Castellucci: None. **C.K. Kovach:** None. **J.D. Greenlee:** None. **M.A. Long:** None.

Poster

136. Voluntary Movements: Cortex

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 136.08

Topic: E.04. Voluntary Movements

Title: Revealing the neural sub-processes that link speech perception and production with unsupervised decomposition

Authors: *A. M. EARLE-RICHARDSON[1,2], D. G. SOUTHWELL[3,4,5], S. R. SINHA[1,5], M. VESTAL[3,5], E. THOMPSON[3,5], C. R. MUH[3,6], M. ZAFAR[1,6,5], G. B. COGAN[1,7,8,5]; [1]Neurol., [2]Biomed. Engin., [3]Neurosurg., [4]Neurobio., [5]Comprehensive Epilepsy Ctr., [6]Pediatrics, [7]Ctr. for Cognitive Neurosci., [8]Psychology and Neurosci., Duke Univ., Durham, NC

Abstract: While typically studied as separate processes, speech perception and production are intrinsically linked in the brain. Evidence for this comes from conduction aphasia (CA) patients with intact speech comprehension and production but deficits with repetition. While traditional models propose a single pathway as the anatomical locus of this linkage, there is evidence that CA cannot be attributed to any one neuroanatomical substrate (Buchsbaum, 2011). Furthermore, there is no one-to-one mapping of sound properties in speech perception to motor properties in speech production (Liberman, 1967). This suggests multiple parallel pathways and neural sub-processes orchestrate the link between speech perception and production (Hickok, 2022). We therefore sought to investigate these neural sub-processes using a method with high spatio-temporal precision: intracranial recordings. We collected data from 33 subjects undergoing intracranial monitoring for surgical treatment of epilepsy (mean age = 31, 18 female). Subjects performed a repetition task where they listened to a single word or sentence that they repeated after a delay, mimed after a delay, or passively listened to (270 trials). Statistical significance of the high gamma response (HG, 70-150 Hz) for each time point on each electrode served as an index of local neural computation (cluster-corrected at $p < 0.05$). We first replicated previous results (Cogan et al. 2014, 2017) by showing distinct auditory (AUD - 163 electrodes), production (PROD - 553), and sensory-motor responses (electrodes with both auditory and production responses: SM - 235). We next investigated the morphology of neural sub-processes by performing a novel unsupervised decomposition of the spatio-temporal profile of HG responses within each electrode category. Results from SM electrodes revealed four distinct components that overlap in time with perception and production processes: a primarily visual response to the instruction/go cue (localized to the occipital and inferior temporal cortex), an early auditory response that also peaked during late production (posterior superior temporal cortex), a later auditory response that also peaked at pre/early production (pre/motor and parietal cortex), and a working memory component that showed sustained higher HG delay activation in the repetition vs. passive listen condition (prefrontal, parietal, and superior temporal cortex). Our results show that speech repetition can be broken down into neural sub-components, which supports the overarching hypothesis that the link between speech perception and production is supported by multiple parallel pathways and neural sub-processes.

Disclosures: A.M. Earle-Richardson: None. **D.G. Southwell:** None. **S.R. Sinha:** None. **M. Vestal:** None. **E. Thompson:** None. **C.R. Muh:** None. **M. Zafar:** None. **G.B. Cogan:** None.

Poster

136. Voluntary Movements: Cortex

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 136.09

Topic: E.04. Voluntary Movements

Support: MOST 110-2314-B-A49A-518 -MY3

Title: Prefrontal cortex is associated with adaptation to inference during mastication - a cross-sectional investigation using voxel-based morphometry

Authors: *C.-S. LIN[1], Y.-C. CHEN[1], T.-C. CHEN[2];
[1]Dept. of Dent., Natl. Yang Ming Chiao Tung Univ., Taipei, Taiwan; [2]Dept. of Stomatology, Taipei Veterans Gen. Hosp., Taipei, Taiwan

Abstract: Background: Neuroimaging studies reveal that brain activation of the sensorimotor area is associated with mastication of standardized food. However, in daily life, individuals need to adapt to changes in oral conditions. For example, after receiving treatment, dental patients need to adapt to their oral conditions for chewing. Until now, there have been few standardized methods for quantifying individual differences in masticatory adaptation and its underlying brain mechanisms have remained unknown. Aims and hypotheses: We aim to test the validity of a new masticatory perturbation task (MPT), which assesses the masticatory performance under an interference. We hypothesize that the MPT performance is associated with structural brain features of motor and prefrontal areas, which play a key role in sensorimotor control and learning. Methods: Healthy adult volunteers were recruited and performed standardized assessments of masticatory performance in two conditions: without perturbation (WoP, by chewing a piece of fruit chew) and with perturbation (WP, by concurrently chewing the fruit chew and a section of paper straw used to perturb normal chewing. Masticatory performance was quantified using the variogram method and calculated respectively for WoP and WP conditions. Gray matter volume was quantified based on T1-weighted structural brain images, using voxel-based morphometry (VBM). Results: 21 healthy volunteers (female:male=9:12, aged 33.9±16.7 years [mean±standard deviation]) were recruited in this preliminary study. The paired t-test revealed a statistically significantly higher variogram score (i.e., worse masticatory performance) in WP (88.3±13.1) compared to WoP conditions (80.6±9.0) (two-tailed $p=0.005$). The scores of both conditions were significantly correlated (Pearson's $r=0.54$, two-tailed $p=0.012$). The VBM analysis revealed that the variogram scores from the WP condition were associated with the gray matter volume at the right middle frontal lobe ([33,44,30], 117 voxels, $z=3.6$) and the left primary motor cortex ([-59, 0,35], 53 voxels, $z=3.4$) (uncorrected $p<0.001$, controlled for sex, age, and total intracranial volume). Conclusion: Our novel findings suggest that MPT is a valid method for quantifying the effect of interference on chewing. Structural variation in motor and prefrontal areas may be associated with individual differences in masticatory adaptation under the interference of chewing.

Disclosures: C. Lin: None. **Y. Chen:** None. **T. Chen:** None.

Poster

136. Voluntary Movements: Cortex

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 136.10

Topic: E.04. Voluntary Movements

Support: KAKENHI #19H01002 to T.N.

Title: Prefrontal and premotor projections to periaqueductal gray vocalization region of macaques

Authors: *S. MIYACHI, A. KANEKO, K. NAKAMURA, T. NISHIMURA;
Ctr. for the Evolutionary Origins of Human Behavior, Kyoto Univ., Inuyama, Japan

Abstract: Periaqueductal gray (PAG) is a center for vocalization, especially for the initiation of natural species-specific calls in many species. To elucidate the anatomical basis of the cortical control of natural vocalization, we injected neuronal tracers into the vocalization region of the PAG of two rhesus macaques, and examined the distribution of the retrogradely labeled neurons in the prefrontal and premotor cortices. Before tracer injections, the vocalization region of the PAG was searched by electrical stimulation. In accordance with previous reports, vocalization was elicited by stimulation of the lateral to dorsolateral portion of caudal PAG. After the electrophysiological mapping, a retrograde tracer (cholera toxin B) was injected into the vocalization region using a microsyringe that holds a Teflon-coated tungsten wire for recording/stimulation. In one monkey, another tracer (cascade blue dextran) was injected into an oculomotor region ventral to the PAG. After injections into the PAG vocalization region, many neurons were labeled in the dorsolateral prefrontal cortex (DLPFC: areas 9, 9/46, and 46d) and the cingulate cortex (ACC: areas 32, 24, and 25). In the ventrolateral region (VLPFC), area 12/47 was well labeled, but area 45 was devoid of neuronal labeling. A distinct cluster of neurons were labeled in area 44. Labeled neurons were also found in the orbitofrontal cortex (OFC: mainly area 13). A few neurons were labeled in area 8. More caudally, the neuronal labeling was observed mainly in the dorsal premotor cortex (PMd, F7) and the ventral premotor cortex (PMv, ventral bank of the arcuate spur, F4/F5). A smaller number of neurons were labeled in the medial bank (F6). From the oculomotor region, like in the cases of PAG, neurons were labeled in the ACC and OFC. The labeled neurons in the DLPFC were much fewer. In the VLPFC, neuronal labeling was found only in area 12/47. Caudally, neurons were labeled in areas F6 and F7, but few neurons were labeled in the PMv. The current data suggest that area 44 and PMv as well as the DLPFC would have important roles in initiation of natural vocalization.

Disclosures: S. Miyachi: None. **A. Kaneko:** None. **K. Nakamura:** None. **T. Nishimura:** None.

Poster

136. Voluntary Movements: Cortex

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 136.11

Topic: E.04. Voluntary Movements

Support: French National Research Agency under Grant Agreement No. ANR- 16- CE19-0005-01 (Neuromeddle)
European Union's Horizon 2020 Research and Innovation Programme under Grant Agreements No. 732032 (BrainCom), No. 696656 (GrapheneCore1), No. 785219 (GrapheneCore2), No 881603 (GrapheneCore3)
financial support by the Bertarelli Foundation, the Wyss Center for bioand Neuroengineering (Grant No. W015-2016)
European Union's Horizon 2020 Research and Innovation Programme under the Marie Skłodowska-Curie grant agreement no. 665667
SNSF National Center of Competence in Research (NCCR) in Robotics

Title: Cortical dynamics underlying vocal production: a comparison between humans and minipigs

Authors: *M. LION[1], M. KHOSH-NEVIS[1], C. ZENGA[1], M. PALMA[1], S. KEFS[2], I. GABELLE-FLANDIN[2], F. FALLEGGER[3], A. TROUILLET[4], S. P. LACOUR[5], C. HERFF[6], P. KAHANE[7], S. CHABARDÈS[7], B. YVERT[1];
[1]Univ. Grenoble Alpes, Inserm, U1216, Grenoble Inst. Neurosciences, Grenoble, France; [2]CHU Grenoble Alpes, Clinique Universitaire de Cancérologie-Radiothérapie, Grenoble, France; [3]École Polytechnique Fédérale De Lausanne, Geneve, Switzerland; [4]Ecole Polytechnique Fédérale de Lausanne, Geneva, Switzerland; [5]Swiss Federal Inst. of Technol., Lausanne, Switzerland; [6]Fac. of Health, Med. and Life Sci., Maastricht Univ., Aachen, Germany; [7]CHU Grenoble Alpes, Dept. of Neurosurg., Grenoble, France

Abstract: Vocal production pathways of non-human primates show strong similarities with those of speech in humans. However, the extent to which they can generalize to non-primate mammals still remains an open question. Here, we developed a new paradigm to investigate this question in miniature pigs, which are social and domestic animals easy to handle and producing spontaneously different vocalizations. Three female Aachner minipigs were chronically implanted with surface ECoG grids over their left hemisphere, covering motor, premotor and/or frontal areas. Cortical activity and vocalizations of these animals were recorded synchronously in a freely moving environment with a wireless system during the production of grunts, which are the most common type of vocalization for the minipig. In one animal implanted over the motor and premotor regions a vocal-evoked cortical potential was observed initiating 45 ms before vocal onset and lasting beyond vocal offset, demonstrating the involvement of motor regions in spontaneous vocalizations. In two animals implanted with larger grids, a slow LFP activity in the inferior frontal region was detected, starting on vocal onset and ending after the end of the vocalization. Interestingly, a similar activity was also detected. Data from two different patients were analysed, one implanted with intracranial EEG electrodes and the second one with a large ECoG covering the left hemisphere. Patients were asked to read sentences aloud and cortical activity was recorded simultaneously with their voice signal. A slow LFP was found on intracranial electrodes in the insular cortex and on ECoG contacts covering this region. These results suggest the existence of similar cortical activity patterns between humans and minipigs, a non-primate species, that we propose as a new model for the study of vocal cortical networks.

Disclosures: **M. Lion:** None. **M. Khosh-Nevis:** None. **C. Zenga:** None. **M. Palma:** None. **S. Kefs:** None. **I. Gabelle-Flandin:** None. **F. Fallegger:** Other; hold various patents in relation with the present work and are cofounder of Neurosoft Bioelectronics SA. **A. Trouillet:** None. **S.P. Lacour:** Other; hold various patents in relation with the present work and are cofounder of Neurosoft Bioelectronics SA. **C. Herff:** None. **P. Kahane:** None. **S. Chabardès:** None. **B. Yvert:** None.

Poster

136. Voluntary Movements: Cortex

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 136.12

Title: WITHDRAWN

Poster

136. Voluntary Movements: Cortex

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 136.13

Topic: E.04. Voluntary Movements

Support: The Intramural Research Program of the National Institutes of Health, NINDS

Title: Behavioral defects in mice with human GNPTAB stuttering mutations: Hyperactivity, Initiations, and Interruptions

Authors: *M. WEINHOLD[1], S. SHEIKHBAHAEI[2];
[1]Natl. Inst. of Neurolog. Disorders and Stroke, Rockville, MD; [2]NINDS, NIH, Rockville, MD

Abstract: Developmental stuttering is a speech disorder that affects 70 million people worldwide, often conferring lifelong social and occupational difficulties to the individual. While the vocalization defects of the disorder are well known, our understanding of the neurobiology and motor deficits of stuttering remain under-characterized. In addition, stuttering has a high co-morbidity with Attention-deficit/hyperactivity disorder (ADHD) and fine motor movements deficits, which further suggest that stuttering might be a disorder of the basal ganglia. It is also proposed that movement deficits and stuttering may share a common pathophysiology (i.e., a dysfunction in the basal ganglia or its immediate connections). Here, we present our findings on the motor behavioral deficits in mice engineered with the *GNPTAB* stuttering gene. We uncover deficits related to overall activity levels and stereotyped, sequential behaviors, which we catalog as hyperactivity, initiations, and interruptions. There was a significantly higher activity level (48 ± 7 in Gnptab-mutant vs 23 ± 7 in control, $p = 0.007$, unpaired t test, n = 6 per experimental

group) among Gnptab-mutant mice, both in total distance traveled and average velocity, mirroring the high comorbidity between stuttering and ADHD in humans. We also observed a difference ($p < 0.001$) between the time required to initiate a grooming bout (median = 6 s in Gnptab-mutant vs. median = 2 s in control ($p < 0.001$, Mann-Whitney test, n = 12 per experimental group). Finally, we found that Gnptab-mutant mice exhibited more frequent grooming bouts (4.0 ± 0.6 in Gnptab-mutant vs 2.5 ± 0.6 in control, $p = 0.012$, unpaired t test, n = 12), with existing grooming bouts more frequently interrupted. These results may help with characterization of the role *Gnptab* plays in stuttering, as well as developing an understanding of other motor deficits in people who stutter.

Disclosures: **M. Weinhold:** A. Employment/Salary (full or part-time):; National Institute of Neurological Disorders and Stroke. **S. Sheikhbahaei:** A. Employment/Salary (full or part-time):; National Institute of Neurological Disorders and Stroke.

Poster

136. Voluntary Movements: Cortex

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 136.14

Topic: E.04. Voluntary Movements

Support: NIH/NIDCD R01-DC018523
NIH/NIDCD K01-DC015831
NIH/NIDCD P50-DC014664
NIH/NIDCD R21-DC014170

Title: Neural oscillatory correlates of vocal sensorimotor impairment in post-stroke aphasia

Authors: *R. BEHROOZMAND[1], K. SARMUKADAM[2], J. FRIDRIKSSON[2];
[1]Univ. of South Carolina, Univ. of South Carolina, Irmo, SC; [2]Univ. of South Carolina, Univ. of South Carolina, Columbia, SC

Abstract: There is emerging evidence for the impairments of lower-level vocal sensorimotor mechanisms contributing to deficits in speech and language production in stroke survivors with aphasia. Following the dual-stream model, damage to predominantly left-lateralized dorsal networks have been shown to result in reduced accuracy for speech error detection and diminished motor compensatory responses to auditory feedback alterations. In the present study, we used an altered auditory feedback (AAF) paradigm to investigate the neural oscillatory correlates of vocal sensorimotor impairment in 34 subjects with aphasia and 46 neurologically intact controls. Electro-encephalography (EEG) signals were recorded during steady vocalizations of the speech vowel sound /a/ while randomized pitch-shift stimuli were delivered to the online auditory feedback (±100 cents, 200 ms, onset time: 750-1250 ms). Event-related spectral power (ERSP) of neural activities were extracted in response to the onset of vocalization and pitch-shift stimuli using the Morlet wavelet within theta (4−8 Hz), alpha (8−13 Hz), low-

beta (13−20 Hz), high-beta (20−30 Hz), and gamma (40−80 Hz) frequency bands, separately. Results indicated aberrant modulations of neural responses in aphasia as indexed by reduced re-synchronization of theta and reduced de-synchronization of alpha, low-beta, high-beta band oscillations before and after vocalization onset under normal auditory feedback (NAF). In contrast, aphasia subjects showed increased gamma re-synchronization in response to NAF. For responses to AAF, neural re-synchronization was reduced in aphasia within the theta band whereas for the alpha band, re-synchronization of neural activities was stronger in both the aphasia and control groups in different electrode distributions. For the low-beta band, stronger neural re-synchronization was observed in aphasia within an earlier time window; however, neural responses were more strongly de-synchronized in a later time window in aphasia compared with controls. In the high-beta band, neural de-synchronization was stronger in controls. No significant gamma-band modulation was observed for responses to AAF pitch-shift stimuli between the aphasia and control groups. These findings highlight the importance of examining band-specific neural oscillations to capture the complex spectro-temporal dynamics of vocal sensorimotor mechanisms and their impaired function in stroke survivors with aphasia. In addition, our data suggest that targeted normalization of neural oscillatory responses may improve clinical interventions for treatment of speech motor disorders in aphasia.

Disclosures: **R. Behroozmand:** A. Employment/Salary (full or part-time):; Salaried full-time associate professor at University of South Carolina. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; PI on funded grants from NIH/NIDCD. **K. Sarmukadam:** A. Employment/Salary (full or part-time):; Salaried full-time post-doctoral fellow at University of South Carolina. **J. Fridriksson:** A. Employment/Salary (full or part-time):; Salaried full-time professor at University of South Carolina. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; PI on funded grants from NIH/NIDCD.

Poster

137. Rhythmic Motor Pattern Generation: Connectivity

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 137.01

Topic: E.07. Rhythmic Motor Pattern Generation

Support: NIH Grant R01DC016413

Title: Clonally related spinal neurons exhibit similar morphology but integrate into distinct circuits

Authors: *S. BELLO ROJAS, M. W. BAGNALL;
Neurosci., Washington Univ. In St. Louis, Saint Louis, MO

Abstract: How does shared lineage affect the formation of neuronal circuitry? Clonally related neurons of the same type in mammalian cortex integrate into shared circuits, while clonally related Notch-dependent hemilineages in Drosophila project to different circuits. In the spinal cord, diverse excitatory and inhibitory circuits emerge from cardinal classes of neurons identified by their progenitor domain and transcription factor expression. Individual precursors in the V2 class, which are labeled by the early onset transcription factor vsx1, undergo terminal differentiation via Notch-dependent signaling into an excitatory V2a neuron and an inhibitory V2b neuron. It is unknown whether these distinct, clonally related sister V2a/b neurons participate in shared or separate circuits. To label clonally related V2a/b neuron pairs, we injected titrated amounts of vsx1:GFP plasmid into zebrafish embryos at the one cell stage. We validated the identity of these sparsely labeled vsx1+ pairs by co-expression of the V2a/b markers chx10 and gata3. In vivo time-lapse imaging of V2a/b neuron pairs demonstrated that sister neurons remain close to each other and send similar trajectories of ipsilateral, descending projections, with areas of axonal overlap. However, circuit analysis through paired whole-cell recordings revealed that sister V2a/b neurons receive input from distinct presynaptic populations and do not form synapses with each other. In addition, optogenetic approaches revealed that sister V2a/b neurons form synapses onto different target neurons. Collectively, these data indicate that although sister V2a/b neurons in spinal cord share morphological characteristics, they integrate into separate circuits. Therefore, clonally related neurons in spinal cord with heterotypic identities participate in distinct circuits, similar to clonally related, Notch-dependent hemilineages in Drosophila.

Disclosures: S. Bello Rojas: None. **M.W. Bagnall:** None.

Poster

137. Rhythmic Motor Pattern Generation: Connectivity

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 137.02

Topic: E.07. Rhythmic Motor Pattern Generation

Support: NSF Grant 1656360

Title: Elucidating Form and Function of Novel Brain Circuitry in a Female Songbird

Authors: *D. W. SHAUGHNESSY, R. BERTRAM, R. L. HYSON, F. JOHNSON;
Florida State Univ., Florida State Univ., Tallahassee, FL

Abstract: Songbirds are a well-studied model organism for their natural propensity for learned vocalizations—songs. The zebra finch (Taeniopygia guttata) is a species in which both sexes produce social calls and the males also learn a song during a developmental critical period. Females do not learn to sing at all. Historically, the sexual dimorphism of zebra finch song has been ascribed to dramatic neuroanatomical differences between the sexes. The neural circuitry involved in learning and production of song (the song network) in male brains was thought to be

nearly or completely absent in female brains. Shaughnessy et al. 2019 applied a novel surgical technique to classic tract-tracing experiments, uncovering some male-typical song circuit connectivity in female brains. Here we describe a new method to visualize the network anatomy of the zebra finch brain. This method - which visualizes myelination - prominently defines several vocal control regions in the female zebra finch brain that are difficult to define by other histological techniques. This finding suggests that sexual dimorphism in song network anatomy is far less extreme that previously believed. Accordingly, we expand here on our prior tract-tracing experiment, establishing the full extent of the "song network" in non-singing female brains. Females possess most if not all the same nodes and connections as males, including nodes attributed to song learning and production, as well as the brainstem vocal-motor output that drives singing in males. Given the conflict between the presence of female song circuity and absence of singing in female zebra finches, we explore the function of the female song network via ablation. We report on our initial studies testing two premotor network nodes known to be involved in learning and production of male song for their necessity in the development or production of female social calling behavior via ablation in adults or juveniles.

Disclosures: D.W. Shaughnessy: None. **R. Bertram:** None. **R.L. Hyson:** None. **F. Johnson:** None.

Poster

137. Rhythmic Motor Pattern Generation: Connectivity

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 137.03

Topic: E.07. Rhythmic Motor Pattern Generation

Support: Supported by CIHR-PG-201610-PJT-378296

Title: Spinal terminations of multi-function descending serotonergic neurons

Authors: *K. ARMSTRONG[1], M. NAZZAL[1], K. C. COWLEY[2], K. STECINA[2];
[2]Physiol., [1]Univ. of Manitoba, Winnipeg, MB, Canada

Abstract: Serotonin (5-hydroxytryptamine, 5-HT) is a well-known modulator of locomotion. The innervation by 5-HT fibers and the location of 5-HT receptors within the spinal cord has been extensively studied, with evidence of 5-HT boutons on motoneurons and both excitatory and inhibitory interneurons. However, it is still unknown whether the same descending 5-HT neurons that terminate on motoneurons collateralize and also terminate in other locations such as the dorsal horn; nor is there a clear consensus on the preferential distribution of 5-HT fibers targeting inhibitory versus excitatory interneurons. The aim of this work was to determine the anatomy and function of a small-subset of caudally located 5-HT neurons and their projections to the spinal cord. First, we optogenetically activated this subset of 5-HT neurons as they have been previously hypothesized to influence locomotion. Further, we aimed to provide a 5-HT axon density map of these optically activated neurons and provide a reconstruction of 5-HT boutons in

close proximity to either excitatory or inhibitory synapses. An adeno-associated viral vector (rAAV) tagged with a fluorescent reporter was injected into subpopulations of 5-HT neurons in genetically modified rats (Tph2-iCre). In this rat model, Cre recombinase is restricted to 5-HT neurons and thus the optogenetic construct and fluorescent reporter is only expressed in the presence of Cre. After in-vivo decerebrate rat fictive locomotion experiments, tissue was harvested and thin spinal cord sections (16-50 µm) were collected. Immunohistochemistry was performed on the collected tissue using an antibody against the fluorescent reporter of the optogenetic construct, an antibody against the 5-HT protein and antibodies against synaptic markers. Imaris was used for semi-automated quantification to determine 5-HT apposition to excitatory and inhibitory synapses. Here, we show that small subpopulations of 5-HT can influence neural activity at various levels of the spinal cord based on the collateralizations observed at multiple levels of the spinal cord. The anatomical evidence provided here suggests that 5-HT neurons can link activity of multiple segments throughout cervical, thoracic and lumbar regions. Functionally, we report that optogenetic activation of these 5-HT neurons is able to concurrently influence ENG activity and increase blood pressure. This small subset of caudo-ventral 5-HT neurons may be involved in circuits responsible for integrating autonomic and motor responses during exercise.

Disclosures: K. Armstrong: None. **M. Nazzal:** None. **K.C. Cowley:** None. **K. Stecina:** None.

Poster

137. Rhythmic Motor Pattern Generation: Connectivity

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 137.04

Topic: E.07. Rhythmic Motor Pattern Generation

Support: Research Manitoba Grant 4249
Craig H. Neilsen Grant 733760
NSERC-CRSNG Grant RGPIN-2015-04810
NSERC-CRSNG Grant RGPIN-2020-07078

Title: Lumbar locomotor-related V3 interneurons project directly onto, and excite thoracic sympathetic preganglionic neurons

Authors: *C. V. NWACHUKWU, C. CHACON, N. SHAHSAVANI, J. W. CHOPEK, K. C. COWLEY;
Physiol. and Pathophysiology, Univ. of Manitoba, Winnipeg, MB, Canada

Abstract: Spinal cord injury (SCI) is a life altering event, causing paralysis and loss of sensory and autonomic function. Sympathetic preganglionic neurons (SPNs) provide all central sympathetic input to the body and are located in the intermediolateral nucleus (IML) in T1 to L1/2 spinal segments. Electrical stimulation of the lumbar spinal cord has emerged as a powerful intervention for people with SCI as clinical trials have shown its ability to improve both

movement and lost autonomic body functions (e.g., bp regulation, sweating, whole body metabolism). Although promising, neural mechanisms mediating observed recoveries using this intervention remain unknown, thus limiting its use for the wider SCI population. We propose that ascending neurons from the lumbar spinal cord provide direct synaptic input onto thoracic sympathetic neurons that in turn, provide homeostatic support for locomotion and exercise. Our lab recently demonstrated that 20% of VGluT2^{+} glutamatergic synaptic inputs to thoracic SPNs arises from lumbar locomotor-related V3 interneurons. In this study, we characterize activity patterns of SPNs before and during fictive locomotion. Spinal cords were isolated from C57BL/6 mice (aged P0-P5, both sexes; n=33). Fluorescent calcium dye was applied to cut thoracic ventral roots (T4-T12) to pre-load and label SPNs in the IML and imaged with a high-speed camera. At baseline, many SPNs were active and showed increased fluorescence intensity levels, while others showed reduced activity, with the appearance of tonic and/or rhythmic locomotor activity. In some experiments, additional SPNs were recruited during lumbar locomotor discharge. Using channelrhodopsinTdTOMV3 mice in combination with optical stimulation and whole-cell patch clamp electrophysiology, we examined if thoracic SPNs receive direct synaptic input from lumbar locomotor-related V3 interneurons. Blue light stimulation over either the lumbar spinal cord or V3 nerve terminals in the IML evoked excitatory post synaptic potentials and/or action potentials in thoracic SPNs. These findings demonstrate lumbar locomotor activity influences thoracic SPN activity in the absence of descending input from supraspinal regions. Further, this is the first demonstration of a functional intraspinal connection between lumbar locomotor-related neurons and SPNs. These findings suggest there is an intraspinal functionally integrated relationship between SPNs and locomotor circuits and can help explain why spinal stimulation to evoke walking after SCI also improves functions mediated by thoracic sympathetic neural circuitry in humans.

Disclosures: C.V. Nwachukwu: None. **C. Chacon:** None. **N. Shahsavani:** None. **J.W. Chopek:** None. **K.C. Cowley:** None.

Poster

137. Rhythmic Motor Pattern Generation: Connectivity

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 137.05

Topic: E.07. Rhythmic Motor Pattern Generation

Support: DFG - 233886668/ GRK1960

Title: Phasic inhibitory synaptic drive from central pattern generators patterns the activity of all leg motor neurons except depressors in an insect

Authors: *A. RUTHE, C. MANTZIARIS, A. BUESCHGES;
Inst. of Zoology, Univ. of Cologne, Cologne, Germany

Abstract: Walking consists of rhythmic motor patterns that are based on a complex interplay between central and sensory neural mechanisms. Central neural networks, known as central pattern generators (CPGs), rhythmically drive the activity of the motor neurons, and sensory information provides feedback on the position and movement of the legs, thus enabling fine-tuning of the motor performance. In the stick insect, distinct CPGs control the movement of each of the three main leg joints, i.e., the thorax-coxa, the coxa-trochanter and the femur-tibia joint. Rhythmic activity in flexor and extensor motor neurons, innervating the muscles of the femur-tibia joint, is generated by tonic activity that is shaped into bursts by phasic inhibitory synaptic drive from the respective joint CPG. Here we examine, whether the mechanisms of rhythm generation are the same for all motor neurons of the main leg joints, i.e. protractor, retractor, levator and depressor motor neurons. We pharmacologically activated the premotor networks within the deafferented mesothoracic ganglion of adult female stick insects (*Carausius morosus)* by bath application of the muscarinic acetylcholine receptor agonist pilocarpine, and we recorded motor neuron activity extracellularly and intracellularly using sharp microelectrodes. The synaptic drive from the CPGs to the motor neurons was studied by measuring the input resistance of the motor neurons and by artificial alteration of the membrane potential during rhythmic activity. We show that the neuronal input resistance of protractor (N=8), retractor (N=8) and levator motor neurons (N=7) is decreased during the inter-burst intervals and oscillation amplitudes decrease and reverse their sign upon hyperpolarization, indicating that patterning of the membrane potential in those motor neurons is primarily based on phasic inhibitory synaptic drive. Only in depressor neurons (N=13) oscillation amplitudes never reversed their sign upon hyperpolarisation, indicating that rhythmic activity of depressor motor neurons is based on excitatory and inhibitory synaptic drive. We are currently investigating, whether motor neurons receive subthreshold inputs, which correlate with the activity of the motor neurons of the other leg joint that would indicate weak coupling between networks.

Disclosures: **A. Ruthe:** None. **C. Mantziaris:** None. **A. Bueschges:** None.

Poster

137. Rhythmic Motor Pattern Generation: Connectivity

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 137.06

Topic: E.07. Rhythmic Motor Pattern Generation

Support: CIHR grant 14392
CIHR grant 180522

Title: Effects of modulating the trigeminal main sensory nucleus on masticatory movements

Authors: *D. FALARDEAU[1,2], O. SANVI[1,2], S. DUBOIS[1,2], A. KOLTA[1,2,3];
[1]Ctr. Interdisciplinaire de Recherche sur le Cerveau et l'Apprentissage (CIRCA), Montréal, QC, Canada; [2]Dept. of Neurosciences, Univ. de Montréal, Montréal, QC, Canada; [3]Dept. of Stomatology, Fac. of Dentistry, Univ. de Montréal, Montréal, QC, Canada

Abstract: Chewing as other repetitive movements is produced by a central pattern generating circuitry which output is rhythmic. Previous work from the laboratory has identified a population of neurons in the dorsal part of the trigeminal main sensory nucleus (NVsnpr) which firing pattern changes from tonic to rhythmic when the extracellular Ca^{2+} concentration decreases. The Ca^{2+} decrease acts by enhancing a sodium persistent current (I_{NaP}) that involves Nav1.6 channels and results from activation of astrocytes and subsequent release of S100b, an astrocytic Ca^{2+} binding protein. However, these findings were obtained in *in vitro* slice preparations. Therefore, the main objective of this project is to validate *in vivo* whether dorsal NVsnpr is sufficient and necessary to produce masticatory movements and whether astrocytes play an essential role in this process. To address these questions, we used transgenic mice expressing channelrhodopsin (ChR2; a blue light-sensitive protein), under the control of the VGluT2 or the Thy1 promoters in which we can induce mastication by electric or optogenetic stimulation of the cortical masticatory area (CMA) while pharmacologically or optogenetically manipulating the NVsnpr. Mapping of the anterolateral frontal cortex between 1.0 and 3.0 mm AP and 1.0 and 3.0 mm ML elicited rhythmic masticatory movements in only 3/31 anaesthetized preparations using electrical stimulation of the CMA, but in most animals (12/16) that were tested awake using right unilateral 10-40 Hz (2.5 ms, pulse duration) optogenetic stimulation of the CMA. The most reliable coordinates to elicit rhythmic (7-9 Hz) masticatory movements are 2.5 mm anterior to Bregma, 2.0 mm lateral to the midline and 0.75 mm in depth. In two animals, movements elicited by stimulation of the CMA were either transiently abolished or greatly reduced in amplitude and frequency after local injection of an I_{NaP} or an Nav1.6 channels blocker (Riluzole, 20 µM, unilateral injection; 4,9-anhydroTTX, 10µM, bilateral injection respectively) in dorsal NVsnpr. Further, bilateral, but not unilateral, optogenetic stimulation of NVsnpr at a frequency of 40 to 60 Hz induced masticatory movements (n=1). These preliminary data suggest that the NVsnpr is involved in the genesis of masticatory movements. Future experiments will involve manipulation of astrocytic networks in NVsnpr to assess their role.

Disclosures: **D. Falardeau:** None. **O. Sanvi:** None. **S. Dubois:** None. **A. Kolta:** None.

Poster

137. Rhythmic Motor Pattern Generation: Connectivity

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 137.07

Topic: E.07. Rhythmic Motor Pattern Generation

Support: Swedish Research Council 2017-02905
Wallenberg Foundation KAW 2018.0010
Swedish Brain Foundation FO2021-0317
Karolinska Institute

Title: Connectivity and developmental switch in function of V0d interneurons in zebrafish

Authors: *P. FONTANEL, L. D. PICTON, R. BJÖRNFORS, I. PALLUCCHI, M. BERTUZZI, A. EL MANIRA;
Dept. of Neurosci., Karolinska Inst., Stockholm, Sweden

Abstract: Animals require flexibility to successfully navigate their environment. In adult zebrafish, speed flexibility is achieved by the sequential recruitment of three speed modules (slow, intermediate, and fast) composed of motoneurons (MNs) and ipsilateral excitatory interneurons (V2a INs). While the circuit organization for speed control is well-described, mechanisms ensuring left-right coordination remain unclear. Here, we first characterize the function of glycinergic, inhibitory, commissural interneurons (V0d INs) in zebrafish both at larval and adult stages and then map their connectivity pattern with V2a INs and MNs in the adult. In larval zebrafish, we show that V0d INs participate and contribute to locomotion only at the highest speeds and their ablation has no apparent effects on slow, spontaneous, explorative swimming. In contrast, in adult, V0d INs become diversified into three speed-dependent subclasses with an overrepresentation of those recruited at the slowest speeds. Ablation of V0d INs in adults disrupts slow explorative swimming, which is associated with a loss of mid-cycle inhibition onto target MNs. The connectivity between V2a and V0d INs was first mapped using dual patch-clamp recordings. We show strong and more frequent excitatory connections between V2a and V0d INs belonging to the same speed-module, suggesting a modular organization of the premotor excitation from V2a to V0d INs, similar to the excitation pattern of MNs. Next, the outputs from V0d INs were mapped using optogenetic stimulation at different rostro-caudal positions in the spinal cord while performing patch-clamp recordings of V2a INs and MNs. Our results reveal stronger inhibition in slow and intermediate MNs by stimulation of V0d INs in rostral segments than from those located in caudal or in the same segments. In contrast, slow and intermediate V2a INs received similar inhibition independent of the location of the stimulated V0d INs. Both MNs and V2a INs of the fast module received only weak or no inhibition in response to optogenetic stimulation of V0d INs. These results show that V0d INs connect to V2a INs and MNs with distinct patterns, but primarily target those of the slow and intermediate modules. These differences are being assessed using dual patch-clamp recordings between V0d INs and V2a INs/MNs. Overall, our results show a shift in the function of the coordinating, V0d population during development of zebrafish, from a role in the highest speeds of locomotion to a function in slow, explorative swimming. In addition, we reveal a connectivity map describing the organization of the inputs to V0d INs as well as their outputs onto MNs and the rhythm-generating V2a INs.

Disclosures: P. Fontanel: None. **L.D. Picton:** None. **R. Björnfors:** None. **I. Pallucchi:** None. **M. Bertuzzi:** None. **A. El Manira:** None.

Poster

137. Rhythmic Motor Pattern Generation: Connectivity

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 137.08

Topic: E.07. Rhythmic Motor Pattern Generation

Support: European Research Council
Novo Nordisk Foundation Laureate Program

Title: Deconstruction of spinal microcircuits to execute muscle synergy programs

Authors: *C. BELLARDITA[1], R. SELVAN[1,2], R. LEIRAS[1], O. KIEHN[1,3];
[1]Dept. of Neurosci., Copenhagen Univ., Copenhagen, Denmark; [2]Dept. of Computer Sci., Univ. of Copenhagen, Copenhagen, Denmark; [3]Dept. of Neurosci., Karolinska Inst., Stockholm, Sweden

Abstract: Mammals have a remarkable capacity to precisely coordinate body movements to generate functionally relevant motor behaviors. Some lines of evidence in human and animal models led to the idea that the motor system may be organized in a modular fashion with meaningful motor behaviors emerging from the combination of basic neural modules. While signs of a modular organization of the motor system emerge at the behavioral and anatomical levels, the neural substrate and the modular logic of the motor system become blurry when looking at the premotor neural activity. Here, we examine the sensory-motor components of a spinal microcircuit for executing muscle synergy programs in which a defined population of propriospinal interneurons, the V2a neurons, represents the core element. Combining mouse intersectional genetics with *in vivo* optogenetic and electrophysiology in adult anesthetized mice, we show that V2a spinal neurons along the spinal cord activate discrete muscles in a topographic arrangement similar to the muscolotopic map formed by motor pools. Anatomical tracing with cell-specific viral approaches combined with simultaneous recordings of opto-identified V2a neurons and muscles allowed anatomical dissection of V2a sensory-motor maps and functional deconstruction of the biological principles driving the sequential recruitment of multiple muscles. V2 neurons together with sensory afferents, motor neurons, and muscles form a feedforward descending excitatory system in the spinal cord that simultaneously drives coordinated activity in multiple muscles. Accordingly, prolonged optical activation of V2a neurons in a specific segment appropriately recruits tens of muscles and their in vivo targeted silencing perturbed coherent muscle activity underlying task-dependent locomotor strategies. This work provides a logical framework on how spinal circuitries sculpt muscle action over time and space for meaningful motor behaviors. These data identify the anatomical substrate and the functional principles of a spinal microcircuit involved in constructing muscle activation sequences to mediate muscle synergy programs.

Disclosures: C. Bellardita: None. **R. Selvan:** None. **R. Leiras:** None. **O. Kiehn:** None.

Poster

137. Rhythmic Motor Pattern Generation: Connectivity

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 137.09

Topic: E.07. Rhythmic Motor Pattern Generation

Support: European Union's Horizon 2020 research and innovation program (REP-SCI-693038)
Novo Nordisk Laureate Program (NNF15OC0014186)
The Swedish Research Council
KID program (Karolinska Institutet)

Title: Lhx9-derived excitatory spinal interneurons and control of locomotor rhythm.

Authors: *M. BERTHO[1,2], L.-J. HSU[2], P. LOW[1], L. BORGIUS[1], O. KIEHN[1,2];
[1]Dept. of Neurosci., Karolinska Institutet, Stockholm, Sweden; [2]Dept. of Neurosci., Univ. of Copenhagen, Copenhagen, Denmark

Abstract: Locomotion is a complex behaviour that allows us to move and interact with our surroundings. Spinal networks that control locomotion produce the rhythm and the left-right and flexor-extensor coordination. Subgroups of excitatory and ipsilaterally projecting neurons are thought to be involved in rhythm-generation. Part of the mouse rhythm-generating networks was unraveled by the identification of two glutamatergic populations, Shox2 non-V2a, and Hb9-derived interneurons. To identify new populations involved in rhythm-generating circuitries, we used RNA-sequencing of spinal glutamatergic neurons of neonatal mice. We found that the transcription factor *Lhx9* is highly expressed by glutamatergic spinal neurons. To characterize the functional role of *Lhx9* neurons in the locomotor network, we then used tamoxifen-inducible *Lhx9::Cre* mice to genetically manipulate Lhx9::Cre-derived excitatory neurons. We found that Lhx9$^+$ neurons, which are distinct from the Shox2 neurons, outline a new ipsilaterally-projecting and excitatory population throughout the ventral spinal cord. Using *in vitro* neonatal spinal cord preparation, we found that optogenetic activation of Lhx9$^+$ neurons initiates locomotor-like activity; it also increases the frequency of the ongoing drug-induced locomotor activities. Moreover, chronic silencing of Lhx9$^+$ neurons leads to a decrease in the frequency of drug-induced locomotor activity. Finally, with calcium-imaging of an entire transverse section of the lumbar spinal cord, we revealed that the Lhx9$^+$ neurons, which are in close proximity, fire together with the same rhythmicity during drug-induced locomotor activity. Together, these data suggest that Lhx9$^+$ neurons are a potential new population involved in the rhythm-generating circuitries of spinal locomotor network.

Disclosures: **M. Bertho:** None. **L. Hsu:** None. **P. Low:** None. **L. Borgius:** None. **O. Kiehn:** None.

Poster

137. Rhythmic Motor Pattern Generation: Connectivity

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 137.10

Topic: E.07. Rhythmic Motor Pattern Generation

Support: NIH Grant R01NS104194
NIH Grant R21NS118226
NIH Grant R01NS112304
NIH Grant R01NS115900
NIH Grant R01NS110550
NSF Grant 2113069
Canadian Institutes of Health Research Grant MOP110950

Title: The role of V3 neurons in speed-dependent interlimb coordination during locomotion in mice

Authors: H. ZHANG[1], N. A. SHEVTSOVA[2], D. A. DESKA-GAUTHIER[1], C. MACKAY[1], K. J. DOUGHERTY[2], ***S. M. DANNER**[2], Y. ZHANG[1], I. A. RYBAK[2];
[1]Dept. of Med. Neurosci., Dalhousie Univ., Halifax, NS, Canada; [2]Dept. of Neurobio. and Anat., Drexel Univ. Col. of Med., Philadelphia, PA

Abstract: Speed-dependent interlimb coordination allows animals to maintain stable locomotion under different circumstances. The V3 neurons are known to be involved in interlimb coordination. We previously modeled the locomotor spinal circuitry controlling interlimb coordination. This model included the local V3 neurons that mediate mutual excitation between left and right rhythm generators (RGs). Here, our focus was on V3 neurons involved in ascending long propriospinal interactions (aLPNs). Using retrograde tracing, we revealed a subpopulation of lumbar V3 aLPNs with contralateral cervical projections. $V3^{OFF}$ mice, in which all V3 neurons were silenced, had a significantly reduced maximal locomotor speed, were unable to move using stable trot, gallop, or bound, and predominantly used a lateral-sequence walk. To reproduce this data and understand the functional roles of V3 aLPNs, we extended our previous model by incorporating diagonal V3 aLPNs mediating inputs from each lumbar RG to the contralateral cervical RG. The extended model reproduces our experimental results and suggests that locally projecting V3 neurons, mediating left-right interactions within lumbar and cervical cords, promote left-right synchronization necessary for gallop and bound, whereas the V3 aLPNs promote synchronization between diagonal fore and hind RGs necessary for trot. The model proposes the organization of spinal circuits available for future experimental testing.

Disclosures: H. Zhang: None. **N.A. Shevtsova:** None. **D.A. Deska-Gauthier:** None. **C. MacKay:** None. **K.J. Dougherty:** None. **S.M. Danner:** None. **Y. Zhang:** None. **I.A. Rybak:** None.

Poster

137. Rhythmic Motor Pattern Generation: Connectivity

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 137.11

Topic: E.07. Rhythmic Motor Pattern Generation

Support: NSF DBI 2015317

Title: Perturbation analysis of different two-layer central pattern generator designs for locomotion

Authors: *K. DENG[1], A. J. HUNT[2], N. S. SZCZECINSKI[3], M. C. TRESCH[4], R. D. QUINN[1], H. J. CHIEL[1];
[1]Case Western Reserve Univ., CLEVELAND, OH; [2]Portland State Univ., Portland, OR; [3]West Virginia Univ., Morgantown, WV; [4]Northwestern Univ., Chicago, IL

Abstract: Mammals can swiftly react to terrain changes during locomotion by dynamically adapting their limb movements. Neural circuits located in the spinal cord called central pattern generators (CPGs) are widely believed to contribute to the generation and adaptation of gaits. Here we present an in-depth investigation into the hypothesized two-layer CPG and describe how a sensitivity analysis of the CPG clarifies the performance of a simulated neuromechanical model in response to perturbations. Although the mammalian locomotor model is still being refined, we analyze components of the system that are currently known. We investigate the functional role of a weak mutual excitatory connection within the rhythm generator, a feature that has not received a great deal of attention. Sensitivity evaluations of deafferented CPG models and the combined neuromechanical model are performed. Locomotion frequency is increased in two different ways for both models to investigate whether the model's stability can be predicted by trends in the CPG's phase response curves (PRCs). Our results show that although changing CPG parameters alters the PRCs in the isolated neuron model and in an air-walking model, both neural models exhibit powerful stability against disturbances in all cases. Further, altering CPG parameters has no effect on step timing in a ground-walking neuromechanical model. Our results also provide guidelines for future computational neuroscience modeling of circuits that control mammalian locomotion.

Disclosures: K. Deng: None. **A.J. Hunt:** None. **N.S. Szczecinski:** None. **M.C. Tresch:** None. **R.D. Quinn:** None. **H.J. Chiel:** None.

Poster

137. Rhythmic Motor Pattern Generation: Connectivity

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 137.12

Topic: E.07. Rhythmic Motor Pattern Generation

Title: Mapping Information Flow within Human Motor Regions

Authors: *N. LIU[1], B. HAN[2], G. R. FINK[1,3], S. DAUN[1,4], Q. CHEN[2];
[1]Inst. of Neurosci. and Med., Forschungszentrum Jülich, Jülich, Germany; [2]Sch. of Psychology, South China Normal Univ., Guangzhou, China; [3]Dept. of Neurol., Univ. Hosp. Cologne, Cologne, Germany; [4]Dept. of Zoology, Univ. of Cologne, Cologne, Germany

Abstract: Both non-human primate studies and observations in humans have suggested the complex functional organization of the motor cortex, especially in subregions like primary motor cortex (M1), premotor cortex (PM) and supplementary motor area (SMA). However, given the limited spatial and temporal resolution of current available recording and imaging techniques, it has remained unclear how information transfer within human motor regions is realized. In the current study, by using cortico-cortical evoked potential (CCEP) recordings and intracranial electroencephalography (iEEG) from patients implanted with intracranial electrodes, we investigated (1) the directional information flow within the intrinsic motor network, (2) how the pattern of signal propagation is modulated, and (3) whether signal flow follows a similar pattern during cognitive experiments. Specifically, during the CCEP recordings, 1-Hz electrical stimulations were delivered to each site along intracranial electrodes implanted in motor regions, while at the same time post-stimulation responses were recorded and measured at response sites. Out of the 20 subjects who underwent CCEP procedures, iEEG was recorded from 3 subjects who additionally performed a detection task. We first identified significant stimulation-response pairs within our regions of interest (ROI) including M1, PM, and SMA. For all the pairs, we calculated Pearson correlations between pre-stimulation power at the stimulation site and CCEP amplitude at the response site between different ROIs. For iEEG data, we computed similar Pearson correlations between pre-stimulus power at the sites within PM and SMA which sent out information to M1 based on the CCEP results and peak latency at 60-140 Hz in the sites within M1 which received information from the other motor regions. The correlations between pre-stimulus power in PM and SMA and peak power in M1 were determined as well. CCEP results showed that PM had more information being sent out than coming in from M1 and SMA, whereas M1 received more information from PM and SMA than sending out. Moreover, the pre-stimulation power at beta and gamma bands in PM influenced the strength of evoked responses in M1 and SMA, which was only observed in the group of subjects with electrodes implanted in the dominant hemisphere. Furthermore, we found that the pre-stimulus power in PM and SMA modulated the after-stimulus peak latency and peak power in M1 via beta and gamma oscillations, respectively, during contralateral hand movement. Together, our results show the directional information flow within human motor regions via beta and gamma oscillations both in the intrinsic and cognitive states.

Disclosures: **N. Liu:** None. **B. Han:** None. **G.R. Fink:** None. **S. Daun:** None. **Q. Chen:** None.

Poster

137. Rhythmic Motor Pattern Generation: Connectivity

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 137.13

Topic: E.07. Rhythmic Motor Pattern Generation

Support: NIH Grant NS070583
NIH Grant NS118606

Title: Multiple modes of feeding in the mollusc Aplysia

Authors: *C. G. EVANS[1], C. N. REAVER[1], M. A. BARRY[1], M. H. PERKINS[1], J. JING[1,2], K. R. WEISS[1], E. C. CROPPER[1];
[1]Icahn Sch. of Med. at Mt. Sinai, Icahn Sch. of Med. at Mount Sinai, One Gustave Levy Place, New York, NY; [2]Nanjing Univ., Nanjing, China

Abstract: Early experiments that determined how the feeding network of *Aplysia* is configured to generate ingestive programs focused on the role of neuropeptides released by the projection neuron, cerebral buccal interneuron-2 (CBI-2). When these peptides configure activity, it gradually becomes ingestive as CBI-2 is repeatedly stimulated (repetition priming occurs). Further, a persistent ingestive state is created. Recent work identified a second mechanism that is effective in preparations in which repetition priming does not occur. In these preparations coactivation of a second projection neuron (CBI-3) makes CBI-2 induced activity immediately ingestive (Evans et al. 2021). We now show that the effect of CBI-3 coactivation is not exclusively observed when priming fails; it also makes activity immediately ingestive when priming occurs. Effects of CBI-3 stimulation do not persist (Evans et al. 2021). This suggests that dynamic switches between intermediate and ingestive activity should be possible. We now demonstrate that this is the case. Taken together our data suggest that there are two modes of feeding; a CBI-2 mediated mode that is consistently ingestive, and a CBI-2/CBI-3 mediated mode that consists of dynamic switching between intermediate and ingestive motor programs. If so, it might be expected there would be situations where CBI-2 is active, but CBI-3 is not and other situations where CBI-2 and CBI-3 are coactivated. Data obtained in semi-intact preparations have, however, not provided support for this idea. Instead, these data suggest that CBI-2 and CBI-3 are mostly coactive (Wu et al., 2014; Jing and Weiss 2005). Reported firing frequencies for CBI-3 do, however, range from ~3-10 Hz. In previous experiments that demonstrated the effect of CBI-2 and CBI-3 coactivation, CBI-3 was stimulated at the upper limit of this range. We now show that there is virtually no effect if CBI-3 is bilaterally stimulated at 3 Hz. Thus, even though CBI-3 and CBI-2 are generally coactive, effects of CBI-3 stimulation will not always be manifested. In previous experiments that studied ingestive behavior *in vivo,* animals were primarily fed seaweed strips that are easily consumed by a series of purely ingestive responses. A final question we addressed is: Is there a situation where animals switch between different types of motor activity? In particular we characterized responses when animals were fed complex (branched) seaweed that was difficult to ingest. We did in fact observe switches between different types of motor activity in all animals tested. Overall, our data are consistent with the idea that there are at least two modes of ingestive behavior in *Aplysia.*

Disclosures: C.G. Evans: None. **C.N. Reaver:** None. **M.A. Barry:** None. **M.H. Perkins:** None. **J. Jing:** None. **K.R. Weiss:** None. **E.C. Cropper:** None.

Poster

137. Rhythmic Motor Pattern Generation: Connectivity

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 137.14

Topic: E.07. Rhythmic Motor Pattern Generation

Support: R01 NS118606-02

Title: Combining fast voltage-sensitive dye, carbon fiber array, and extracellular nerve electrodes to stimulate and record hundreds of neurons simultaneously using 3-D printed manipulators

Authors: *C. NEVEU[1], R. M. COSTA[2], P. R. PATEL[3], C. A. CHESTEK[4], J. H. BYRNE[5]; [1]6431 Fannin St, MSB 7.310, UTHealth, Houston, TX; [2]Neurobio. and Anat., The Univ. of Texas Hlth. Sci. Ctr. at Houston, Houston, TX; [3]Univ. of Mchigan, Univ. of Mchigan, Ann Arbor, MI; [4]Biomed. Engin., Univ. of Michigan, ANN ARBOR, MI; [5]McGovern Med. Sch. of UTHSC at Houston, McGovern Med. Sch. of UTHSC at Houston, Houston, TX

Abstract: The need to understand the flow of information in the complex circuitry underlying motor behavior has hastened the development of technologies for stimulating and recording 100s of neurons simultaneously with single-neuron precision. Among the technologies being applied include voltage-sensitive dye recording, electrode array recording and traditional extracellular recording from single electrodes. However, little progress has been made in integrating the various technologies. The purpose of this study was to integrate two high-throughput recording methods, wide field voltage-sensitive dye imaging (fVSDi) and a 16-electrode high density carbon fiber (HDCF) array, while recording motor pattern output with eight extracellular nerve electrodes. The feeding motor program generated by the buccal ganglion of *Aplysia* was used as a test system. Buccal ganglia were treated with the voltage-sensitive dye Di-4-ANNEPS, the HDCF array contained 50-90 um exposed, sharpened tips coated with platinum-iridium and was positioned in place by a 3-axis micromanipulator and extracellular electrodes were positioned in proximity to eight peripheral nerves of the buccal ganglia by 2-axis manipulators. All nerves relevant to buccal motor patterns were recorded, including the intrinsic nerve 2 and left and right buccal nerves 1-3 that represent translocation and opening of the tongue-like radula, and the radula nerve that represent closure of the radula. The recording chamber and manipulators were printed using the MakerBot Replicator Z18 3-D printer with poly-lactic acid (PLA) filament and designed so that all fit on a portable recording chamber that can be positioned under the microscope objective for imaging. Spike-triggered averaging indicated that the fVSDi and HDCF array simultaneously recorded spontaneous bursts of action potentials of individual neurons during motor patterns. These technologies were able to distinguish between ingestion and rejection patterns. This study sets the stage for integrating multiple high-throughput recording techniques to understand the complex circuitry underlying motor patterns.

Disclosures: C. Neveu: None. **R.M. Costa:** None. **P.R. Patel:** None. **C.A. Chestek:** None. **J.H. Byrne:** None.

Poster

137. Rhythmic Motor Pattern Generation: Connectivity

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 137.15

Topic: E.07. Rhythmic Motor Pattern Generation

Support: NSF Grant IOS1754869

Title: Neurons that function as sensory neurons, motor neurons and interneurons

Authors: *Y. HUAN[1], J. P. GILL[1], E. E. FAULK[1], H. J. CHIEL[2];
[1]Biol., [2]Biology, Neurosciences, Biomed. Engin., Case Western Reserve Univ., Cleveland, OH

Abstract: Buccal neurons B4/B5 are known as interneurons in the feeding circuitry of *Aplysia* that can modulate feeding behavior. They inhibit multiple key motor neurons in the circuitry (Gardner, 1977) and play a critical role in regulating rejection behavior (Ye et al, 2006). Other studies suggest that the B4/B5 neurons may have additional functions. We have shown that axons of the B4/B5 neurons can transmit signals both towards and from the periphery in a reduced preparation and during *in vivo* recordings in intact-behaving animals. We therefore hypothesized that B4/B5 have additional sensory and motor functions. To test the possible sensory functions, we used isolated buccal ganglia with only buccal nerve 3 (BN3) connected to the feeding apparatus. By extracellularly recording from two sites on the nerve and intracellularly recording from the soma, we traced the signaling direction and found that touching the I1/I3 muscle complex elicited action potentials that traveled into the nervous system. These responses were still observed after polysynaptic or monosynaptic connections were blocked by high divalent cation (Hi-Di) solution or high calcium low cobalt solution respectively, suggesting that the sensory responses were direct. To test the possible motor functions, we recorded from the I1/I3 muscles and monitored the change in generated force. The EMG signals recorded in both I1 and I3 muscles were one-to-one matched to the B4/B5 action potentials. These signals were still observed after polysynaptic connections were blocked by a Hi-Di solution. Furthermore, the polarity of the I1/I3 signals generated by the B4/B5 neurons was opposite to that generated by the I1/I3 motor neurons. We also found that simultaneous stimulation of one I1/I3 motor neuron and one B4/B5 neuron reduced the force generated in the muscles when the interneuronal inhibitory effect was overcome by increasing the stimulation amplitude. The effect on EMG polarity and force change suggest that B4/B5 have a motor effect that is antagonistic to the I1/I3 motor neurons. In conclusion, *Aplyisa* neurons B4/B5 may have a sensory and a motor function in addition to their interneuronal function. Since B4/B5 can be activated both by sensory inputs and descending interneuronal inputs, they could be important for regulating feeding behavior.

Disclosures: Y. Huan: None. **J.P. Gill:** None. **E.E. Faulk:** None. **H.J. Chiel:** None.

Poster

137. Rhythmic Motor Pattern Generation: Connectivity

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 137.16

Topic: E.07. Rhythmic Motor Pattern Generation

Support: NIH Grant NS066587
NIH Grant NS118606

Title: Peptide induced motor programs in the feeding network of the mollusc Aplysia

Authors: *C. N. REAVER[1], C. G. EVANS[1], M. A. BARRY[1], J. JING[1,2], P. R. PATEL[3], C. A. CHESTEK[3], K. R. WEISS[1], E. C. CROPPER[1];
[1]Mount Sinai Sch. of Med., New York, NY; [2]Nanjing Univ., Jiangsu, China; [3]Univ. of Michigan, Ann Arbor, MI

Abstract: Feeding circuit activating peptide (FCAP) and cerebral peptide 2 (CP-2) are released when the feeding network in *Aplysia* is activated by an ingestive input, the projection neuron cerebral buccal interneuron 2 (CBI-2) (Koh et al., 2003). Small cardioactive peptide (SCP) is released when the same network is activated by an egestive input, the esophageal nerve (EN) (Wu et al., 2010). Previous studies have primarily focused on determining how FCAP/CP-2 and SCP configure motor programs. These experiments characterized divergent circuit modifications, i.e., modulatory effects exerted by FCAP/CP-2 not exerted by SCP and vice versa (e.g., Wu et al., 2010; Friedman et al., 2015; Perkins et al., 2018; Siniscalchi et al. 2016). More recently we demonstrated that FCAP/CP-2 and SCP additionally act convergently; they increase the excitability of B63, a neuron that is part of the central pattern generator (CPG) (Due et al., 2022). An increase in B63 excitability would not be expected to bias the network towards either an ingestive or egestive output. A question we are addressing is, what is its functional significance? Sieling et al. (2014) demonstrated that dynamic clamp subtraction of a potassium leak current in B63 increases the frequency of buccal motor programs induced by nerve stimulation. To determine whether program induction is altered by peptide application, we conducted experiments in which we applied exogenous FCAP/CP-2 or SCP and monitored activity using both intracellular and extracellular recording techniques. Intracellular recordings were obtained from B63, and the radula closer motor neuron B8. B8 recordings were used to classify activity as ingestive, egestive, or intermediate. Extracellular recordings were obtained using a suction electrode to record activity from the I2 nerve, and carbon fiber electrodes (CFE) organized into a linear array to record from the neuropil on the rostral surface of the buccal ganglion (Huan et al., 2021). CFE arrays were fabricated in the laboratory of Dr. Cynthia Chetek at the University of Michigan and had a high-density configuration. I2 recordings define the protraction phase of the motor program. The carbon fiber array recordings were used to monitor retraction. Recordings were obtained before, during, and after peptide superfusion. Before peptide application, we did not record any complete cycles in the preparations except for one motor program cycle in one preparation. Multiple programs were, however, recorded in all preparations after FCAP/CP-2 or SCP application. These results are consistent with the idea that peptide induced increases in the B63 excitability facilitate program induction.

Disclosures: C.N. Reaver: None. **C.G. Evans:** None. **M.A. Barry:** None. **J. Jing:** None. **P.R. Patel:** None. **C.A. Chestek:** None. **K.R. Weiss:** None. **E.C. Cropper:** None.

Poster

137. Rhythmic Motor Pattern Generation: Connectivity

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 137.17

Topic: E.07. Rhythmic Motor Pattern Generation

Support: NIH Grant 1R01NS118606-01
Israel Science Foundation Grant 2396/18
U.S. - Israel Binational Science Foundation Grant No. 2017624

Title: Connections and plasticity of Aplysia buccal ganglia S1 mechanoafferents to motor neurons effecting feeding behavior

Authors: I. HURWITZ[1], H. J. CHIEL[2], J. P. GILL[3], J. JING[4], ***A. J. SUSSWEIN**[1];
[1]Bar-Ilan Univ., Bar-Ilan Univ., Ramat-Gan, Israel; [2]Case Western Res. Univ., University Heights, OH; [3]Biol., Case Western reserve Univ., Cleveland, OH; [4]Nanjing Univ., Nanjing Univ., Jiangsu, China

Abstract: The S1 neurons in the *Aplysia* buccal ganglia are sensorin-positive mechanoafferents differing from mechanoafferent initiating gill and tail withdrawal in that connectivity to followers is complex, with different combinations of fast and slow monosynaptic EPSPs and IPSPs elicited. Connectivity to followers changes after learning that food is inedible biasing motor activity to rejection. To gain insight into functions of connections from S1 afferent to followers, we examined monosynaptic connectivity and plasticity to neurons of known function: B3, B4/B5, B8a/b, B31/B32, B61/B62. In naïve animals and in animals showing long-term memory after learning with inedible food, S1 neurons were stimulated with 3 trains of 5 spikes and PSPs were recorded in followers. Data were examined separately for 4 sub-areas of the S1 cluster. Fast connections to B4/B5 and B31/B32 were exclusively excitatory. Other followers responded with a mixture of fast EPSPs and IPSPs, with a bias to inhibition in B3, and to excitation in B8a/b and B61/B62. Within-trains connections showed a decrement from the 1st to the 5th fast EPSP or IPSP. Between-trains there were increases and decreases in PSP amplitude, depending on the identity of the post-synaptic neuron or on the sign of the connection (*i.e.* EPSPs and IPSPs may undergo opposite plastic changes). For 2 motor neurons connectivity depended on S1 cells location with larger amplitude connections to B4/B5 in lateral S1 areas and larger net inhibition to B3 in medial regions. Learning produced increases in net inhibition to B3 and net excitation to B4/B5 and B61/B62. The net increase in B3 inhibition arose by increasing the proportion of cells producing IPSPs at the expense of unconnected cells and those producing EPSPs with an opposite effect accounting for increased excitation to B61/B62. For B8a/b proportions of EPSPs and IPSPs increased at the expense of unconnected cells. For some cells, learning affected within-train or between-train plasticity. For B4/B5, learning-dependent changes were restricted to medial areas of the cluster, but for other motor neurons changes were generally similar in all regions of S1. Slow PSPs were generally smaller in amplitude than were fast EPSPs, and were more sparsely distributed. For B3 and B61/B62, the net slow PSPs were opposite in sign to fast PSPs. Learning did not affect the net amplitude of slow PSPs, but could affect the distribution of their sign. Plasticity in how fast and slow inhibition and excitation are combined suggests that learning, changes in motivational state, or choice of different feeding behaviors, could recruit different combinations of synaptic connectivity for different behavioral goals.

Disclosures: **I. Hurwitz:** None. **H.J. Chiel:** None. **J.P. Gill:** None. **J. Jing:** None. **A.J. Susswein:** None.

Poster

137. Rhythmic Motor Pattern Generation: Connectivity

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 137.18

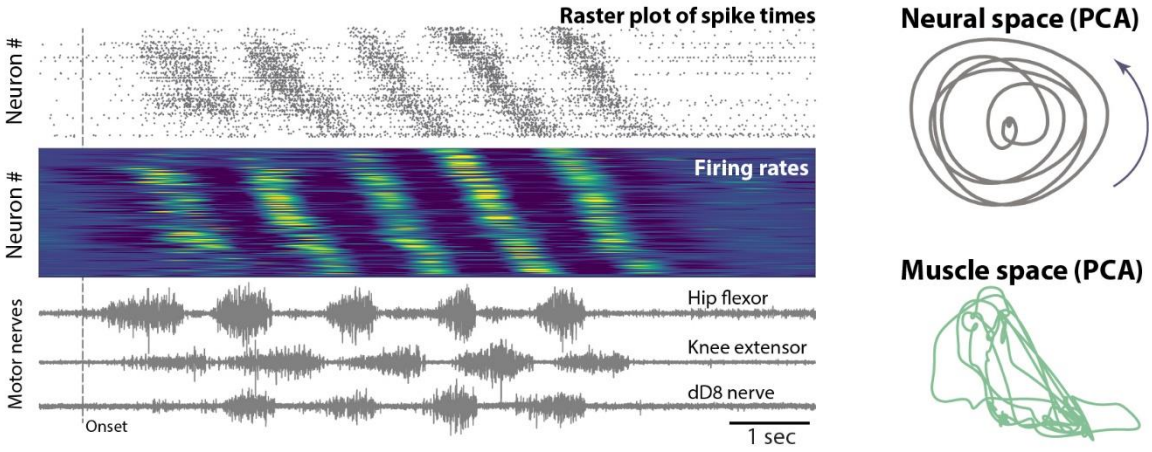
Topic: E.07. Rhythmic Motor Pattern Generation

Support: DFF 8020-00436B
Carlsberg foundation CF18-0845
Lundbeck foundation R366-2021-233

Title: Rotational population dynamics in spinal motor networks and a new theory of generation of movements: the balanced sequence generator (BSG)

Authors: *R. W. BERG[1], J. KAUR[1], S. A. KOMI[1], P. C. PETERSEN[1], M. VESTERGAARD[2], H. LINDÉN[1];
[1]Univ. of Copenhagen, Univ. of Copenhagen, Copenhagen, Denmark; [2]Max-delbrück-Centrum Für Molekulare Medizin, Max-delbrück-Centrum Für Molekulare Medizin, Berlin, Germany

Abstract: The neural principles behind movement have remained elusive for decades, but the core elements behind movements such as locomotion are known to be generated in the spinal cord. Since it is experimentally challenging to access interneurons in the spine during rhythmic movements, most of the previous investigations are based on nerve recordings. Such nerve recordings demonstrate that the flexor/extensor muscles alternate during rhythmic movements, and therefore it is often assumed that the generation is accomplished by neuronal modules that alternate in opposition. Here, we test the hypothesis of alternating modular structure in spinal motor networks, by recording large populations of neurons using multi-electrode arrays in the lumbar spinal cord of turtles and rats. We find that, rather than alternating, the neuronal population is performing a "rotation" (Figure), i.e., cycling continuously through all phases. Rotational dynamics are observed across trials as well as behaviors, and the radius of rotation correlates with the muscle force. Since such rotation is difficult to explain using existing models of alternating neuronal groups, we propose a new theory called the *Balanced Sequence Generator* (BSG). The BSG consists of a network model with recurrent excitatory and inhibitory connectivity of rate-based neurons, where the eigenvalues of the connectivity matrix have non-zero imaginary parts close to the stability line. Such a simple network can readily explain rotational dynamics. Furthermore, the BSG does not rely on pacemaker properties for the generation of the rhythm, and it is not necessary to assume a modular structure. Tonic input to the network controls the rhythm and pattern depending on the task. The model also reproduces other experimental observations and provides a mechanism for multifunctionality, e.g., walk, trot, and bound.



Disclosures: **R.W. Berg:** None. **J. Kaur:** None. **S.A. Komi:** None. **P.C. Petersen:** None. **M. Vestergaard:** None. **H. Lindén:** None.

Poster

137. Rhythmic Motor Pattern Generation: Connectivity

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 137.19

Topic: E.07. Rhythmic Motor Pattern Generation

Support: NIH Grant R01 DC016413
McKnight Scholar Award (M.W.B)
PEW Scholar Award (M.W.B)

Title: The curious case of coincident inhibition: V2b neurons in axial motor control

Authors: *M. SENGUPTA, M. W. BAGNALL;
Neurosci., Washington University, Med. Sch., Saint Louis, MO

Abstract: Local interneurons in the spinal cord guide activity of specific motor neurons and musculature to produce movements. Traditionally, spinal excitation and inhibition is conceptualized as alternating with each other for driving rhythmic movements. Surprisingly, recent evidence demonstrates that spinal inhibition can occur concurrently with excitation. Coincident inhibition is widespread in the brain and known to shape network output by influencing synaptic gain, spike timing and membrane potential oscillations; however, the functional significance of such coincident inhibition to motor output remains unknown. In this study, we focus on a cardinal spinal population, V2b neurons and show that these neurons are in fact active in phase with peak excitation, identifying them as a prominent source of coincident inhibition. V2b neurons have previously only been implicated for limb movements but are

present all along the spinal cord in axial networks governing body musculature yet their function in axial motor control is less understood. Leveraging the unique advantages of the larval zebrafish model system, we describe a broad map of V2b connectivity and function in axial motor circuits. V2b neurons project axons ipsilaterally and caudally, each axon extending approximately 25% of the total spinal cord length. Using optogenetic assisted circuit mapping we show that V2bs inhibit not only different motor neurons but also prominent excitatory and inhibitory premotor populations in the ventral horn like V2a and V1 neurons, respectively. Such robust connectivity to multiple post synaptic partners ideally places V2b neurons for orchestrating network output. Interestingly, V2b neurons did not show any appreciable connectivity to dorsal horn sensory targets indicating that their connectivity is specific and that their function is primarily motor related. Furthermore, we recorded V2b spiking during fictive locomotion and observed that V2b neurons are specifically active during high amplitude, extended motor bursts. Such motor signatures are indicative of powerful muscle contractions and therefore these data indicate that V2b neurons are selectively recruited for vigorous movements. In order to pinpoint the specific behaviors that recruit V2b neurons, currently we are recording population activity in V2bs during visually evoked behaviors. Together, by delineating activity, connectivity, and recruitment of V2b neurons, this study will reveal a prominent source of coincident inhibition and its impact on spinal motor control at a mechanistic level.

Disclosures: **M. Sengupta:** None. **M.W. Bagnall:** None.

Poster

137. Rhythmic Motor Pattern Generation: Connectivity

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 137.20

Topic: E.07. Rhythmic Motor Pattern Generation

Support: DFF 8020-00436B
Carlsberg foundation CF18-0845
Lundbeck foundation R366-2021-233

Title: Rotational population dynamics of rat spinal cord during locomotion and whole body freezing

Authors: *J. KAUR, N. BERTRAM, S. A. KOMI, R. W. BERG;
Neurosci., Univ. of Copenahgen, Copenhagen, Denmark

Abstract: The neuronal population activity in motor circuits of the mammalian spinal cord has so far not been investigated during volitional locomotion. Recently, it was demonstrated that rhythmic limb movement is associated with rotational dynamics in the turtle spinal cord (Lindén et al, 2022). To verify this in mammals, we implanted recording electrodes (128-channels from Neuronexus) in the rat spinal cord to record during volitional locomotion. Further, we investigated the impact of a perturbation of movement on the population dynamics, by

optogenetic stimulation of the pedunculopontine nucleus (PPN, in the midbrain). Stimulation was accomplished using an implanted optical fiber where neurons had expressed an opsin (ChrimsonR) delivered by an AAV virus with CamKIIa promoter. First, we found that the movement was accompanied by rotational dynamics in the spinal locomotor networks. Second, when stimulating the PPN the locomotion was arrested and the whole body of the rat was completely frozen. This response was surprising, given that PPN is a part of the midbrain locomotor region, where electrical stimulation has been found to induce locomotion (hence the name) in numerous reports. However, the body freezing observation agrees with the observation by Carvalho et al 2020. During the PPN stimulation and movement arrest, we further found that the firing rate of lumbar spinal neurons was significantly reduced leading to a collapse of the rotational population dynamics of the lumbar spinal networks. The post-mortem analysis of the infected PPN neurons indicated more than 50% were VGluT2+, with a smaller subset of GABAergic and cholinergic neurons. Lastly, an analysis of the whole PPN region using tissue clearing and light-sheet microscopy revealed an overall very low infection of the cholinergic neurons. These results support that, rotational population dynamics are marker of spinal dynamics during locomotion in rats (and turtles, Lindén et al, 2022) and the whole body freezing in rats collapses the rotation.

Disclosures: **J. Kaur:** None. **N. Bertram:** None. **S.A. Komi:** None. **R.W. Berg:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; DFF 8020-00436B, Carlsberg foundation CF18-0845, Lundbeck foundation R366-2021-233, University of Copenhagen.

Poster

137. Rhythmic Motor Pattern Generation: Connectivity

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 137.21

Topic: E.07. Rhythmic Motor Pattern Generation

Support: NIH/NINDS NS110605

Title: Modulation of spinal interneuronal firing following intrathecal delivery of BDNF in spinal cats

Authors: J. PAZ AMAYA[1], F. MARCHIONNE[1], M. ZABACK[2], *M. A. LEMAY[1];
[1]Bioengineering, [2]Bioengineering//Health and Rehabil. Sci., Temple Univ., Philadelphia, PA

Abstract: Spinal cord injury (SCI) results in severe motor deficits and loss of sensation below the site of injury. Brain-derived neurotrophic factor (BDNF) has been shown to promote spontaneous locomotor behavior in animals with SCI. Even though it is thought that BDNF reengages the lumbar spinal locomotor circuitry, we do not understand how BDNF affects the behavior of spinal interneurons. We used multi-channel electrode array neuronal recordings and

EMG activity to explore neuronal changes as they relate to locomotion in saline or BDNF treated spinal cats. We delivered BDNF (50ng/day) into the lumbar cisterna for 6 weeks post-transection in the experimental group and saline in controls. Locomotor performance during treadmill locomotion was evaluated at 3 and 5 weeks. The BDNF-treated group recovered plantar weight-bearing stepping while the saline treated animals did not. At week 6, we used two 64-channel electrode arrays to record extracellular activity from the L4-L7 spinal segments during evoked air-stepping. To explore the way in which interneurons fired, we looked at their firing frequency, number of active units per trial, and other parameters across groups. We also looked at measures of connectivity between the recording sites by performing coherence analysis and fitting a point-process generalized linear model where the firing of neighboring neurons and past firing history are weighted linearly to describe neuronal connections. Finally, we explored changes in the timing of firing relative to the step cycle by calculating the preferred firing phase of each neuron. During the terminal experiments we observed that some BDNF-treated animals display spontaneous locomotor movement with flexor/extensor and right/left alternation in hindlimb muscle activity following decerebration. This was never noted in saline treated animals. We found that units in the BDNF-treated group had a significantly higher firing frequency, and a different distribution of firing patterns (unimodal, bimodal, tonic, etc.). Interestingly, we did not find any significant differences in measures of connectivity, mean preferred phase of firing, or number of active units per trial. While some of the differences in neuronal activity may be negated by Clonidine which is used to facilitate locomotion in both groups of animals, our results suggest that the effects of BDNF on connectivity are small but distributed enough to have an overall effect on locomotor output.

Disclosures: **J. Paz Amaya:** A. Employment/Salary (full or part-time):; Temple University. **F. Marchionne:** A. Employment/Salary (full or part-time):; iMotions A/S. **M. Zaback:** A. Employment/Salary (full or part-time):; Temple University. **M.A. Lemay:** A. Employment/Salary (full or part-time):; Temple University.

Poster

137. Rhythmic Motor Pattern Generation: Connectivity

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 137.22

Topic: E.04. Voluntary Movements

Support: Mackpesquisa
Capes
Fasig

Title: Effects of the exposure of rats to botulinum toxin a during pregnancy or lactation: pilot study to evaluate locomotor activity andtoxicological parameters

Authors: *E. L. RICCI[1], L. PANTALEON[2], L. DE PAULA[2], G. RIBEIRO[2], V. ROMANATO[1], M. ROSSETI[1], S. LOPES[1], J. ZACCARELLI MAGALHÃES[2], G. RAMOS

ABREU[2], J. DELORENZI[1], A. FUKUSHIMA[2], H. SPINOSA[2];
[1]Presbyterian Mackenzie Univ., Presbyterian Mackenzie Univ., São Paulo, Brazil; [2]São Paulo Univ., São Paulo, Brazil

Abstract: Botulinum toxin A (BoNtA) is a neurotoxin used in several human therapies. Nevertheless, there is a lack of information about its effects at some stages of life, such as pregnancy and lactation. In pre-clinical studies, it's necessary to use animal models, however, the quality of life and animal welfare must be ensured. Thus, the present work aim to evaluate the possible toxic and locomotor effects of the exposure of rats to BoNtA. For this, 12 female adult rats with 70 days of life received a single dose of BoNtA (4 or 8 U/kg) or saline solution (n= 4 animals/group) intramuscularly. Locomotor activity was evaluated through open field and gait tests and toxicological effects were evaluated through the "Functional Observatinal Battery" (FOB), weight gain and water and food intake for 22 days after administration, and through the calculation of the relative weight of kidneys, liver and muscle (gastrocnemius and soleus). The results of the locomotor activity evaluation show that, in the open field test, between 48h and 7 days after exposure, there was a decrease in locomotion and rearing, but this effect was transient and didn't paralyze the animal; and in the gait test, there was a change in the extension of the fingers and of the foot of the limb that were exposed to BoNtA. The results of the toxicological evaluation show that animals treated with BoNtA had lower water and food intake and weight loss, that may be related to the muscle atrophy seen in the muscle tissues and to the increase in the relative weight of the kidneys. However, in the FOB evaluation there was no difference in the parameters analyzed. These data suggest that, despite muscle atrophy, there was no impairment in the locomotor activity and in the general health of the animals, proving that this is a safe protocol to analyze the effects of the BoNtA during pregnancy and lactation in rats.
Acknowledgements: MackPesquisa and CAPES.

Disclosures: **E.L. Ricci:** None. **L. Pantaleon:** None. **L. de Paula:** None. **G. Ribeiro:** None. **V. Romanato:** None. **M. Rosseti:** None. **S. Lopes:** None. **J. Zaccarelli Magalhães:** None. **G. Ramos Abreu:** None. **J. Delorenzi:** None. **A. Fukushima:** None. **H. Spinosa:** None.

Poster

138. Airways, Breathing, and Neural Networks Intersect

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 138.01

Topic: E.08. Respiratory Regulation

Support: Tenovus Scotland Grant T20-09

Title: Modulation of respiratory-related output from phrenic motoneurons by spinal cholinergic pathways

Authors: *G. CALABRESE, M. J. BROADHEAD, L. MOTHERWELL, S. A. SHARPLES, G. B. MILES;
Sch. of Psychology and Neurosci., Univ. of St Andrews, St Andrews, United Kingdom

Abstract: Breathing is arguably the most fundamental biological function and must be readily adjusted to meet changing metabolic demands. Whilst it is well established that the respiratory rhythm is generated in the brainstem, there is mounting evidence that cervical spinal interneurons (INs) may play a role in adjusting respiratory output. However, we still do not know how this spinal modulation is achieved. Here we aim to investigate cholinergic modulation of phrenic motoneurons (MNs) and respiratory-related motor output with a focus on the C-bouton system, a large cholinergic modulatory synapse derived from $Pitx2^+$ spinal INs. C-boutons have previously been shown to facilitate the output of lumbar MNs in a task-dependent manner, via M2 muscarinic receptor signaling. We used a combination of mouse genetics, immunohistochemistry, *in-vitro* calcium imaging and electrophysiology to study cholinergic modulation of breathing and interrogate the underlying neural mechanisms. Anatomical investigations were performed on cervical spinal cord slices from mice at postnatal days 7 to 9 (P7-9), and respiratory-related activity was recorded with extracellular suction electrodes from C3 and C4 ventral roots in isolated brainstem-spinal cord preparations obtained from mice at P3-4. We found that C-bouton synapses, derived from $Pitx2^+$ INs, are present on the soma and proximal dendrites of cervical MNs at level C3 to C5, with a bias toward $MMP9^+$ fast MNs compared to $ErrB^+$ slow MNs. We also found that cervical $Pitx2^+$ INs are active during respiration, albeit not in phase with individual bursts of respiratory-related motor output. Moreover, pharmacological blockade of M2 receptors reduced the amplitude and increased the frequency of respiratory-related activity, suggesting a role for M2 receptors in the control of the respiratory rhythm and motor output. Interestingly, the reduction in amplitude was reproduced when M2 receptors were selectively blocked in the cervical spinal cord using a split chamber, suggesting that phrenic motoneurons are modulated by endogenous cholinergic signaling through M2 receptors. However, chemogenetic inhibition of $Pitx2^+$ INs did not alter respiratory-related activity, suggesting that these INs might not be involved in maintaining respiratory output during eupneic breathing at the early postnatal period *in-vitro*. Together, these data demonstrate a role for cholinergic modulation in the maintenance of respiratory output that is intrinsic to the cervical spinal cord, although the contribution of C-boutons to this modulation remains unclear.

Disclosures: G. Calabrese: None. **M.J. Broadhead:** None. **L. Motherwell:** None. **S.A. Sharples:** None. **G.B. Miles:** None.

Poster

138. Airways, Breathing, and Neural Networks Intersect

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 138.02

Topic: E.08. Respiratory Regulation

Support: NIH Grant R01HD052772

Title: Serotonin neurons make a major contribution to chemosensitivity of retrotrapezoid neurons.

Authors: Y. WU, E. BRAVO, ***G. RICHERSON**;
Univ. of Iowa, Iowa City, IA

Abstract: Serotonergic neurons of the raphe and *Phox2b* neurons of the retrotrapezoid nucleus (RTN) have both been proposed to be central respiratory chemoreceptors (CRCs). One of the properties required of CRCs is intrinsic sensitivity to CO_2 / pH. We recently reported that *Phox2b* neurons in the location where RTN neurons were first described (Mulkey et al, 2004) owed much of their pH response to input from 5-HT neurons (Wu et al, 2019). Here we formally measure the intrinsic response of RTN neurons after acute dissociation. RTN neurons were obtained from P6 to P10 *Phox2b*-Cre mice (provided by Paul Gray) crossed with floxed tdTomato mice (www.jax.org/strain/007909) and *ChAT*−eGFP mice (www.jax.org/strain/007902). RTN neurons were dissected ventral to the VII nucleus, and identified as those expressing tdTomato but not GFP. 5-HT neurons were obtained from the r. pallidus, magnus and obscurus of P11-P19 *ePet*-EYFP mice (Evan Deneris). Tissue was digested with papain prior to trituration. Dissociated cells were plated on coverslips and perforated patch recordings were made 1-3 days after plating. We compared the response of RTN neurons and 5-HT neurons to a change in CO_2 from 5% to 9% (pH 7.4 to 7.2). 49% of 5-HT neurons (n=70) increased their firing rate by more than 50% with a mean increase of 201%. In contrast, only 19% of RTN neurons (n=21) increased their firing rate by more than 50% with a mean increase of 76%. We then repeated these experiments using isocapnic changes in pH from 8.0 to 7.0. 70% of 5-HT neurons (n=61) increased their firing rate by more than 50% with a mean increase of 417%. In contrast, 31% of RTN neurons (n=126) increased their firing rate by more than 50% with a mean increase of 199%. RTN neurons developed greater chemosensitivity after being cultured for longer than 3 days, but those neurons with a larger response were more likely to be closely associated with neurites immunoreactive for microtubule associated protein - a marker of axons. We prepared co-cultures of RTN neurons with 5-HT neurons that expressed channelrhodopsin under control of the promoter for tryptophan hydroxylase 2. After 33-62 days *in vitro*, 50% of RTN neurons (n=20) increased their firing rate by more than 200% (mean of 802%; baseline constrained at >0.2 Hz) in response to CO_2 (5% to 9%) and also increased firing rate from a mean of 0.04 Hz to 1.62 Hz in response to laser activation of 5-HT neurons at 5 Hz (compared to 0.29 to 0.43 Hz in CO_2 nonresponders). These results indicate that most of the response of RTN neurons to a physiologically relevant change in pH is due to input from 5-HT neurons rather than being intrinsic. RTN neurons may play a more important role as relays of chemoreceptor input than as pH sensors.

Disclosures: Y. Wu: None. **E. Bravo:** None. **G. Richerson:** None.

Poster

138. Airways, Breathing, and Neural Networks Intersect

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 138.03

Topic: E.08. Respiratory Regulation

Support: R01 HL130249
R01 HL161142
UM1 HG006348
R01 DK114356

Title: Automation of the neonate autoresuscitation assay and its analysis

Authors: *C. S. WARD, D. PATEL, M. GARCIA ACOSTA, B. RUIZ, S. BARNETT, E. AISSI, R. RAY;
Baylor Col. of Med., Houston, TX

Abstract: Background: Sudden Infant Death Syndrome is thought to partly result from unseen brain abnormalities affecting cardio-respiratory function, but for which no clear genetic or environmental mechanisms are known. Mouse genetic and exposure models present an opportunity to uncover molecular and environmental mechanisms. However, measuring cardio-respiratory function in neonate mice is expensive, difficult, and inefficient. One major challenge is the time needed to carry out such measurements. The neonate autoresuscitation assay, consisting of repeated anoxic exposures followed by recovery, requires the full attention of an observer for the multi-hour duration of a single-subject assay, limiting throughput. To address this, we developed a closed-loop feature detection platform for automated neonate cardio-respiratory measurements.
Methods: Our platform design consists of:
1) a pneumotachograph face-mask for precise respiratory measurements.
2) a micro-controller automated bell-housing gas switching system for rapid induction of respiratory challenges.
3) a micro-computer-based data-acquisition system with real-time feature detection and outputs for controlling gas exposure.
4) a data analysis suite that assists with recordkeeping and provides a facile method to extract key outcome measures.
Results: Gas challenges are administered via the rotating bell housing system. A python program detects waveform features in real-time, such as apnea and bradycardia. Upon apnea detection, the system switches to a rescue gas. Resumption of normal breathing and heart rate can also be detected and incorporated into criteria for automated initiation of the next anoxic exposure trial. Data is stored for later offline automated analysis using the data analysis suite.
Conclusions: The system offers a relatively inexpensive approach for automated high throughput neonate cardio-respiratory assessment. The improvements permitting increased throughput and reduced variation in experimental parameters makes the system suitable for screening of genetic and exposure risks as well as potential therapeutics for Sudden Infant Death Syndrome.

Disclosures: C.S. Ward: None. **D. Patel:** None. **M. Garcia Acosta:** None. **B. Ruiz:** None. **S. Barnett:** None. **E. Aissi:** None. **R. Ray:** None.

Poster

138. Airways, Breathing, and Neural Networks Intersect

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 138.04

Topic: E.08. Respiratory Regulation

Support: NIH P20M103436

Title: In vitro evoked swallow elicits slow-timecourse modulation of respiration consistent with airway protection.

Authors: T. PITTS[1], N. TOPORIKOVA[5], J. TABAK[6], L. LANE[2], K. E. ICEMAN[3], J. CAI[7], B. GOURÉVITCH[8], ***N. MELLEN**[4];
[1]Dept. of Neurolog. Surgery, Univ. of Louisville, Louisville, KY; [2]Univ. of Louisville, LOUISVILLE, KY; [3]Neurolog. Surgery, [4]Neurol., Univ. of Louisville, Louisville, KY; [5]BIology, Washington and Lee Univ., Lexington, VA; [6]Col. of Med. and Hlth., Univ. of Exeter, Exeter, United Kingdom; [7]Pediatrics, Univ. of Louisville Sch. of Med., Louisville, KY; [8]Unité de Génétique et Physiologie de l'Audition, Inst. Pasteur, Paris, France

Abstract: To survive, newborn mammals must be able to feed themselves and breathe in a coordinated manner to avoid aspirating food. Both behaviors are mediated by medullary networks: breathing is regulated by networks of respiration-modulated neurons distributed along the ventral respiratory column (VRC). Networks controlling swallow are distributed along the dorsal swallow group (DSG) and the ventral swallow group (VSG) contained within the nucleus tractus solitarius and medullary reticular formation. In the sagittally sectioned rodent hindbrain (SSRH) preparation, the DSG, VSG and VRC are exposed at the surface of the preparation. To study interactions between these networks, optical recordings were carried out in neonate mice expressing the genetically encoded Ca2+ indicator GCaMP6F in the germline, enabling an unbiased and inclusive sampling of the heterogeneous neurons mediating these behaviors. Respiratory motor output was recorded from hypoglossal (XIIn) and phrenic (C4) nerves via suction electrode. During optical recording bouts (20Hz-50Hz, 600 s) fictive swallow was evoked by electrical stimulation in DSG (6V, 20 Hz, 600 ms), triggered from inspiratory burst onset. Swallow was characterized by a burst at XIIn unaccompanied by activity at C4; and a sequential activation of the rostral portion of the nucleus ambiguus (NA), followed by activation of a more caudal portion of the NA. Based on anterograde tracing studies labeling esophageal, pharyngeal, and laryngeal (pre)motoneurons, this sequential activation qualitatively reproduces the coordinated motor pattern of swallow in intact animals. At the end of the experiment, brainstems were fixed and the sagittal face of the preparation was sectioned off in a 400 µm thick section for immunoprocessing, enabling a taxonomy of respiratory and swallow network constituents based on activity pattern and protein markers. To assess whether networks preserved in the SSRH could coordinate fictive swallow and breathing, we compared the effect on expiratory duration of swallows evoked in the early (1.5 s) or late (4 s - 7 s, depending on average period) portion of expiration. We found that normalized period was significantly longer ($p=0.004$) in cycles where swallow was evoked late in expiration, compared to cycles where swallow was evoked early. In addition, NA activation and XIIn activity was sometimes observed seconds after stimulus offset, and always just before or after the inspiratory burst. Together, these findings suggest that circuits necessary for the adaptive intercalation of breath and swallow are preserved in the SSRH preparation, and are mediated by slow processes.

Disclosures: **T. Pitts:** None. **N. Toporikova:** None. **J. Tabak:** None. **L. Lane:** None. **K.E. Iceman:** None. **J. Cai:** None. **B. Gourévitch:** None. **N. Mellen:** None.

Poster

138. Airways, Breathing, and Neural Networks Intersect

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 138.05

Topic: E.08. Respiratory Regulation

Support: NIH R01 HL126523
NIH R01 HL144801
NIH R01 HL151389
NIH P01 HL090554
NIH F32 HL159904

Title: Latent neural population dynamics underlie normal and disrupted breathing

Authors: *N. BUSH[1], J.-M. RAMIREZ[1,2,3];
[1]Seattle Children's Res. Inst., Seattle, WA; [2]Neurolog. Surgery, [3]Pediatrics, Univ. of Washington, Seattle, WA

Abstract: The generation of the breathing rhythm involves the coordinated activity of diverse populations of medullary neurons. Here, we use high-density electrophysiological recordings (Neuropixels) to record spiking activity simultaneously from hundreds of neurons across the ventral respiratory column (VRC, including the Bötzinger, post-inspiratory and pre-Bötzinger complexes) in anesthetized, freely breathing mice. We identify the genotype of subsets of these neurons with optogenetic tagging, and identify each neuron's anatomical location with 3D histological reconstructions. Across the over 13,000 neurons recorded, we find that respiratory-related neural activity tiles the breathing phase such that discrete functional cell classes cannot be quantitatively defined. Further, we use neural population dynamics analyses to show that the neural populations are constrained to latent trajectories through a low-dimensional neural manifold. Analyses of these trajectories indicate that the termination of inspiration ("inspiratory-off switch") represents an attractor in the low-dimensional neural space. We next perturb the respiratory neural populations with pharmacological and physiological challenges. Administration of opioids causes diverse reconfigurations in single neurons activities and subsequent respiratory depression. The evolution of the population trajectories slowed, but the population activity manifold structure was preserved. By contrast, hypoxia induces gasping fundamentally alters the respiratory neural manifolds. The population activity trajectories transition to a ballistic dynamic mode strikingly different than eupnea or opioid induced respiratory depression (OIRD). Together these data suggest that simple, low-dimensional population dynamics emerges from a diverse and heterogeneous network distributed along the entire VRC.

Disclosures: **N. Bush:** None. **J. Ramirez:** None.

Poster

138. Airways, Breathing, and Neural Networks Intersect

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 138.06

Topic: E.08. Respiratory Regulation

Support: Research was funded by the Canadian Institutes of Health Research and AF was supported by an Ontario Graduate Scholarship and a St. Michael's Hospital Research Training Centre Top-Up Award.

Title: Midbrain periaqueductal gray somatostatin-expressing cells constitute a key circuit modulating breathing and respiratory depression by opioids

Authors: *A. FURDUI[1,2], C. SCARPELLINI[1], G. MONTANDON[1,2,3];
[1]Keenan Res. Ctr. for Biomed. Sci., St. Michael's Hosp., Toronto, ON, Canada; [2]Inst. of Med. Sci., [3]Div. of Respirology, Dept. of Med., Univ. of Toronto, Toronto, ON, Canada

Abstract: Breathing is a universal function in mammals that is essential to sustain life. Yet, it can be modulated by pain or stress or can be paused during vocalization. Although the neural circuits underlying rhythmic breathing have been well identified, the circuits inherent to voluntary or conscious modulation of breathing are less well understood. One region implicated in pain and defensive or complex behaviours, such as vocalization, is the midbrain periaqueductal gray (PAG). A subpopulation of somatostatin (SST)-expressing cells in the PAG have reciprocal connections with the preBötzinger Complex, a medullary site involved in the generation of respiratory rhythm. In addition to its role in vocalization, the PAG is involved in pain and expresses mu-opioid receptors (MORs) and may play a key role in opioid-induced respiratory depression (OIRD). Here, we aimed to determine the role of the midbrain PAG SST-expressing cells in the modulation of the respiratory cycle during eupneic breathing and OIRD. We hypothesized that optogenetic activation of SST-expressing cells in the PAG would stimulate breathing and modulate respiratory depression by the opioid fentanyl. In addition, we propose that SST and MOR mRNA are co-expressed in the PAG. To this aim, we used a Cre-lox recombination approach to create transgenic mice expressing the excitatory light-sensitive receptor channelrhodopsin-2 linked to an enhanced yellow fluorescence protein (eYFP) in SST-expressing cells (SST-ChR2-eYFP$^{+/+}$). To determine the role of PAG SST-expressing cells in breathing and OIRD, mice were anesthetized, placed in a stereotaxic frame and an optical fibre was lowered dorsally above the PAG to activate SST-expressing cells using a blue light (470nm). Electrodes were inserted to record diaphragm and genioglossus muscle activity and an intramuscular injection of fentanyl (5 μg/kg) was used to induce respiratory depression. To determine co-expression of MOR and SST mRNA, we used *in situ* hybridization in midbrain sections containing the PAG. Preliminary findings showed that activation of PAG SST-expressing cells in SST-ChR2-eYFP$^{+/+}$ mice (n=3, male and female, 3-5 months old) increased

respiratory rate by shortening the time between inspirations. Activation of SST-expressing cells in the PAG also increased respiratory rate during respiratory depression induced by fentanyl. We also found that SST and MOR mRNAs were expressed in the PAG, with a subset of cells in the lateral and ventrolateral PAG co-expressing SST and MOR mRNA. Taken together, our preliminary findings suggest that PAG SST-expressing cells may constitute a population of cells that can modulate eupneic breathing and OIRD.

Disclosures: **A. Furdui:** None. **C. Scarpellini:** None. **G. Montandon:** None.

Poster

138. Airways, Breathing, and Neural Networks Intersect

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 138.07

Topic: E.08. Respiratory Regulation

Title: Whole-brain analysis of CO_2 chemosensitive regions and identification of the retrotrapezoid and medullary raphé nuclei in common marmoset (Callithrix jacchus)

Authors: *A. TURK, S. SHEIKHBAHAEI;
Natl. Inst. of Neurolog. Disorders and Stroke, Bethesda, MD

Abstract: Respiratory chemosensitivity is an important mechanism by which the brain senses changes in blood partial pressure of CO_2 (PCO_2). It is proposed that special neurons and astrocytes in various brainstem regions play key roles as CO_2 central respiratory chemosensors in rodents. Although common marmosets (*Callithrix jacchus*), New-World non-human primates, show similar respiratory responses to elevated inspired CO_2 as rodents, the chemosensitive regions in marmoset brain have not been defined yet. Here, a hypercapnic environment was induced using whole-body plethysmography to activate brainstem regions integral to respiration. We used c-fos immunostainings to identify brain-wide CO_2-activated brain regions in common marmosets. In addition, we mapped the location of the retrotrapezoid nucleus (RTN) and raphé nuclei in the marmoset brainstem based on colocalization of CO_2-induced c-fos immunoreactivity with histology immunostaining using Phox2b and TPH, respectively. We also mapped location of preBötzinger complex (preBötC) and locus coeruleus (LC) based on NK1R, SST, ChAT, and TPH immunostaining. In addition, we found higher c-fos expression in certain brain regions in marmosets exposed to acute 6% CO_2. These regions include ventrolateral periaqueductal grey (0.07 ± 0.009 vs. 0.01 ± 0.0004 in control, $p = 0.02$, unpaired t test), lateral hypothalamus (0.2 ± 0.03 vs. 0.02 ± 0.004 in control, $p = 0.03$, unpaired t test), paraventricular thalamus (0.05 ± 0.01 vs. 0.03 ± 0.0003, $p = 0.067$, unpaired t test), insula (0.07 ± 0.03 vs. 0.005 ± 0.003 in control, $p = 0.006$, unpaired t test), and area 24 in the cerebral cortex (0.07 ± 0.002 vs. 0.02 ± 0.0004 in control, $p = 0.002$, unpaired t test). Our data also indicated that, similar to rodents, some astrocytes in marmoset RTN express Phox2b and have long processes that create a meshwork structure at the ventral surface of medulla. These data suggest that the common

marmoset is a good primate model for studying respiratory responses to hypercapnia and might be helpful to fill the gap and translate rodent breathing data to humans.

Disclosures: A. Turk: None. **S. SheikhBahaei:** None.

Poster

138. Airways, Breathing, and Neural Networks Intersect

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 138.08

Topic: E.08. Respiratory Regulation

Support: Louis and Harold Price Foundation
H & H Evergreen Foundation
J. Yang Family Foundation
National Institute of Drug Abuse (R01DA047637)

Title: Ventral Cervical Spinal Cord electrical epidural stimulation induced phase resetting of Respiration in the presence of opioid in human.

Authors: *A. PATEL[1], R. HUANG[1], E. GARNER[2], Y. ZHOU[1], M. MADHAVAN[1], S. WANG[3], T. HOMSEY[2], T. LOU[2], H. VINTERS[2], N. SALAMON[4], M. R. NUWER[5], I. WU[6], J. C. LEITER[7], D. C. LU[1];
[1]Dept. of Neurosurg., [2]Dept. of Neurosci., [3]Dept. of Intrnl. Med., [4]Dept. of Radiology, [5]Dept. of Neurol., [6]Dept. of Anesthesiol., Univ. of California Los Angeles, Los Angeles, CA; [7]Dept. of Mol. and systems biology, Darthmount, Hanover, NH

Abstract: Opioid overdose is one of the leading causes of overdose related deaths in the United States of America, accounting for 70.6% of overdose fatalities in 2019 alone. A leading cause of death among opioid overdoses is respiratory depression. Epidural electrical stimulation (EES) emerges as a novel approach of facilitating rhythmic motor activities such as locomotion and respiration. Previous studies conducted in humans and rodent models demonstrated respiratory augmentations induced by EES delivered to the dorsal cervical spinal cord. Importantly, EES at the dorsal cervical spinal cord opposes opioid-induced respiratory depression in human. To reveal the mechanisms underpinning cervical EES modulation of the respiratory neural circuit, we conducted a comparative study between dorsal cervical EES and ventral EES in patients with opioid-induced respiratory suppression or depression. We hypothesize that the ventral cervical EES activates the local motor neuronal pools while the dorsal EES recruits both sensory and motor cervical circuits as well as accesses supraspinal structures in the medulla. We recruited and consented 25 patients who underwent anterior (ventral) cervical spinal cord surgery compared the effect of ventral cervical EES with a dataset from 18 similar patients treated with dorsal cervical stimulation. In the 25 patients, the EES was deliver to the ventral surface of spinal cord ranging from cervical level 3 to 7 (C3 to C7) for no more than 90 seconds at the optimal intensity ranging from 0.5 mA to 5 mA with stimulation frequencies 5 Hz or 30 Hz. In both the

dorsal and ventral EES groups, the subjects were anesthetized with low- or high-dose remifentanil that partially or completely depressed voluntary respiration. We observed three main differences between the dorsal and ventral cervical EES effects on respiration in the presence of remifentanil. First, dorsal cervical EES induced resetting of inspiratory onsets while the ventral cervical EES did not. Second, dorsal but not ventral cervical EES induced persistent respiratory modulation after the stimulation stopped. Third, dorsal cervical EES induced both frequency and amplitude changes of respiration whereas ventral cervical EES modulated only the amplitude of the respiration significantly. Thus, dorsal and ventral cervical EES may facilitate respiration via different neural circuits.

Disclosures: **A. Patel:** A. Employment/Salary (full or part-time):; University of California Los Angeles. **R. Huang:** A. Employment/Salary (full or part-time):; University of California Los Angeles. **E. Garner:** A. Employment/Salary (full or part-time):; University of California Los Angeles. **Y. Zhou:** None. **M. Madhavan:** None. **S. Wang:** A. Employment/Salary (full or part-time):; University of California Los Angeles. **T. Homsey:** A. Employment/Salary (full or part-time):; University of Sothern California. **T. Lou:** None. **H. Vinters:** A. Employment/Salary (full or part-time):; University of California Los Angeles. **N. Salamon:** A. Employment/Salary (full or part-time):; University of California Los Angeles. **M.R. Nuwer:** A. Employment/Salary (full or part-time):; University of California Los Angeles. **I. Wu:** A. Employment/Salary (full or part-time):; University of California Los Angeles. **J.C. Leiter:** A. Employment/Salary (full or part-time):; University of California Los Angeles, Darthmount College. **D.C. Lu:** A. Employment/Salary (full or part-time):; University of California Los Angeles. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Louis and Harold Price Foundation, H & H Evergreen Foundation, J. Yang Family Foundation, National Institute of Drug Abuse (R01DA047637). E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Restore Technologies, inc.

Poster

138. Airways, Breathing, and Neural Networks Intersect

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 138.09

Topic: E.08. Respiratory Regulation

Support: University of Minnesota BIRCWH/Women's Health Research Program Seed Grant
National Heart Lungs Brain Institute R01HL146477
Rehabilitation Science Graduate Program, UMN Medical School

Title: The impact of estrogen, aging, and ovariectomy on hypoxic sensitivity and respiratory neuroplasticity

Authors: *J. GRITTNER[1], S. MILLER[1], B. J. DOUGHERTY[2];
[1]Univ. of Minnesota, Minneapolis, MN; [2]Rehabil. Med., Univ. of Minnesota, MINNEAPOLIS, MN

Abstract: Respiratory neuroplasticity is dependent on 17β-estradiol in adult female rats. Circulating 17β-estradiol is the most abundant and neuroactive form of estrogen and levels fluctuate significantly across the normal estrus cycle. Our prior work demonstrated that female rats express respiratory neuroplasticity only during the proestrus stage of the estrus cycle when circulating 17β-estradiol levels are high. Plasticity is not expressed during stages with low circulating 17β-estradiol or following the removal of the ovaries (ovariectomy; OVX). Estrogen supplementation restores neuroplasticity after OVX, supporting the idea that 17β-estradiol is necessary for the expression of neuroplasticity in female rats. As part of the natural aging process, estrous-cycle related fluctuations in 17β-estradiol levels gradually cease. Accordingly, we hypothesized that age-related reductions in circulating estrogen would eliminate the expression of respiratory neuroplasticity. We additionally postulated that the loss of neuroplasticity would be independent of hypoxic chemosensitivity, as both neural and ventilatory responses to hypoxia do not differ in female rats across the estrus cycle or following OVX. Three experimental groups of female rats were used: old rats (>24 mos old) in persistent diestrus (n=6), young rats (3 mos old) during proestrus (per vaginal cytology; n=4), and young OVX (n=4). Contrary to our hypothesis, the old group demonstrated a robust and significantly enhanced expression of phrenic long-term facilitation (pLTF), a well characterized model of respiratory neuroplasticity, compared with young and OVX groups ($p<0.05$). Cardiovascular changes in the old group may have influenced these findings. Chemosensitivity was measured during progressive hypoxic challenges at 15%, 12%, and 9% oxygen (O_2) with unrestrained barometric plethysmography. All groups exhibited intact chemosensitivity as demonstrated by a significant change in respiratory neural drive at 9% O_2, calculated as the ratio of tidal volume (VT) to inspiratory time (Ti), controlling for metabolism ($VT/Ti/VCO_2$; < 0.05). Further analysis showed that proestrus rats also demonstrated greater sensitivity to hypoxia as compared to the old and OVX groups. $VT/Ti/VCO_2$ reached significance ($p < 0.05$) at 12% and 9%, and multiple linear regression showed a steeper slope of change in proestrus rats that approached significance ($p = 0.06$) in our small sample. Collectively, these data suggest that aging impacts respiratory function in complex and unique ways that differ from OVX in female rats. This may be significant since OVX is commonly used as a model of age-related physiological changes.

Disclosures: J. Grittner: None. **S. Miller:** None. **B.J. Dougherty:** None.

Poster

138. Airways, Breathing, and Neural Networks Intersect

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 138.10

Topic: E.08. Respiratory Regulation

Support: National Heart Lungs Brain Institute R01HL146477
Rehabilitation Science Graduate Program, UMN Medical School

Title: A western diet influences ventilation in a sex specific manner and prevents expression of phrenic long term facilitation

Authors: *R. BAROK[1], B. J. DOUGHERTY[2];
[2]Rehabil. Med., [1]Univ. of Minnesota, Minneapolis, MN

Abstract: Respiratory neuroplasticity is influenced by circulating sex hormones (e.g., estrogen and testosterone). In particular, the well-defined model of respiratory neuroplasticity, phrenic long-term facilitation (pLTF), characterized as a progressive augmentation of phrenic neural output following acute intermittent hypoxia (AIH) depends on circulating estrogen, and without estrogen present, pLTF is abolished. Many biological factors influence estrogen levels such as age, gender, and diet. Indeed, the Western Diet is associated with increased levels of circulating estradiol in low estrogen populations of women. The Western Diet is defined by high intakes of red and processed meats, sweets, fried food, and refined grains as well as high intakes of sugar, salt, omega-6 fatty acids, and a reduction in omega-3 fatty acids. This diet is typical among cultures in the Western Hemisphere, an area commonly dominated by metabolic diseases such as cardiovascular disease, diabetes, and hypertension. Because the Western Diet is linked with increased estrogen, and estrogen is essential to the expression of respiratory neuroplasticity, we examined the impact of Western Diet on respiratory function and the expression of AIH-induced pLTF. Rats of both sexes were placed on a diet of Western Diet pellets or standard chow for 12 weeks. Whole-body plethysmography was used to measure ventilatory responses over the course of the diet. After 12 weeks, plethysmography data showed no change in normoxic ventilation in either sex over the course of the diet. However, in response to hypoxia (12% and 9% O_2), male Western Diet rats showed an increase in tidal volume while the females showed a decrease in tidal volume but an increase in frequency. At study conclusion, AIH-induced pLTF was examined in anesthetized, vagotomized, and mechanically ventilated rats to quantify respiratory neuroplasticity. Females in the Western Diet group showed a loss of pLTF (-1.5% pLTF at 60-min post-hypoxia) relative to rats provided standard chow (36% pLTF at 60-min post-hypoxia). Males also appeared to lose the expression of AIH-induced pLTF (-7% pLTF at 60-min post-hypoxia). The diet did not increase body mass and produced sex-specific effects on circulating estradiol. These preliminary findings indicate that a Western Diet may influence respiratory function in a sex-specific manner and may impede the induction of respiratory neuroplasticity.

Disclosures: R. Barok: None. **B.J. Dougherty:** None.

Poster

138. Airways, Breathing, and Neural Networks Intersect

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 138.11

Topic: E.08. Respiratory Regulation

Support: HHMI
Damon Runyon Fellowship

Title: Moleuclarly distinct lung mechanoreceptors in breathing regulation

Authors: *Y. LIU[1], A. J. DIAZ DE ARCE[2], M. KRASNOW[1];
[2]Dept. of Biochem., [1]Stanford Univ., Stanford, CA

Abstract: Sensory neurons innervating the lungs monitor chemical and mechanical signals inside the organ and transmit this information into the central nervous system to regulate respiratory and autonomic functions. Here, we generated a comprehensive transcriptomic atlas of mouse vagal pulmonary sensory neurons and defined 10 molecular subtypes that differ in developmental origin, myelination, receptive fields, terminal morphologies, and cell contacts. To our surprise, 7 out of the 10 subtypes express mechanosensitive channels Piezo1 and/or Piezo2, thus are putative lung mechanoreceptors. By combining subtype-specific genetic manipulations with physiological assessment of breathing behaviors, we found that two Piezo2-expressing molecular subtypes, forming distinct terminals in the lungs, regulate eupneic breathing in a complementary manner. Mapping of their central projections in the brainstem revealed separate targeting regions, indicating differential downstream circuits mediating their functions. Overall, our results suggest that lung mechanoreceptors are highly diverse, rivaling the level of cutaneous mechanoreceptors, and their distinct functions and downstream circuits enable fine-tuning of breathing.

Disclosures: Y. Liu: None. **A.J. Diaz De Arce:** None. **M. Krasnow:** None.

Poster

138. Airways, Breathing, and Neural Networks Intersect

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 138.12

Topic: E.04. Voluntary Movements

Support: HHMI
Simons Collaboration on the Global Brain
CIHR
NIH Grant NS112312
NIH Grant NS113110
McKnight Foundation

Title: Activity maps of orofacial rhythms

Authors: *L. D. LIU[1], A. FINKELSTEIN[3], S. WEST[4], K. SVOBODA[5], N. LI[2];
[1]Baylor Col. of Med., [2]Neurosci., Baylor Col. of Med., Houston, TX; [3]Dept. of Physiol. and Pharmacol., Tel Aviv Univ., Tel Aviv, Israel; [4]Univ. Col. London, London, United Kingdom; [5]HHMI / Janelia Farm Res. Campus, Ashburn, VA

Abstract: Orofacial movements are rhythmic behaviors that require coordination of many muscles. For example, our speech and breathing are coordinated so we speak only on exhalations. How these behaviors are coordinated at the level of neural circuits remains poorly understood. We use Neuropixel probes to map rhythmic activity related to breathing and licking in the mouse brainstem. Mice licked one of nine spatial targets for a water reward. Facial movements were tracked with high-speed videography, while breathing was recorded with an airflow meter. Licking frequency was 5.8 +/- 1.2 Hz, while breathing frequency was 4.0 Hz +/- 1.0 Hz. We performed 340 Neuropixels probe recordings in 31 animals, corresponding to 19,000 units. The recordings were aligned to the Allen Mouse Brain Common Coordinate Framework. This facilitated comparisons of recorded activity to an anatomical map of motor and premotor neurons for the airway, jaw, and tongue muscles. Distinct spatial clusters of medulla neurons exhibited rhythmic activity that was phase-locked with breathing and licking. Units synchronized to breathing were localized to the ventral intermediate reticular nucleus, preBotzinger complex and the nucleus ambiguous. The units synchronized to licking overlapped with premotor and motor neurons for the jaw and tongue, as mapped by retrograde labeling (Takatoh et al. 2021). The breathing-related units in the ventral intermediate reticular nucleus preferentially fire at the deflated phase of the breath, whereas the breathing-related units at the preBotzinger complex preferentially fire at the expiration phase of the breath. Most of the licking-related units preferentially fire at the protracted phase of the lick. Units in the licking oscillator preferentially fire for licking in the ipsilateral direction. Breathing and licking movements are coupled, so that licking was phased-locked to breathing and does not overlap with inhalation. Similarly, the rhythmic activity of breathing and licking neurons are coordinated. In recording sessions in which both types of neuron were simultaneously recorded, typically with two Neuropixels probes, the neurons show anti-correlated activity. Despite the coupling of licking to inhalation, mice can initiate licks at much shorter latency than a cycle of breath. We find that mice preemptively adjust their breathing phase before licking initiation, and the phase of breathing reset at the onset of licking bouts.

Disclosures: L.D. Liu: None. **A. Finkelstein:** None. **S. West:** None. **K. Svoboda:** None. **N. Li:** None.

Poster

138. Airways, Breathing, and Neural Networks Intersect

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 138.13

Topic: E.08. Respiratory Regulation

Support: HL-126523
HL-144801
HL-151389
HL-144454
HL154558
HL145004

Title: Inspiratory rhythm generation is stabilized by I_h

Authors: *N. J. BURGRAFF[1], R. S. PHILLIPS[1], L. J. SEVERS[2], N. E. BUSH[1], N. A. BAERTSCH[3], J. M. RAMIREZ[1];
[1]Seattle Children's Res. Inst., Seattle, WA; [2]Physiol. and Biophysics, The Univ. of Washington, Seattle, WA; [3]Ctr. for Integrative Brain Res., Univ. of Washington, Seattle, WA

Abstract: The generation of rhythmicity is a fundamental property of the nervous system. Common amongst all rhythmogenic networks is the ability to reconfigure and adapt to changes in metabolic and behavioral demands. Yet, this flexibility, must be counter-balanced by the need to maintain stability. A group of neurons collectively known as the preBötzinger complex (preBötC) within the ventral respiratory column of the medulla assemble in a network that is both necessary and sufficient for inspiratory rhythm generation. Fundamental to generating rhythmic activity within the preBötC is a heterogenous distribution of ionic currents across the network. One ionic current which plays a key role in the generation of rhythm across multiple neural networks of the CNS is the hyperpolarization activated inward cation current (I_h). I_h is a voltage-dependent mixed cationic current that is activated upon phasic hyperpolarization. The role of I_h in rhythmogenesis within the preBötC is inconclusive. Some reports find that blocking I_h has minimal effect, while others conclude that this increases the rate of rhythmic bursting. To date, I_h was specifically studied in bursting cells which only comprise a small subset of the preBötC. Thus, the question remains about expression of I_h amongst the other cells, including tonically spiking and inhibitory cells. Herein we characterized the distribution of I_h amongst the population of tonically active and inhibitory cells of the preBötC. Additionally, we tested whether removing I_h in-vitro and in-vivo renders the network more susceptible to inhibitory-based challenges. Using in-vitro patch clamping we found that I_h showed greatest expression amongst tonically active excitatory (68% of $DBX1^+$), and inhibitory (67% of $VGAT^+$) cells of the preBötC. Additionally, removing I_h using ZD7288 silenced nearly all tonic spiking within the preBötC. This showed minimal effect on the rhythmic activity of fully synchronized bursts from the preBötC, but significantly increased the incidence of burstlet activity. Despite the minimal effect on fully synchronized burst activity, removing I_h and reducing tonic activity rendered the preBötC more susceptible to silencing following opioid (DAMGO) and CNQX administration. This effect was recapitulated in-vivo with microdialysis of ZD7288 into the preBötC. In summary, I_h plays a complex role within the rhythm generating network of the preBötC. At rest, I_h is not necessary for bursting within the network. However, I_h becomes increasingly important during inhibitory challenges within the network. Without I_h, the ability for the network to generate rhythmic bursting is confined to a smaller dynamic range.

Disclosures: N.J. Burgraff: None. **R.S. Phillips:** None. **L.J. Severs:** None. **N.E. Bush:** None. **N.A. Baertsch:** None. **J.M. Ramirez:** None.

Poster

138. Airways, Breathing, and Neural Networks Intersect

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 138.14

Topic: E.08. Respiratory Regulation

Support: NHLBI R00HL145004
HHMI

Title: A parabrachial tachykinin1 circuit controls state-dependent breathing patterns

Authors: J. W. ARTHURS[1], R. D. PALMITER[2], *N. A. BAERTSCH[3,4];
[2]Biochem., [3]Pediatrics, [1]Univ. of Washington, Seattle, WA; [4]Ctr. for Integrative Brain Res., Seattle Children's Res. Inst., Seattle, WA

Abstract: Breathing is regulated automatically by neural circuits in the medulla that integrate chemo-feedback to ensure homeostasis is maintained. However, in awake animals, breathing is also conditionally modified by behavior and emotion. In mice, this is exemplified by rapid breathing patterns that are unique to the awake state and are distinct from, and suppressed by, breathing driven by chemoreflexes. Manipulations of medullary neurons that are critical for the automatic control of breathing have not reproduced these rapid breathing patterns. Because the neural circuits that mediate this state-dependent control of breathing are not well understood, we hypothesized that the parabrachial nucleus (PBN), an integrative hub for many affective states and behaviors including breathing, may contain such a circuit. Using optogenetics to manipulate transcriptionally defined subsets of PBN neurons, we found that photoactivation of tachykinin1-expressing neurons (*Tac1*) produced breathing patterns that resembled rapid breathing in the awake state but differed from chemoreflex-driven breathing patterns. Conversely, photoactivation of PBN neurons that express CGRP (*Calca*) suppressed rapid breathing patterns. Because *Tac1* and *Calca* expressing neurons partially overlap, we selectively activated *Tac1* neurons that do not express *Calca* (*Tac1+;Calca-*). Optogenetic activation of this subset of neurons drove breathing to even higher frequencies, consistent with *Tac1* and *Calca* neurons having opposing roles in respiratory control. Repetitive stimulation of *Tac1+;Calca-* neurons entrained breathing frequency up to ~12 Hz, matching the maximum rates produced spontaneously by awake mice. Single, brief stimulations potently advanced the onset of the next breath independent of when the stimulation occurred during the respiratory cycle. Similar effects were observed during stimulation of *Tac1+;Calca-* axonal projections within the ventral intermediate reticular zone of the medulla (vIRt). Importantly, all effects of activating *Tac1+Calca-* neurons or their projections in the vIRt were eliminated under light anesthesia. These results identify a subset of PBN neurons that specifically controls state-dependent breathing patterns and may be important for the integration of breathing with behavior and emotion.

Disclosures: J.W. Arthurs: None. **R.D. Palmiter:** None. **N.A. Baertsch:** None.

Poster

138. Airways, Breathing, and Neural Networks Intersect

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 138.15

Topic: E.08. Respiratory Regulation

Support: Supported by Renée James Seed Grant (AGH)

Title: Maternal opioids age-dependently impair the central respiratory control network.

Authors: *S. A. BEYELER, N. R. MORRISON, A. G. HUXTABLE;
Univ. of Oregon, Univ. of Oregon, Eugene, OR

Abstract: Infants exposed to maternal opioids are often diagnosed with Neonatal Abstinence Syndrome (NAS) and have respiratory deficits. In a maternal opioid animal model, neonates had destabilized breathing and blunted acute opioid responses immediately after birth (postnatal day 0 to 1, P0-1), which normalized with age (P2-5). To test central contributions to these deficits, we hypothesized that maternal opioids age-dependently impair central brainstem and spinal respiratory networks. In isolated brainstem-spinal cords (BSSCs), respiratory burst frequencies decreased in P0-1 neonates after maternal opioids (8±1 bursts/min, n=6) compared to P0-1 neonates after maternal no treatment (neonates after MNT, 12±2 bursts/min, n=5; $p<0.05$), but were similar to frequencies in older neonates (P2-5 neonates after maternal opioids 11±2 burst/min, n=6; P2-5 neonates after MNT 11±1 burst/min, n=5; $p>0.9$). In reduced preparations targeting rhythm generating networks (preBötzinger Complexes, preBötCs), however, burst frequencies were similar in all treatments and ages (neonates after maternal opioids: P0-1 21±5 burst/min, n=5, P2-5 15±5 burst/min, n=6; neonates after MNT: P0-1 20±2 burst/min, n=4, P2-5 17±4 burst/min, n=2; $p>0.1$), supporting central, age-dependent deficits beyond the preBötC. Using opioid receptor antagonism (10μM naloxone) to test the role of opioid receptors in central deficits, burst amplitude increased in isolated respiratory networks (BSSCs) P0-1 neonates after maternal opioids (11±1% baseline, n=2), but not in P0-1 neonates after MNT treatment (-18±2% baseline, n=2) or older neonates (P2-5 neonates after maternal opioids -10±2% baseline, n=2; P2-5 neonates after MNT -12±2% baseline, n=2), suggesting circulating opioids, likely of maternal origin, may contribute to reduced central respiratory activity after maternal opioids. Increased amplitude, but not frequency, supports effects on respiratory premotor neurons, motoneurons, or other modulating centers. After opioid receptor agonism, burst frequencies were maintained in P0-1 neonates after maternal opioids and acute opioids (10μM methadone: -48±25% baseline, n=6; $p<0.05$), but not in older neonates after maternal opioids (P2-5 -77±25% baseline, n=6; $p>0.9$) or neonates after MNT (P0-1 -100±0% baseline, n=6; P2-5 -97±7% baseline, n=6; $p>0.9$), supporting central changes in opioid receptor activity, which are similar to blunted breathing responses to acute opioids after maternal opioids. Thus, maternal opioids age-dependently impair neonatal central respiratory networks, which may contribute to neonatal breathing deficits after maternal opioids and in NAS infants.

Disclosures: S.A. Beyeler: None. **N.R. Morrison:** None. **A.G. Huxtable:** None.

Poster

139. Neuroendocrine Anatomy and Physiology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 139.01

Topic: F.02. Neuroendrocrine Processes and Behavior

Support: University of Houston–National Research University Fund grant R0503962 to B.A.A
Beckman Young Investigator Award to B.A.A
NIH grant R35GM142799 to B.A.A

Title: Single-cell sequencing the social brain: Cell-level RNA expression profiles in the hypothalamus of the social cichlid fish Astatotilapia burtoni

Authors: *A. P. HOADLEY[1], M. B. CASTILLO[2], P. H. GUNARATNE[2], B. A. ALWARD[1]; [1]Dept. of Psychology, [2]Dept. of Biol. and Biochem., Univ. of Houston, Houston, TX

Abstract: The cichlid fish *Astatotilapia burtoni* has a complex, but relatively well-characterized social system, which has supported decades of research into its behavior and neurobiology. Additionally, modern functional genetics tools like CRISPR/cas9 gene editing have been optimized for use in this species. *A. burtoni* has been useful in elucidating key principles of the hormonal control of socially relevant behaviors, including dominance, aggression, and courtship. However, we do not yet have a comprehensive understanding of the cell-types involved in these processes, or molecular characterization of those cells that would facilitate an even deeper understanding of the hormonal control of brain and behavior. To further *A. burtoni*'s development as a genetically tractable model system, we are using Single-cell RNA-sequencing (scRNA-seq) to profile cell-type specific molecular markers of the hypothalamus. These individual markers, or groups of co-expressing markers, will allow us to unambiguously identify cell types in future observational and experimental work. We present preliminary data exploring the cellular landscape of the hypothalamus using scRNA-seq. This region is central to the vertebrate brain's 'social behavior network', allowing us to build a molecular profile of socially relevant cell populations. Unbiased clustering analysis has allowed us to identify at least 19 putative cell types in among individuals that vary according to socially relevant traits such as social status, reproductive status, and sex. Our findings represent the first single-cell resolution expression analysis of *A. burtoni*, and indeed of any cichlid fish to our knowledge. This dataset further develops the resources available for better understanding the cellular and molecular mechanisms driving behavioral plasticity.

Disclosures: A.P. Hoadley: None. **M.B. Castillo:** None. **P.H. Gunaratne:** None. **B.A. Alward:** None.

Poster

139. Neuroendocrine Anatomy and Physiology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 139.02

Topic: F.02. Neuroendrocrine Processes and Behavior

Support: University of Houston - National Research University Fund Grant R0503962 to B.A.A
Beckman Young Investigator Award to B.A.A
NIH Grant R35GM142799 to B.A.A

Title: Characterizing sex-typical aggressive behaviors and their neural substrates in Astatotilapia burtoni

Authors: *L. R. JACKSON[1], M. DUMITRASCU[1], B. A. ALWARD[1,2];
[1]Dept. of Psychology, [2]Dept. of Biol. and Biochem., Univ. of Houston, Houston, TX

Abstract: Aggression is ubiquitous among social species, maintains social dominance hierarchies, and is tightly linked to reproductive physiology and steroid hormones. The African cichlid fish *Astatotilapia burtoni* is an ideal study species for studying aggression due to their unique and flexible dominance hierarchy. However, female aggression in this species and the neural basis of aggression in both sexes is not well understood. To further understand the potential sex differences in aggression in this species, we have characterized aggression in male and female *A. burtoni* using a mirror assay and are identifying the brain regions activated following an aggressive interaction with immunohistochemistry by detecting the phosphorylated ribosome marker phospho-S6 ribosomal protein (pS6), a marker for neural activation. Using the general aggression model (GAM) in humans as a framework to understand neural mechanisms of behavior in *A. burtoni*, the nuclei essential in the 'social behavior network' and the 'social decision-making network' (SDMN) will be investigated for neural activation following an aggressive assay. We have found that *A. burtoni* males (n=8) and females (n=7) can both perform some of the same aggressive behaviors, such as attacks and lateral displays, providing a rare opportunity to isolate and compare intrasexual aggression in males and females. Nonetheless, males and females do perform distinct aggressive behaviors. For instance, females, but not males, perform a male-typical reproductive behavior, quivers, during the assay, while males, but not females, perform rostral displays. These findings may indicate that the same behaviors in males and females are used for different functions and are elicited differentially by intrasexual context. By characterizing sex-typical aggressive behaviors in male and female *A. burtoni* and identifying the brain regions activated to produce these behaviors, we can begin to further understand the neural mechanisms of behavior.

Disclosures: L.R. Jackson: None. **M. Dumitrascu:** None. **B.A. Alward:** None.

Poster

139. Neuroendocrine Anatomy and Physiology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 139.03

Topic: F.02. Neuroendrocrine Processes and Behavior

Support: NIH grant R35GM142799 to BAA
Startup Grant UH R0503962 to BAA
Beckman Young Investigator Award to BAA

Title: Lack of androgen receptor reduces brain aromatase expression in the African cichlid Astatotilapia burtoni

Authors: *M. S. LOPEZ[1], B. A. ALWARD[1,2];
[1]Psychology, [2]Biol., Univ. of Houston, Houston, TX

Abstract: Social behaviors are regulated, in part, by steroid hormones such as androgens and estrogens. However, the specific hormonal mechanisms and the roles that hormones play in modulating social behavior remain to be elucidated. Across different species, androgens are known to play a role in the production of social behaviors, through the direct action of androgens via androgen receptors (ARs) or through the conversion of androgens to estrogens by the enzyme aromatase. Thus, studying the specific actions of androgens, aromatase, and estrogens can give insight into the mechanisms that produce social behaviors. Our research program investigates the role of hormonal signaling on social behavior using the African cichlid *Astatotilapia burtoni,* an ideal model species due to its genetic tractability, highly social nature, and social flexibility. The males of the species come in two forms, dominant (D) males which are brightly colored and perform aggressive and reproductive behaviors, and non-dominant (ND) males which are drably colored and perform subordinate behavior. Due to a teleost-specific whole-genome duplication event, *A.burtoni* has two functional androgen receptor (AR) genes. In males, ARα is necessary to produce aggressive and reproductive behavior, while ARβ is required for dominant-typical coloration and large testes. I propose to investigate whether some actions of androgen signaling may occur indirectly through the control of estradiol synthesis by examining the expression of brain-specific aromatase (*aromb)* in male and female fish lacking a functional ARα gene. Preliminary results show that *aromb* is differentially expressed in ARα deficient males compared to wild type males, in specific brain regions related to behavioral production, such as the preoptic area (POA) of the telencephalon. These studies will provide novel insights into the hormonal mechanisms of social behavior and lay a foundation for future functional studies.

Disclosures: M.S. Lopez: None. **B.A. Alward:** None.

Poster

139. Neuroendocrine Anatomy and Physiology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 139.04

Topic: F.02. Neuroendrocrine Processes and Behavior

Support: NIH grant DA046160
NIH grant DK120891

Title: Transcriptomic study reveals changes in gene expressions in the lateral hypothalamic area in socially isolated animals

Authors: D.-M. LI, *X.-B. GAO;
Comparative Med., Yale Univ. Sch. of Med., New Haven, CT

Abstract: There has been ample evidence that social isolation (SI) has profound effects on physiological functions and behaviors in animals. As a stressor, social isolation results in altered energy balance and sleep homeostasis, drug addiction, and mental disorders/diseases. It has been proposed that brain circuitry regulating social homeostasis has a central role in mediating effects of social isolation on animals. The lateral hypothalamus (LH) is a classic brain center regulating homeostatic processes, such as energy balance, sleep homeostasis and others, in animals. It is still understudied whether the LH serves as a regulator of social homeostasis. To address this question, we examined in this study changes in gene expressions in the LH in male mice under acute social isolation. Group housed male mice (C57BL/6, 2-3 months old) were randomly divided into three groups: control, SI (mice were separated and singly housed for 24 hours) and SI with recovery (mice were allowed to return to their home cages for 24 hours after an acute SI episode). Brain tissue from the LH area was collected and total RNA was extracted from all three groups of mice; transcriptomic analysis was performed with Clariom ^{TM} S mouse Assay. Our preliminary results indicated that 443 genes were significantly ($P<0.05$, t test) up- (fold change >1.5) or down-regulated (fold change < -1.5) in mice under SI as compared with controls. 351 genes were significantly ($P<0.05$, t test) up- (fold change >1.5) or down-regulated (fold change < -1.5) in mice under SI with recovery as compared with controls. Specifically, genes encoding proteins responsible for neurotransmitter receptors and neurotransmission (GABA-A receptor subunits), neuropeptides (Trh and Crh) and neuropeptide receptors (Trhr and Crhr1) were significantly up- or down-regulated in the LH area in SI mice, implying that neural circuits underwent re-programming in the LH area in socially isolated animals. In summary, our results suggest that neuronal systems in the LH area respond to acute social isolation and that the LH may serve as a homeostatic center for sociability.

Disclosures: D. Li: None. **X. Gao:** None.

Poster

139. Neuroendocrine Anatomy and Physiology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 139.05

Topic: F.02. Neuroendrocrine Processes and Behavior

Support: NSERC Discovery Grant RGPIN-2017-06272 (MJC)
NSERC Canadian Graduate Scholarship (BSB)
I-CUREUS (CL)

Title: Distribution of beta-klothomRNA in the hypothalamus, amygdala, hippocampal formation, and subiculum of female mice

Authors: *B. S. BONO, C. S. LEMARQUAND, M. J. CHEE;
Neurosci., Carleton Univ., Ottawa, ON, Canada

Abstract: Beta-Klotho (KLB) is a co-receptor that is essential for the diverse actions of fibroblast growth factor 21 (FGF21), such as in energy metabolism, sucrose preference, and alcohol aversion. FGF21 can have sex-dependent effects, for example to promote infertility in female mice by suppressing ovulation, however KLB expression has only been examined in male animals. Here, we described the distribution of *Klb* mRNA hybridization in the hypothalamus, amygdala, hippocampal formation, and subiculum of female mice and compared it to that recently described in male mice (Bono et al., 2022). We performed *in situ* hybridization using RNAscope technology to label *Klb* mRNA hybridization in brain tissue from female wildtype mice. *Klb* mRNA hybridization appeared as punctate dots that colocalized to a 4′,6-diamidino-2-phenylindole (DAPI)-labeled soma, and *Klb* cells may have low (1-3 dots/cell; low-*Klb*), medium (4-9 dots/cell; medium-*Klb*), or high (10+ dots/cell; high-*Klb*) amount of *Klb* mRNA per cell. We then mapped *Klb* hybridization onto *Allen Reference Atlas* templates to determine the spatial distribution of *Klb* cells. The distribution pattern of *Klb* cells within the hypothalamus, amygdala, or hippocampus was comparable between female and male brains. However, the number of *Klb* cells may vary in a region-specific manner. In the hypothalamus and amygdala, the pattern and number of low-, medium-, or high-*Klb* cells were similar between sexes. For example, the lateral hypothalamic area contained the highest number of *Klb* cells in both the female and male hypothalamus. In the amygdala, the central amygdalar nucleus was the most prominent *Klb*-expressing region and comprised the most medium- and high-*Klb* cells in both sexes. By contrast, while the distribution pattern of *Klb* cells in the pyramidal layers of the hippocampal formation and subiculum remained consistent, there was notably more *Klb* cells throughout the hippocampal formation and subiculum of female brains. The abundance of *Klb* cells in the hippocampus of female brains was observed in low-, medium-, and high-*Klb* cells, though their relative proportion remained the same. As hippocampal activation may inhibit ovulation, the prevalence *of Klb* cells in the hippocampus may underlie FGF21-mediated infertility in female mice. Overall, our results suggest that *Klb* expression may be more abundant in the female brain. However, the differences between sexes were region-specific and varied in the quantity of *Klb* cells rather than the emergence of *Klb* cells in additional brain regions.

Disclosures: B.S. Bono: None. **C.S. Lemarquand:** None. **M.J. Chee:** None.

Poster

139. Neuroendocrine Anatomy and Physiology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 139.06

Topic: F.02. Neuroendrocrine Processes and Behavior

Support: CIHR Project Grant 452284
Natural Sciences and Engineering Council of Canada - Canada Graduate Scholarship Master's
Natural Sciences and Engineering Council of Canada - Postgraduate Scholarships Doctoral
Ontario Graduate Scholarship
Queen Elizabeth II Graduate Scholarship

Title: Impact of dietary fructose on the synaptic adaptability of arcuate NPY neurons

Authors: *A. SANKHE, M. A. PAYANT, M. J. CHEE;
Carleton Univ., Ottawa, ON, Canada

Abstract: Fructose is a sugar naturally found in fruits but often consumed in excess via added sugars in processed or packaged foods. Fructose intake promotes obesity, and our preliminary data suggest that the obesogenic actions of fructose may have neural origins. Male or female mice fed a 60% high fructose diet ate more calories than chow-fed mice. Interestingly, *ex vivo* patch-clamp recordings from Neuropeptide Y (NPY) cells of the arcuate nucleus revealed an increase in excitatory synaptic input following fructose feeding. As the stimulation of NPY cells promote food intake and weight gain, increasing synaptic excitation may drive the obesogenic actions of fructose. Here, we determined if the increase in excitatory input to NPY cells may be reversed upon the cessation of fructose feeding.Male and female NPYhrGFP mice expressing a green fluorescent protein in NPY neurons were fed chow for five weeks; a 60% high fructose diet (HFrD) for five weeks; or HFrD for four weeks and chow for one week. All HFrD-fed male mice ate more calories (84 ± 1 kcal) than their chow-fed littermates (70 ± 2 kcal) over the first four weeks, but this hyperphagia was relieved when HFrD-fed mice were returned to a chow diet (67 ± 3 kcal). Interestingly, female HFrD-fed mice (69 ± 1 kcal) did not display hyperphagia relative to their chow-fed counterparts (67 ± 1 kcal). There were no differences between the body weight of chow- or HFrD-fed mice of either sex. At the end of the 5-week diet period, we performed patch-clamp recordings to determine the frequency of excitatory postsynaptic current (sEPSC) events arriving at NPYhrGFP cells. The sEPSC frequency at NPY cells of both male (10.8 ± 3.1 Hz) and female (8.6 ± 1.9 Hz) HFrD-fed mice was higher than their respective male (6.3 ± 0.7 Hz) and female (4.9 ± 1.5 Hz) chow-fed counterparts. Subsequently, NPY cells of male HFrD-fed mice that returned to chow received a lower frequency of sEPSC events (5.6 ± 1.5 Hz) than mice fed HFrD only; this excitatory input was comparable to chow-fed mice. Interestingly, the frequency of sEPSC events (10.8 ± 1.2 Hz) at NPY cells of female HFrD-fed mice that returned to chow remained elevated. Our findings reflected a sex difference in HFrD-mediated feeding and neural outcomes. While the synaptic responses of HFrD-fed male mice were linked with hyperphagia, female HFrD-fed mice exhibited an upregulation of excitatory input at NPY cells without hyperphagia. Furthermore, this excitatory drive was sustained even upon the cessation of HFrD feeding. Taken together, these results indicate that dietary fructose may produce long-lasting neurological outcomes that promote feeding.

Disclosures: **A. Sankhe:** None. **M.A. Payant:** None. **M.J. Chee:** None.

Poster

139. Neuroendocrine Anatomy and Physiology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 139.07

Topic: F.02. Neuroendrocrine Processes and Behavior

Title: Role of serotonin 2C receptors expressed by CRH neurons

Authors: *E.-S. YOO[1], M. SA[2], C. J. LEE[2], J.-W. SOHN[1];
[1]Biol. Sci., Korea Advanced Inst. of Sci. and Technol., Daejeon, Korea, Republic of; [2]Ctr. for Cognition and Sociality, Inst. For Basic Sci. (IBS), Daejeon, Korea, Republic of

Abstract: The anorexigenic (appetite-suppressing) effects of serotonin 2C receptor (*Htr2c*) agonists have been largely attributed to *Htr2c* expressed by the pro-opiomelanocortin (POMC) neurons in the arcuate nucleus of the hypothalamus. However, *Htr2c* is widely expressed in various brain regions, and it is possible that other neuronal populations that express *Htr2c*s may also contribute to *Htr2c*-induced anorexigenic effects. Here, we show the role of *Htr2c* expressed by the corticotropin-releasing hormone (CRH) neurons through the generation of conditional knock-out (KO) mice. We found that energy balance and glucose homeostasis of the conditional KO mice are not significantly changed, but the anorexigenic effects of the *Htr2c* agonist are significantly attenuated. We performed additional experiments to delineate the mechanisms involved in this phenotype. Taken together, we suggest that *Htr2c*s expressed by the CRH neurons are responsible for the anorexia induced by *Htr2c* agonists.

Disclosures: E. Yoo: None. **M. Sa:** None. **C.J. Lee:** None. **J. Sohn:** None.

Poster

139. Neuroendocrine Anatomy and Physiology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 139.08

Topic: F.02. Neuroendrocrine Processes and Behavior

Support: Swedish Research Council Distinguished Professor Program (2021-00671)
European Research Council Advanced Grant (TOGETHER)
Knut och Alice Wallenbergs Stiftelse
Internal funds from Stockholm University

Title: Glutamatergic neurotransmission modulates neuroendocrine tuberoinfundibular dopamine (TIDA) network activity through metabotropic receptors in male rats

Authors: *O. NETSYK, C. BROBERGER;
Dept. of Biochem. and Biophysics, Stockholm Univ., Stockholm, Sweden

Abstract: Neuroendocrine tuberoinfundibular dopamine (TIDA) neurons, located in the hypothalamic dorsomedial arcuate nucleus, provide a tonic inhibition of release of the hormone, prolactin, from the pituitary gland. The precise control of prolactin is necessary for successful maternal behaviours, such as nursing, and to provide low baseline levels of prolactin in both sexes under most other conditions. TIDA neurons in the male rat are characterised by a distinct stereotyped slow (ca. 0.2 Hz) oscillatory electrical activity, where periods of relative hyperpolarization and quiescence (DOWN states) transit gradually into UP states of depolarization crowned by action potentials. The dynamics of rat TIDA oscillations depend intimately on strong electrical synapses within the network, and is modulated by several hormones, peptides and monoamine transmitters. The effects of the brain's predominant excitatory transmitter, glutamate, on this system, remain poorly understood, however. Here, we addressed this issue by whole-cell patch-clamp recordings performed on TIDA neurons in hypothalamic slices from male Sprague Dawley rats (P21-28). The effect of ionotropic glutamate receptors was relatively modest under basal conditions. AMPA receptor blockade resulted in a slowing of the TIDA oscillations (control vs GYKI 53655 (10 μM): 0.27 ± 0.02 Hz vs 0.25 ± 0.01 Hz, n=8 cells, paired t test, $p<0.05$ respectively). Blockage of NMDA receptors did not alter TIDA oscillation frequency (n=6). In contrast, metabotropic glutamate receptors (mGluR) were found to exert large effects on the TIDA oscillation. Thus, application of group I mGluR agonist, (S)-3,5-DHPG (100 μM) modulated the TIDA oscillation and prolonged the active phase duration (control vs (S)-3,5-DHPG: 2 ± 0.2 s vs 6 ± 1.1 s, n=4 cells, $p<0.05$ respectively) as well as the action potential instantaneous frequency (control vs (S)-3,5-DHPG: 7.8 ± 1.3 Hz vs 5.9 ± 0.9 Hz, n=6 cells, paired t test, $p<0.05$ respectively) and kinetics. Application of (S)-3,5-DHPG in the presence of Na^+ channel blocker TTX (500 nM) depolarised the membrane potential of the TIDA neurons by ~ 5 mV (n=9 cells, paired t test, $p<0.001$). Interestingly, activation of group I mGluR alters the rhythmicity, but not TIDA network synchrony (based on dual patch-clamp recordings of electrically connected neurons). These data suggest that glutamatergic neurotransmission differentially modulates state/timing of the TIDA network in male rats by activating different subtypes of GluR. Thus, slow excitatory input from yet-unidentified glutamatergic afferents could modulate the dopamine release and consequently the state of the lactotropic axis.

Disclosures: O. Netsyk: None. **C. Broberger:** None.

Poster

139. Neuroendocrine Anatomy and Physiology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 139.09

Topic: F.02. Neuroendrocrine Processes and Behavior

Support: R15 DK121246

Title: Acute peripheral oxytocin causes a decrease in skeletal muscle thermogenesis in mice

Authors: *A. HAUPT[1], C. A. WATTS[2], J. SMITH[3], A. MALIK[3], R. GIACOMINO[3], D. WALTER[3], H. K. CALDWELL[4], C. M. NOVAK[4];
[1]Kent State Univ., Kent State Univ. Sch. of Biomed. Sciences, Program In Neurosciences, Kent, OH; [2]Kent State Univ., East Lyme, CT; [4]Kent State Univ., [3]Kent State Univ., Kent, OH

Abstract: Oxytocin, while important to the regulation of social and reproductive behaviors, has also been implicated in several facets of energy homeostasis. Evidence suggests that oxytocin and its receptors can modulate the activation of thermogenesis. Specifically, long-term treatment with oxytocin contributes to the elevation of body temperature, and oxytocin may be a mediator of social hyperthermia. Since one potential source of heat is skeletal muscle thermogenesis, we wanted to explore how an acute peripheral injection of oxytocin would affect skeletal muscle temperature. We hypothesized that injection of oxytocin would increase skeletal muscle temperature in mice. To test this hypothesis, remote IPTT-300 temperature transponders were surgically implanted adjacent to the right gastrocnemius of both male and female wild-type mice. Using a hand-held reader, skeletal muscle temperatures of the hind leg were measured after an intraperitoneal (IP) injection of oxytocin or saline vehicle. After the recovery period, mice were habituated four times to the testing environment and procedure; there was a slight decrease in temperatures for each session confirming they habituated to the environment. Muscle temperatures were measured during acclimation and after IP injection of oxytocin (2 mg/kg) or vehicle for 3 hours after injection. We found that oxytocin treatment resulted in a sharp decrease in skeletal muscle temperature of approximately 3 degrees Celsius, starting from the time of injection and peaking at 30 minutes. Muscle temperatures declined in both males and females, and returned to baseline after 90 minutes. These data suggest that the acute peripheral injection of oxytocin decreases skeletal muscle thermogenesis. Future studies should directly compare the peripheral and central administration of oxytocin on thermogenesis. It will also be important to explore the difference between acute and chronic administration of oxytocin on skeletal muscle temperatures.

Disclosures: A. Haupt: None. **C.A. Watts:** None. **J. Smith:** None. **A. Malik:** None. **R. Giacomino:** None. **D. Walter:** None. **H.K. Caldwell:** None. **C.M. Novak:** None.

Poster

139. Neuroendocrine Anatomy and Physiology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 139.10

Topic: F.02. Neuroendrocrine Processes and Behavior

Support: NIH Grant R01 MH114994

Title: Oxytocin via oxytocin receptor excites neurons in the endopiriform nucleus of juvenile mice

Authors: *L. M. BIGGS, E. A. D. HAMMOCK;
Program in Neuroscience, Psychology Dept., Florida State Univ., Tallahassee, FL

Abstract: The neuropeptide oxytocin (OXT) modulates social behaviors across many different species. Although the OXT system has been the focus of much research over the last few decades, little is known regarding the role of the endopiriform nucleus (EPN), which expresses high, stable levels of OXT receptor (OXTR) throughout development and into adulthood. EPN integrates olfactory and gustatory input and has reciprocal connections with several limbic areas, including the entorhinal cortex and amygdala, areas important for learning and memory and processing social information. Thus, EPN could act as an association area for social stimuli via olfactory and gustatory input with further modulation via OXT released in the brain during social interactions. The role of OXTR signaling in EPN is unknown, so we sought to provide anatomical and electrophysiological information about OXTR signaling in mouse EPN neurons. We found via in situ hybridization that most EPN neurons co-express *Oxtr* mRNA and the marker for VGlut1, an indicator of glutamatergic cells. We hypothesized, based on high levels of OXTR ligand binding in EPN, that oxytocin application would modulate activity in these cells as measured by whole-cell patch-clamp electrophysiology. Bath application of OXT or OXTR specific ligand (TGOT) increased the excitability of EPN neurons in wild-type, but not OXTR-knockout tissue. These results show an effect of OXT on a VGlut1+ cell population within EPN. Given the robust, relatively stable OXTR expression in EPN throughout life, OXTR in this multi-sensory and limbic integration area may be important for modulating activity in response to an array of social or other salient stimuli throughout the lifespan and warrants further study.

Disclosures: L.M. Biggs: None. **E.A.D. Hammock:** None.

Poster

139. Neuroendocrine Anatomy and Physiology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 139.11

Topic: F.02. Neuroendrocrine Processes and Behavior

Support: NIH R01 MH114994

Title: Neonatal motor response to oxytocin paired with tactile stimulation in mice

Authors: *K. R. DAY[1], C. SMITH[1], E. A. HAMMOCK[2];
[2]Psychology, [1]Florida State Univ., Tallahassee, FL

Abstract: Oxytocin (OXT) is an essential neuropeptide involved in social behaviors such as mother-infant attachment. Breastmilk and saliva contain OXT produced by the mother that may be shared with the infant during care, such as grooming or breastfeeding. Maternal skin to skin contact (kangaroo care) is known to benefit infant growth and development and improve outcomes for human infants admitted to the NICU. We have previously identified oxytocin receptor (OXTR) in the orofacial region of neonatal mice, which may be sensitive to maternal

(exogenous) OXT cues during the neonatal period. We propose that exogenous OXT may cue the infants' oxytocin receptors (OXTR) to label maternal touch as "social" since OXT is not available from non-social tactile stimuli. To investigate this potential role, we hypothesize that OXT co-applied with tactile stimulation will modulate acute infant behavior responses to orofacial touch. Postnatal day 0 (P0) male and female wildtype mice without prior nursing experience were habituated to a socially isolated environment for two hours on the day of birth (P0). After habituation, tactile stimulation was applied to the face of neonates for 30 seconds with a paintbrush coated in either saline, a low dose (1.56pg/uL) of OXT in saline, or a high dose (1.25ng/uL) of OXT in saline. Neonates were observed for an additional 60 seconds after stimulation. This experiment establishes an ethogram for investigating motor behavior of neonatal mice on the day of birth and examines trends in motor behaviors among subjects that received tactile orofacial stimulation paired with exogenous OXT exposure in a socially isolated setting. Exogenous OXT paired with somatosensory stimulation may facilitate optimal nursing and infant attachment in early social development.

Disclosures: K.R. Day: None. **C. Smith:** None. **E.A. Hammock:** None.

Poster

139. Neuroendocrine Anatomy and Physiology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 139.12

Topic: F.02. Neuroendrocrine Processes and Behavior

Support: Leverhulme Trust Grant RPG-2017-287
BBSRC Grant BB/R016879/1
United Arab Emirates University (UAEU)-Program for Advanced Research UPAR-31M242
FAPESP, 2019/27581-0
The UIUC NIDA Center for Neuroproteomics P30 DA018310
BBSRC Grant BB/M009122/1
British Heart Foundation FS/17/60/33474

Title: Transcriptome plasticity of the core hypothalamic osmoregulatory control centre of the Arabian dromedary camel

Authors: *P. LIN[1], B. GILLARD[1], A. PAUŽA[1], F. IRAIZOZ[1], M. ALI[2], A. MECAWI[3], F. ALIM[4], E. ROMANOVA[5], P. BURGER[6], M. GREENWOOD[1], A. ADEM[7], D. MURPHY[1]; [1]Univ. of Bristol, Bristol, United Kingdom; [2]United Arab Emirates Univ., Al-Ain, United Arab Emirates; [3]Federal Univ. of São Paulo, São Paulo, Brazil; [4]Univ. Blida, Blida, Algeria; [5]Univ. of Illinois Urbana-Champaign, Urbana, IL; [6]Vetmeduni Vienna, Vienna, Austria; [7]Khalifa Univ., Abu Dhabi, United Arab Emirates

Abstract: To survive in arid environments places enormous evolutionary pressure on water conservation mechanisms. These are epitomised by the numerous adaptations manifested in those mammals, such as the dromedary camel (Camelus dromedarius), that thrive in the scorching heat of the Arabian deserts. At the level of the kidney, the dromedary produces low volumes of highly concentrated urine, more so when water is scarce, to conserve body water. Two hormones, arginine vasopressin (AVP) and oxytocin (OXT), both produced in the supraoptic nucleus (SON), the core hypothalamic osmoregulatory control centre, are vital for this adaptive process. Studies on rats (Pauža et al. 2021) have shown that the rat SON transcriptome undergoes dramatic function-related plasticity during water deprivation (WD), but the mechanisms that enable the camel SON to cope with osmotic stress are not known. Thus, to investigate the central control of water homeostasis in the camel, we have performed RNAseq transcriptome studies on the SON under control (water ad libitum) and WD conditions. We first used multiplex fluorescence in situ hybridization (RNAscope) to build three dimensional models of the camel SON based on the expression of the AVP and OXT mRNAs in order to facilitate sampling. We then compared the transcriptomes of the SON under control and WD conditions and identified genes that change in expression due to hyperosmotic stress. By comparing camel and rat datasets, we have identified common elements of the WD transcriptomic response network, as well as elements that appear to be unique to the dromedary camel and essential for adaptations necessary for life in the desert. In the follow-up study, we used 3D RNAseq pipeline (Guo et al. 2021) to analyze the RNAseq data with greater resolution identifying differential transcript, differential alternative splicing and differential transcript usage (3D), which revealed a list of genes with important post-transcriptional regulation and transcript-specific functions that might be involved in the response to WD-induced stress.

Disclosures: P. Lin: None. **B. Gillard:** None. **A. Pauža:** None. **F. Iraizoz:** None. **M. Ali:** None. **A. Mecawi:** None. **F. Alim:** None. **E. Romanova:** None. **P. Burger:** None. **M. Greenwood:** None. **A. Adem:** None. **D. Murphy:** None.

Poster

139. Neuroendocrine Anatomy and Physiology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 139.13

Topic: F.02. Neuroendrocrine Processes and Behavior

Support: R1012700

Title: Rasd1: a small G protein with a complex role in vasopressin magnocellular neurones

Authors: *G. ELSAMAD[1], D. MURPHY[2], M. P. GREENWOOD[1], A. G. PAUZA[1], A. PATERSON[1];
[2]Bristol Med. Sch., [1]Univ. of Bristol, Bristol, United Kingdom

Abstract: RASD1 is a member of the Ras family of monomeric G proteins that is known to regulate several signaling pathways. We have previously shown that RASD1 is expressed in vasopressin (AVP) magnocellular neurons (MCNs) of the supraoptic nucleus (SON) and paraventricular nucleus of the hypothalamus. In response to osmotic stress, *Rasd1* expression is robustly increased in both these brain nuclei. To identify signalling pathways being regulated by RASD1 in rat AVP MCNs, we selectively knocked down (KD) *Rasd1* expression using an AVP promoter driven specific miRNA. The polyadenylated transcriptome of KD SONs was determined by RNA sequencing and mined to generate comprehensive catalogues of functional classes of genes. The significant transcript changes were analysed to describe enriched gene ontology categories, KEGG and Reactome pathways. We identified the gene coding for nitric oxide synthase 1 adaptor protein (NOS1AP) to be differentially expressed in KD SONs and further validated interactions between RASD1, NOS1AP, and neuronal nitric oxide synthase in the SON by coimmunoprecipitation. We propose that Rasd1 forms a tertiary complex involving NOS1AP and nNOS to modulate signalling pathways in AVP MCNs.

Disclosures: G. Elsamad: None. **D. Murphy:** None. **M.P. Greenwood:** None. **A.G. Pauza:** None. **A. Paterson:** None.

Poster

139. Neuroendocrine Anatomy and Physiology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 139.14

Topic: F.02. Neuroendrocrine Processes and Behavior

Support: CIHR (FDN-143337)

Title: Sub-membrane actin cortex fenestrae in rat supraoptic nucleus (SON) magnocellular neurosecretory cells (MNCs).

Authors: *A. MURTAZ, C. W. BOURQUE;
McGill Univ., Montreal, QC, Canada

Abstract: Osmosensory transduction (OT) is a mechanical process where an N-terminal variant of the transient receptor potential vanilloid 1 (ΔN-Trpv1) channel is activated by a “push” force from microtubules during hypertonicity-induced cell shrinkage (Prager-Khoutorsky et al., 2014). MNCs also feature a dense and thick layer of actin filaments which are also essential for OT, but their exact contribution or whether the actin cortex has specific features important for OT is unknown. In this project, we used immunocytochemistry and proximity ligation assay (PLA) with super-resolution imaging to examine the actin cytoskeleton of acutely isolated MNCs of the rat SON. We found that the actin cortex features fenestrae of ~0.5 µm of lowered fluorescence in vasopressinergic (VP) MNCs (n=50; 4 preparations). There is on average one gap per micron (n=25). Average VP MNC cortical actin thickness is 0.34 µm (n=25). PLA confirmed previously known TRPV1-α tubulin interactions (Prager-Khoutorsky et al., 2014). Specifically, we observed

~20-40 interaction sites per cell perimeter across the midline (n=15; 6 preparations). In contrast, no interaction sites were detected when PLA was performed using antibodies directed against β-actin and TRPV1 (n=17, 3 preparations). We used super-resolution fluorescence microscopy with a FV 3000 Olympus confocal microscope (FV-OSR; 120 nm xy resolution) to obtain stacks of 4-10 images (Z stacks) of 0.32 µm Z spacing. Each stack of images was deconvoluted using constrained iterative with 5 iterations (cellSens software, Olympus Canada Ltd). In conclusion, this study reveals that the sub-membrane actin cortex of MNCs is fenestrated with TRPV1-tubulin interactions occurring significantly more in the fenestrae compared to the rest of the cytoskeleton. It also shows that TRPV1 interacts with α-tubulin and not with β-actin.

Disclosures: A. Murtaz: None. **C.W. Bourque:** None.

Poster

139. Neuroendocrine Anatomy and Physiology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 139.15

Topic: F.02. Neuroendrocrine Processes and Behavior

Support: NIH Grant R15HD090606

Title: Vasopressin 1a receptor localization in oxytocin receptor knockout mice

Authors: *E. J. SOMMER, H. K. CALDWELL;
Dept. of Biol. Sci., Kent State Univ., Kent, OH

Abstract: There is growing evidence to suggest that both the oxytocin (Oxt) and vasopressin (Avp) systems contribute to early brain development. Specifically, pharmacological and transgenic manipulations of the Oxt system suggest that disrupted signaling through the Oxt receptor (Oxtr) during embryonic development impacts adult behavior. Unfortunately, at this time, very little is known or understood about the interaction of these two systems during embryonic development. In mice, the Oxtr is present in both sexes as early as embryonic day (E) 16.5, while the production of Oxt is temporally offset between females and males. In females, Oxt mRNA is found as early as E12.5, but in males it is not transcribed until postnatal day (P) 2. In contrast, mRNA transcripts for Avp are found as early as E13.5 and the Avp 1a receptor (Avpr1a) is measurable in both sexes at E14.5. While both the Oxtr and the Avpr1a are present at E16.5 in a variety of brain regions, only within certain brain regions to they appear to be functional. At E16.5, within both sexes, the Oxtr is functional in the ventricular and subventricular zones of the cortical neuroepithelium, ventricular and subventricular zones of the septal neuroepithelium, and the developing amygdalar area. Avpr1a, on the other hand, is only functional in the ventral hypothalamic area in both sexes at E16.5. In order to better understand the interaction of systems in development we sought to determine how disruption to Oxtr signaling might affect brain region- and sex-specific distribution of the Avpr1a at P2 and P90. Thus, we utilized receptor autoradiography in male and female P2 and P90 mice to localize the

Avpr1a in oxytocin receptor knockout mice. Changes in brain region- and sex-specific localization of the Avpr1a across the lifespan can help begin to explain the interplay between the Oxt and Avp systems.

Disclosures: E.J. Sommer: None. **H.K. Caldwell:** None.

Poster

139. Neuroendocrine Anatomy and Physiology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 139.16

Topic: F.02. Neuroendrocrine Processes and Behavior

Support: CIHR FDN-143337
Healthy Brains for Healthy Lives (HBHL)

Title: Mechanisms of MDMA Induced Hyponatremia in Rats

Authors: *J. WYROSDIC, Z. S. THIROUIN, C. W. BOURQUE;
McGill Univ. Hlth. Ctr., Montreal, QC, Canada

Abstract: Clinical data has shown that a significant fraction of individuals ingesting the club drug MDMA (ecstasy) can develop life threatening hyponatremia, however the mechanisms responsible for this pathology are not understood. Experiments have disclosed a large increase in the body's antidiuretic hormone vasopressin after ingestion of MDMA, which may contribute to hyponatremia by promoting renal fluid retention. Interestingly, it is also hypothesized that MDMA increases water intake by inducing the sensation of thirst, however this has not been confirmed. Additionally, studies have suggested that the effects of MDMA are mediated by the reverse transport of the serotonin transporter (SERT). However, the mechanisms by which MDMA causes the release of vasopressin remains unknown. In this study I examined the effects of MDMA on water intake and the basis of vasopressin activation in rats. To examine if MDMA increases drinking behavior in rats, 10mg/kg of MDMA was injected IP, and water intake was measured. Unexpectedly, water intake did not change between the two groups. Suggesting that MDMA induced hyponatremia is caused by either vasopressin alone, or a combination of vasopressin with water intake motivated by factors other than thirst. To test these possibilities, I examined the effects of a water load, MDMA alone, and the combination of MDMA + water load. My findings indicate that MDMA alone is not sufficient to cause hyponatremia. Nonetheless, when MDMA is combined with a water load serum sodium drops to hyponatremic levels (less than 135mmol/L). To investigate the neurophysiological mechanisms underlying the activation of vasopressin neurons I performed experiments brain slices obtained AVP-eGFP transgenic rats. Whole cell current clamp as well as voltage clamp recordings from identified vasopressin neurons reveal that a bath application of 20μm of MDMA causes an excitatory response; mediated by membrane depolarization; which could be blocked by the 5HT1A receptor

antagonist. These results suggest that MDMA can act indirectly via the release of 5HT on neurons controlling vasopressin release fluid balance thereby promoting hyponatremia.

Disclosures: J. Wyrosdic: None. **Z.S. Thirouin:** None. **C.W. Bourque:** None.

Poster

139. Neuroendocrine Anatomy and Physiology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 139.17

Topic: F.02. Neuroendrocrine Processes and Behavior

Support: ORWH-U54-MH118919

Title: Cellular composition of the brainstem in light of auricular vagal nerve stimulation in mice.

Authors: *E. CASTELLANOS, S. A. TOBET;
Biomed. Sci., Colorado State Univ., Fort Collins, CO

Abstract: The vagus nerve (VN) is a major component of the autonomic nervous system. It influences multiple components of visceral sensation, motor activity, and homeostasis. As the most extensive cranial nerve, it passes through the neck into the thorax and abdomen, and of particular interest for this project, to the ear as its auricular branch. Stimulation of the vagus auricular branch has been proposed as a non-invasive alternative neuromodulatory therapy for treating several disorders, including depression. Unlike the invasive method of vagal nerve stimulation where surgery is done to implant a device to stimulate the entire nerve, activation of the auricular branch stimulates a small portion of the vagus. The cervical branch of the VN synapses through the nodose ganglia, directly going to the caudal portion of the nucleus of the solitary tract (NTS), while the auricular branch of the vagus synapses through the superior nodose or jugular ganglion where there are afferent inputs to the NTS, but also other brainstem nuclei such as the paratrigeminal nucleus. To begin mapping the chemoarchitecture of the likely auricular vagus targets in the NTS and paratrigeminal nucleus, mice were perfused with 4% paraformaldehyde and processed for immunohistochemistry. Initial neurochemical targets were calcitonin gene-related peptide (CGRP), Glutamate Decarboxylase 67 (GAD67), and Tyrosine Hydroxylase (TH). The distribution of each substance was seen in the caudal NTS (cNTS) at the greatest density. There was immunoreactive (ir) CGRP throughout the caudal to rostral NTS (rNTS), fibers were most dense in the cNTS and in the rNTS it was more evenly distributed. In the paratrigeminal nucleus, ir-CGRP was most dense in the spinal trigeminal tract from the caudal to rostral portions, with some fibers in the spinal trigeminal nucleus. The catecholaminergic neurons were most concentrated in the cNTS as well in the area postrema. There were sparse amounts of ir-TH neurons in the paratrigeminal nucleus throughout the brainstem. In the cNTS and in the caudal spinal trigeminal tract had greater densities of ir-GAD67 than in the middle and rostral portions. Ongoing studies are examining other neurochemical markers along with mapping cFOS activation as a function of auricular vagal

nerve stimulation and the underlying chemoarchitecture. Therefore, this study reinforces previous literature of cellular components in the brainstem and will establish activity of the auricular branch of the vagus nerve.

Disclosures: E. Castellanos: None. **S.A. Tobet:** None.

Poster

139. Neuroendocrine Anatomy and Physiology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 139.18

Topic: F.02. Neuroendrocrine Processes and Behavior

Support: PEIC-OSMO-2021

Title: Analysis of the expression of µ1-muscarinic receptors and 17β-estradiol receptors in celiac ganglion neurons of vagotomized adult rats vs non-vagotomized adult rats.

Authors: *J. BRAVO[1], D. BARRERA VALENCIA[2], K. PACHECO VILLAVICENCIO[2], M. RIVERA CASTRO[4], C. MORAN[5], V. BOHORQUEZ[3], A. CAMELO[3];
[1]BENEMERITA UNIVERSIDAD AUTONOMA DE PUEBLA, PUEBLA, Mexico; [2]RedOSMO, Oaxaca de Juarez, Mexico; [3]RedOSMO, Oaxaca, Mexico; [4]Inst. de Investigaciones Cerebrales, Univ. Veracruzana, Xalapa, Mexico; [5]Benemérita Univ. Autonoma de Puebla, Puebla, Mexico

Abstract: The extrinsic innervation of the ovaries has been extensively studied since it has been shown to regulate follicular development, steroidogenesis, and ovulation. It is known that estrogen receptors are expressed in the sympathetic and parasympathetic neurons that innervate the ovary. For its part, the celiac ganglion, which is the main innervation to the ovaries, regulates ovarian functions. In different animal models, the neurotransmitters such as NA and Ach, and VIP regulate ovarian steroidogenesis depending on the stage of the estrous cycle. In studies described in our laboratory, it is mentioned that the neurons of the celiac ganglion of the intact adult rat present variations in their activity throughout the reproductive cycle of the rat. Therefore, in the present work, we analyze if the parasympathetic innervation participates in the activation of the celiac ganglion neurons during the proestrus stage. We analyzed the expression of 17β-estradiol and µ1-muscarinic receptors in celiac ganglion neurons of vagotomized and non-vagotomized rats. Eight adult female rats from 3 to 5 months of age were divided into two groups (intact rats vs. vagotomized rats), which were recorded on the day of the estrous cycle to determine that they were on the day of proestrus to cut the vagus nerve. After surgery (24 hours), the animals were sacrificed to obtain the celiac ganglion and perform the immunohistochemical procedure for 17β-estradiol and µ1-muscarinic receptors. Histological analysis showed that there was greater expression of the markers used in animals without vagotomization (13731±2.5 vs 330.1±4.413 ($p<0.05$), and the area and size of the neurons also have a significant difference ($p<0.05$). Therefore, we would be concluding that the parasympathetic innervation affects the

expression of celiac ganglion hormone receptors influencing estradiol production within the ovary.

Disclosures: **J. Bravo:** None. **D. Barrera Valencia:** None. **K. Pacheco Villavicencio:** None. **M. Rivera Castro:** None. **C. Moran:** None. **V. Bohorquez:** None. **A. Camelo:** None.

Poster

139. Neuroendocrine Anatomy and Physiology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 139.19

Topic: F.02. Neuroendrocrine Processes and Behavior

Support: NIH-R15MH118692

Title: Various populations of corticotropin releasing factor neurons co-express androgen receptor, estrogen receptor alpha, and stress induced c-Fos in a sex-dependent manner

Authors: ***K. A. RYBKA**, J. J. LAFRICAN, Z. J. ROSINGER, D. O. ARIYIBI, M. R. BROOKS, J. S. JACOBSKIND, D. G. ZULOAGA;
Psychology, Univ. at Albany State Univ. of New York, Albany, NY

Abstract: Prevalence rates of mood disorders such as anxiety and depression are nearly twice as high in women when compared to men, with suggested mechanisms involving exposure to sex-dependent gonadal hormones and dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis. Actions of gonadal hormones through both androgen receptor (AR) and estrogen receptor alpha (ERα) have previously been implicated in the regulation of HPA axis responsiveness and anxiety-like behaviors, while corticotropin releasing factor (CRF) is known to regulate the HPA axis, anxiety, and depression. We first tested whether CRF expressing neurons, which are widely known to regulate neuroendocrine and behavioral stress responses, co-express AR and ERα as a potential mechanism for gonadal hormone regulation of these responses. Using Crh-IRES-Cre: Ai9 (tdTomato) reporter mice, we report high co-localization of AR in CRF neurons within the medial preoptic area (MPOA), bed nucleus of the stria terminalis (BST), medial amygdala (MeA), and ventromedial hypothalamus (VMH), moderate levels within the central amygdala (CeA), and low levels in the paraventricular hypothalamus (PVN). Sex differences in CRF/AR co-expression were found in the BST, CeA, and VMH where males showed higher levels of co-expression within these regions when compared to females. CRF co-localization with ERα was generally lower relative to AR co-localization, however, high co-expression was found within the MPOA and VMH, moderate levels in the arcuate nucleus and low levels in the PVN and CeA. Sex differences in CRF/ERα co-localization were found where females showed higher levels of co-localization in the MPOA and PVN when compared to males. Finally, to assess neural activation of CRF cells within these regions during psychogenic stress, we restrained mice for 30 minutes and assessed co-localization with the neural activation marker c-Fos. Females expressed greater CRF/c-Fos co-expression compared to males within the principal nucleus of

the BST, with no other sex differences found in other regions. Data will also be presented showing co-localization patterns of a receptor for CRF (CRFR2) with AR and ERα as another mechanism through which gonadal hormones may alter CRF signaling and function. Given the known role of CRF in the regulation of anxiety, depression, and the HPA axis, the presence of AR and ERα and sex-specific activation of discrete CRF cell groups indicate potential mechanisms for the regulation of sex differences in these functions.

Disclosures: K.A. Rybka: None. **J.J. Lafrican:** None. **Z.J. Rosinger:** None. **D.O. Ariyibi:** None. **M.R. Brooks:** None. **J.S. Jacobskind:** None. **D.G. Zuloaga:** None.

Poster

139. Neuroendocrine Anatomy and Physiology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 139.20

Topic: F.02. Neuroendrocrine Processes and Behavior

Support: DGAPA-PAPIIT IA200820
DGAPA-PAPIIT IA202218
DGAPA-PAPIIT IN214822
DGAPA-PAPIIT IN204718
CONACYT A1S8948

Title: Prolactin modulates sexual pheromone perception and accessory olfactory bulb cell activation in female mice

Authors: V. CERBANTEZ-BUENO, V. VIÑUELA-BERNI, D. E. MUNOZ-MAYORGA, **T. MORALES**, *R. CORONA;
Inst. de Neurobiología, Querétaro, Mexico

Abstract: Olfactory cues from opposite sex can induce neuroendocrine changes to promote sexual maturation and reproduction in female mice. These signals are processed by the olfactory bulb (OB), mainly by the accessory olfactory bulb (AOB) region with a less contribution of main olfactory bulb (MOB). Prolactin (PRL) is one of the hormones involved in these neuroendocrine effects. Previous reports showed expression of the prolactin receptor (PRLR) within the OB, however there was no clear evidence of the role of PRL within the OB during sexual maturation and sexual pheromone-exposure. In this work, we evaluate the mRNA expression of PRL and PRLR (*Prl* and *Prlr-l)* along with the expression of the PRLR, through Western blot, in the OB of female mice. The evaluations were performed in the onset of puberty, sexual maturation (first ovulation period) and adulthood. We found that although *Prl* and *Prlr-l* remain constant during these stages, the expression of PRLR-L in AOB is lower in adulthood compared with previous ages. The circulating levels of PRL, quantified with ELISA technique, also remain constant during these maturational stages. Later, we evaluate the role of PRL in the processing of sexual pheromones. Further, we administrate an acute PRL injection to adult female mice in estrous-

phase and exposed them to sexual experienced male soiled bedding. Using immunohistochemistry, we quantified the number of positive cFos cells, a marker of cellular activation, within the AOB and MOB along with their first central projections, the medial amygdala (MeA) and the piriform cortex (PirC), respectively. Our results show that within the AOB, PRL prevents the increased mitral cell activation expected for the exposure to the male soiled bedding; additionally, PRL promotes a higher activation in the anterior part, region specially involved in the processing of sex odorant cues. In this condition, PRL also promotes more activation in mitral cells located in the dorsal MOB. For the central projections we found that PRL augmented the cell activation within the MeA but no changes were observed in PirC. Finally, we evaluate the exploration trajectory of the mice during the pheromone exposure finding that females that received PRL augmented their exploration of the sexual relevant olfactory stimulus. In conclusion, our results suggest that PRL might participate in the sexual maturation of the females, since the PRLR expression is higher before adulthood, however, once adults, PRL could be participating in perception and behavioral responses triggered by male pheromones, and this response could be mediated by the mitral cells within the AOB and MOB, but also by the MeA.

Disclosures: V. Cerbantez-Bueno: None. **V. Viñuela-Berni:** None. **D.E. Munoz-Mayorga:** None. **T. Morales:** None. **R. Corona:** None.

Poster

139. Neuroendocrine Anatomy and Physiology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 139.21

Topic: F.02. Neuroendrocrine Processes and Behavior

Support: NIH R01DK131558
Klingenstein Fund and Simons Foundation, AHA 857082

Title: Differential effects of sugars on hunger circuits

Authors: *A. D. MCKNIGHT[1], A. VARGAS[2], A. L. ALHADEFF[2];
[1]Univ. of Pennsylvania, Philadelphia, PA; [2]Monell Chem. Senses Ctr., Philadelphia, PA

Abstract: Activity in hypothalamic hunger circuits drives feeding behavior. Our recent work demonstrated that different macronutrients (i.e., sugar and fat) inhibit neural activity in hypothalamic agouti-related protein (AgRP)-expressing neurons via distinct neural gut-brain mechanisms. However, there is a wide variety of sugars and fats in our modern diet. Here, we examined whether different sugars have differential effects on neural activity in the brain. We focused on glucose and fructose, which are sugars with the same caloric value but are metabolized differently. We confirmed previous findings that sugar-naive mice when given a choice between glucose and fructose (8% w/v) robustly prefer glucose ($n=16$, $p<0.001$), and demonstrated that this preference develops within ~60 min of sugar exposure. We next examined

how glucose and fructose impact activity in hypothalamic hunger neurons. We engineered mice to express GCaMP6s in AgRP neurons to monitor calcium signaling as a proxy for neural activity using *in vivo* fiber photometry. The same mice were also implanted with intestinal catheters to receive direct infusions of sugar into the gut. Equicaloric intestinal infusions (0, 8%, or 16% w/v, 1 ml infusion, 0.1 ml/min) of fructose were significantly less effective than glucose at inhibiting AgRP neuron activity ($n=10$, $p<0.01$ for 8% and $p<0.001$ for 16% sugar). We also discovered that the time to maximally inhibit AgRP activity was slower after fructose infusion compared to glucose infusion ($n=10$, $p<0.01$ for 8%, $p<0.05$ for 16%), suggesting that fructose may modulate hunger circuits in a paracrine fashion rather than through a neural circuit. We therefore investigated the role of humoral signaling in the fructose-mediated inhibition of AgRP neuron activity. Pretreatment with a Y2 receptor antagonist (the receptor for the satiation signal Peptide YY) attenuated fructose-induced inhibition of AgRP neuron activity ($n=8$, $p<0.05$), whereas pretreatment with antagonists for other satiation signal receptors (CCKAR, 5-HT_3R, GLP1R, or CALCR) had no effect. Overall, these data show that fructose is less effective as glucose at modulating central hunger circuits, and that Y2 receptor signaling is involved in the fructose-mediated inhibition of AgRP activity.

Disclosures: A.D. McKnight: None. **A. Vargas:** None. **A.L. Alhadeff:** None.

Poster

139. Neuroendocrine Anatomy and Physiology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 139.22

Topic: F.02. Neuroendrocrine Processes and Behavior

Support: KIBM #2020-1710

Title: Top-down brain circuit for slow breathing drives relief-like anxiolysis

Authors: *J. JHANG, S. LIU, S. HAN;
Salk Inst. for Biol. Studies, La Jolla, CA

Abstract: Breathing is more than simply the respiratory response to maintain gas homeostasis. Breathing rhythms are entrained by various purposeful and emotional behaviors that require orofacial and pharyngeal activity. Moreover, breathing rhythms can be controlled by conscious effort in humans - volitional breathing. Despite cumulating evidence indicating the presence of top-down circuits that control breathing, however, precise circuits and neurons that relay high-order cortical inputs to brainstem breathing centers remain unknown. Here, we identify a subset of neurons in the dorsal anterior cingulate cortex (ACCd) which projects to the pontine reticular nucleus (PnC) as a key modulator of slow breathing. Optogenetic activation of ACCd→PnC neurons reduces breathing rate and specifically alleviates anxiety-like behaviors without altering valence in mice. Calcium response of ACCd→PnC neurons was correlated with behaviorally entrained breathing cycles, as well as relief-like slow breathing patterns observed in anxiety

tests. Our tracing experiments show that ACCd neurons are targeting inhibitory neurons in the PnC area, which in turn project to the pontomedullary breathing centers. Moreover, axon collaterals of the ACCd→PnC neurons are projecting to anxiety-related structures in the forebrain, thus comprising a neural network that synchronously modulates the breathing and the internal state of fear and anxiety. Together, our study expands the understanding of brain circuits for central breathing control and provides useful knowledge for treating breathing- and anxiety-related psychiatric illnesses.

Disclosures: **J. Jhang:** None. **S. Liu:** None. **S. Han:** None.

Poster

139. Neuroendocrine Anatomy and Physiology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 139.23

Topic: F.02. Neuroendrocrine Processes and Behavior

Support: Spanish Ministry of Science, Innovation, and Universities (MCIU), State Research Agency (AEI), and European Regional Development Fund (FEDER); PGC2018-098229-B-100
Séneca Foundation (19904/GERM/15)

Title: Hypothalamic distribution of Tyrosine Hydroxilase following the prosomeric model in rats

Authors: M. G. BILBAO[1], D. GARRIGOS[2], M. MARTINEZ-MORGA[2], A. TOVAL[2], Y. KUTSENKO[2], R. BAUTISTA[2], A. BARREDA[2], B. RIBEIRO DO-COUTO[3], L. PUELLES[2], ***J. L. FERRAN**[2];
[1]Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Buenos Aires, Argentina; [2]Dept. of Human Anat. and Psychobiology,, Sch. of Medicine, Univ. of Murcia, Murcia, Spain; [3]Dept. of Human Anat. and Psychobiology,, Fac. of Psychology, Univ. of Murcia, Murcia, Spain

Abstract: Most of the studies on neurochemical mapping, connectivity, and physiology in the hypothalamic region were carried out in rats and under the columnar morphologic paradigm. According to the columnar model, the entire hypothalamic region lies ventrally within the diencephalon, which includes preoptic, anterior, tuberal, and mamillary anteroposterior regions, and sometimes identifying dorsal, intermediate, and ventral hypothalamic partitions. This model is weak in providing little or no experimentally corroborated causal explanation of such subdivisions. In contrast, the modern prosomeric model uses different axial assumptions based on the parallel courses of the brain floor, alar-basal boundary, and brain roof (all causally explained). This model also postulates that the hypothalamus and telencephalon jointly form the secondary prosencephalon, separately from and rostral to the diencephalon proper. The hypothalamus is divided into two neuromeric (transverse) parts called peduncular and terminal hypothalamus (PHy and THy). The classic anteroposterior (AP) divisions of the columnar

hypothalamus are rather seen as dorsoventral subdivisions of the hypothalamic alar and basal plates. In this study, we offered a prosomeric immunohistochemical mapping in the rat of hypothalamic cells expressing tyrosine hydroxylase (TH), which is the enzyme that catalyzes the conversion of L-tyrosine to levodopa (L-DOPA) and a precursor of dopamine. This mapping was also combined with markers for diverse hypothalamic nuclei [agouti-related peptide (Agrp), arginine vasopressin (Avp), cocaine and amphetamine-regulated transcript (Cart), corticotropin releasing Hormone (Crh), melanin concentrating hormone (Mch), neuropeptide Y (Npy), oxytocin/neurophysin I (Oxt), proopiomelanocortin (Pomc), somatostatin (Sst), tyrosine hidroxilase (Th), and thyrotropin releasing hormone (Trh)]. TH-positive cells are particularly abundant within the periventricular stratum of the paraventricular and subparaventricular alar domains. In the tuberal region, most labeled cells are found in the acroterminal arcuate nucleus and in the terminal periventricular stratum. The dorsal retrotuberal region (PHy) contains the A13 cell group of TH-positive cells. In addition, some TH cells appear in the perimamillary and retromamillary regions. The prosomeric model proved useful for determining the precise location of TH-positive cells relative to possible origins of morphogenetic signals, thus aiding potential causal explanation of position-related specification of this hypothalamic cell type.

Disclosures: **M.G. Bilbao:** Other; Facultad de Ciencias Veterinarias, Universidad Nacional de La Pampa, General Pico, Argentina. **D. Garrigos:** Other; Institute of Biomedical Research of Murcia – IMIB, Virgen de la Arrixaca University Hospital, Murcia, Spain. **M. Martinez-Morga:** Other; Institute of Biomedical Research of Murcia – IMIB, Virgen de la Arrixaca University Hospital, Murcia, Spain. **A. Toval:** Other; Institute of Biomedical Research of Murcia – IMIB, Virgen de la Arrixaca University Hospital, Murcia, Spain, PROFITH "PROmoting FITness and Health Through Physical Activity" Research Group, Department of Physical Education and Sports, Faculty of Sport Sciences, University of Granada, Granada, Spain. **Y. Kutsenko:** Other; Institute of Biomedical Research of Murcia – IMIB, Virgen de la Arrixaca University Hospital, Murcia, Spain. **R. Bautista:** Other; Institute of Biomedical Research of Murcia – IMIB, Virgen de la Arrixaca University Hospital, Murcia, Spain. **A. Barreda:** Other; Institute of Biomedical Research of Murcia – IMIB, Virgen de la Arrixaca University Hospital, Murcia, Spain. **B. Ribeiro Do-Couto:** Other; Institute of Biomedical Research of Murcia – IMIB, Virgen de la Arrixaca University Hospital, Murcia, Spain. **L. Puelles:** Other; Institute of Biomedical Research of Murcia – IMIB, Virgen de la Arrixaca University Hospital, Murcia, Spain. **J.L. Ferran:** Other; Institute of Biomedical Research of Murcia – IMIB, Virgen de la Arrixaca University Hospital, Murcia, Spain.

Poster

139. Neuroendocrine Anatomy and Physiology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 139.24

Topic: F.02. Neuroendrocrine Processes and Behavior

Support: DGAPA PAPIIT IT201120
IPN SIP 20211114
CONACYT Scholarship 807546

Title: Gastric and intestinal tissue morphology and molecular mechanisms underlying chronic constipation in patients with Parkinson's Disease

Authors: *V. E. GALLEGOS-HERNÁNDEZ[1], E. GARCÍA-VALDÉS[2], P. VERGARA-ARAGON[3], M. R. JAIME-FONSECA[2], S. GALAVIZ-HERNÁNDEZ[2];
[1]CICATA Legaria, Inst. Politécnico Nacional, Miguel Hidalgo, Mexico; [2]CICATA Legaria, Inst. Politécnico Nacional, Mexico City, Mexico; [3]Facultad De Medicina, Mexico DF, Mexico

Abstract: Introduction: Little is known aboutthe impact of specific gastrointestinal symptoms on the quality of life ofpatients with Parkinson's Disease (PD). Abdominal pain, inflammation, andchronic constipation (CD) are conditions, which often worsen the quality oflife of patients. To date, the molecular mechanisms underlying the pathogenesisof abdominal inflammation and PD/CD are only partially understood.**Objectives and methods:** The objectivewas to investigate the morphological, neuropathological and neurochemicalcharacteristics in biopsies of the gastric tract, small intestine and colon ofPD rats and induced chronic constipation (loperamide) and that were treatedwith penumbra (gastroprotective and laxative). Through biopsies, the standardhistological procedure with HE was performed. On the other hand, total proteinswere extracted and analyzed by Western blot to quantify glial fibrillary acidicprotein (GFAP, as index of glial activation) and vasoactive intestinalpolypeptide (VIP) and its receptors (VPAC1 and VPAC2) as markers of subsets ofvasomotor secretory neurons.**Results:** In PD and PD/CD ratsthere were atrophic/pyknotic nerve plexus cells, ie, signs of ganglionicdegeneration in the submucosal and/or myenteric plexus. In the remaining cases,no morphological alterations were observed. Western blot data showed nosignificant differences in VIP protein expression levels in PD/EC vs. CE vs.controls and GP (one-way ANOVA, P = 0.3). Similarly, VPAC1 and VPAC2 expressiondid not appear significantly different between groups (P=0.8 and P=0.1,respectively). However, the expression levels of VIP and VPAC2 showed atendency to decrease in the PD/EC and EC groups compared to the other groups,including the control. Furthermore, GFAP expression did not show significantdifferences between groups (P = 0.5).**Conclusion:** The study showed morphological alterations in thedigestive tract. However, there were no significant changes in the expressionof VIP, VPAC1, VPAC2 and GFAP proteins in patients with PD/CD and CD vs.controls. Taken together, our data support the concept of selective proteinabnormalities that may underlie distinct mechanisms in PD/CD and painfulabdominal inflammation.

Disclosures: V.E. Gallegos-Hernández: None. **E. García-Valdés:** None. **P. Vergara-Aragon:** None. **M.R. Jaime-Fonseca:** None. **S. Galaviz-Hernández:** None.

Poster

139. Neuroendocrine Anatomy and Physiology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 139.25

Title: WITHDRAWN

Poster

139. Neuroendocrine Anatomy and Physiology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 139.26

Topic: F.02. Neuroendrocrine Processes and Behavior

Support: CONACYT

Title: Effect of prolactin on DU-145 cell migration and MMP-2 and MMP-9 activity

Authors: J. M. CARRASCO-CEBALLOS[1], I. D. RAMOS-TRUJILLO[2], J. LOCIA-ESPINOZA[2], D. BARRERA-HERNÁNDEZ[5], C. L. SAMPIERI[3], J. A. LARA-REYES[4], C. A. PÉREZ[4], M. E. HERNÁNDEZ-AGUILAR[4], J. MANZO-DENES[4], D. HERRERA-COVARRUBIAS[4], G. E. ARANDA-ABREU[4], *F. ROJAS-DURÁN[4];
[1]Doctorado en Investigaciones Cerebrales, [2]Facultad de Química Farmacéutica Biológica, [3]Inst. de Salud Pública, [4]Inst. de Investigaciones Cerebrales, Univ. Veracruzana, Xalapa, Veracruz, Mexico; [5]Biología de la Reproducción “Dr. Carlos Gual Castro”, Inst. Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Ciudad de México, Mexico

Abstract: Prolactin (PRL) is a polypeptide hormone synthesized and released mainly by lactotrophs in the adenohypophysis. The release of this hormone is controlled by neuronal stimuli and its level is regulated by the hypothalamic-pituitary axis. PRL is involved in mammary gland development, milk production, growth, cell proliferation and differentiation, behavior, and reproduction. It exerts its biological effects through its interaction with specific membrane receptors that are widely distributed in the organism. In addition to its physiological functions, PRL has also been shown to be involved in the development of diseases such as breast and prostate cancers. One of the main problems in these cancers is their ability to metastasize (the main cause of death in cancer patients), with cell migration playing a fundamental role. Although PRL has already been shown to be involved in cell migration, little is known about its involvement in prostate cancer cell migration. Therefore, we investigated the effect of PRL stimulation on the DU-145 prostate cancer cell line, and on the activity of the metalloproteases MMP-2 and MMP-9, which are known to be involved in cell migration and invasion. The results showed that PRL (50 nM) significantly increased the migration of DU-145 cells without inducing changes in the activity of MMP-2 and MMP-9. The data suggest that PRL may be involved in metastasis by inducing cell migration.

Disclosures: J.M. Carrasco-Ceballos: None. **I.D. Ramos-Trujillo:** None. **J. Locia-Espinoza:** None. **D. Barrera-Hernández:** None. **C.L. Sampieri:** None. **J.A. Lara-Reyes:** None. **C.A. Pérez:** None. **M.E. Hernández-Aguilar:** None. **J. Manzo-Denes:** None. **D. Herrera-Covarrubias:** None. **G.E. Aranda-Abreu:** None. **F. Rojas-Durán:** None.

Poster

139. Neuroendocrine Anatomy and Physiology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 139.27

Topic: F.02. Neuroendrocrine Processes and Behavior

Support: DGAPA-UNAM
SIP-IPN
CONACYT # 302799

Title: Neuroprotective effect of artichoke on the dentate gyrus and CA1 area of the hippocampus in a rat menopausal model

Authors: *L. TEXCO-MARTINEZ[1], F. MALLON-MERCADO[2], A. J. ESPADAS-ALVAREZ[3], P. VERGARA-ARAGON[4];
[1]Fisiología, Universitdad Nacional Autonoma de Mexico, Ciudad De Mexico, Mexico; [2]Tecnología Avanzada, Inst. Politecnico Nacional, Ciudad de México, Mexico; [3]Biociencias e Ingeniería, Inst. Politécnico Nacional, Mexico, Mexico; [4]Fisiología, Univ. Nacional Autonoma de México, Ciudad de Mexico, Mexico

Abstract: Artichoke is has used as alternative treatment for weight loss in obesity, because has lipid-lowering, hepatoprotective and hypoglycemic activity, however there not scientific evidence of artichoke effect on obesity caused by menopausal status. Estrogens are involved in the regulation of appetite. In rats, mice, and monkeys ovariectomized increases food intake and body weight with an increase in adipose tissue. In menopausal women, the level of estrogen decreases, favoring cardiovascular diseases, other ailments, and obesity. We tested the artichoke extract in ovariectomized rats and this induced decrease in glucose, cholesterol, and triglyceride levels, compared to the groups without treatment and without surgery. We also measured progesterone and 17-B estradiol and the results suggests that artichoke extract does not participate in the hypothalamic-pituitary-gonadal axis. In addition, estradiol deficiency affects the structure and function of the hippocampus. In the same groups, we analyzed the cytoarchitecture of the dentate gyrus and the CA1 area of rat hippocampus and observed that in ovariectomized rats with artichoke treatment there is a neuroprotective effect in contrast to the groups without treatment.

Disclosures: L. Texco-Martinez: None. **F. Mallon-Mercado:** None. **A.J. Espadas-Alvarez:** None. **P. Vergara-Aragon:** None.

Poster

140. Cellular Actions of Stress

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 140.01

Topic: F.03. Stress and the Brain

Support: NIH Grant F32DK124963
NIH Grant R01DK047320

Title: Maternal consumption of glucocorticoids alters selenoprotein expression in the brains of offspring mice

Authors: P. TOH, L. A. SEALE, M. J. BERRY, *D. J. TORRES;
Pacific Biosci. Res. Ctr., Univ. of Hawai'i at Manoa, Honolulu, HI

Abstract: Aberrant activation of the stress-response system in early life can alter neurodevelopment and lead to long-term changes in mood, cognition, and social behavior. Activation of the hypothalamic-pituitary-adrenal (HPA) axis causes the release of glucocorticoid hormones into the bloodstream, which induces tissue-specific changes throughout the body to help the organism adapt to the stressful stimulus. High levels of glucocorticoids can cause cellular oxidative stress, however. The brain is highly responsive to glucocorticoid levels and is particularly susceptible to the accumulation of reactive oxygen species (ROS), which are implicated in a host of adverse neurological conditions. Selenium is an essential micronutrient and trace element that is obtained through diet and selenium supplementation has been shown to mitigate damage caused by glucocorticoid induced oxidative stress. Selenium is used to make selenoproteins, a family of proteins that help maintain redox homeostasis and are particularly important for proper brain function. Glucocorticoids have shown an ability to impair antioxidant enzymes in the brain, with evidence suggesting an influence on selenoprotein expression and activity. While it has long been established that maternal stress can have deleterious effects on the developing brain, the impact of these effects on selenoprotein expression and activity has been under-investigated. We hypothesize that exposure to high levels of glucocorticoids can disrupt selenoprotein expression in the developing brain, which may contribute to the development of long-term neurological deficits. We used C57 wild-type dams treated with corticosterone, the main active glucocorticoid in mice, to investigate the impact of maternal stress on selenoprotein expression in offspring. Corticosterone (75 µg/ml) was added to the drinking water of dams starting the day following birth of a litter, postnatal day 1 (PND1). We collected whole brains, or specific brain regions—prefrontal cortex, hippocampus, and hypothalamus—from offspring on PND15 to assess selenoprotein expression and activity via western blot and commercial activity assays respectively. This study will determine the effects of early life exposure to high glucocorticoid levels on selenium utilization in the developing brain. Further testing of varying maternal stressor types, as well as behavioral assessments later in life, will fully elucidate the role of selenium in the effects of maternal stress on neurodevelopment.

Disclosures: P. Toh: None. **L.A. Seale:** None. **M.J. Berry:** None. **D.J. Torres:** None.

Poster

140. Cellular Actions of Stress

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 140.02

Topic: F.03. Stress and the Brain

Support: NIH Grant DK047320

Title: The effect of glucocorticoids on hippocampal selenoproteins

Authors: *J. NICHOLSON[1,2], M. W. PITTS[1], S. REMIGIO[1], L. A. SEALE[2], M. J. BERRY[2], D. TORRES[2];
[1]Cell and Mol. Biol., [2]Pacific Biosci. Res. Center, Sch. of Ocean and Earth Sci. and Technol., Univ. of Hawai'i at Manoa, Honolulu, HI

Abstract: Selenium is an essential trace element obtained through the diet that is used to synthesize selenoproteins. This family of antioxidant proteins is vital for limiting oxidative stress and is particularly important for proper brain function. Glucocorticoids, a class of steroid stress hormones, are known to cause oxidative stress when chronically elevated, leading to cellular damage and neurological dysfunction. The hippocampus is particularly sensitive to glucocorticoids, which can cause problems with memory and spatial processing. Glucocorticoids can also impair the antioxidant capabilities in the brain, which includes inhibiting activity of the glutathione peroxidase (GPx) family of selenoproteins. Using a mouse hippocampal cell line, we sought to characterize the alterations in selenoprotein levels with exposure to glucocorticoids. We treated HT22 cells with increasing concentrations of corticosterone, a glucocorticoid, for varying lengths of time. We found, using Western Blotting, that after 7 days there were significant alterations in selenoprotein levels including a reduction in GPx1 and an increase in GPx4. This could suggest that the cells are responding to pro-ferroptotic conditions. Transferrin receptor levels trended upwards, indicating that these cells may be taking in more iron leading to ferroptosis. Thus, glucocorticoids have the capability of altering levels of multiple members of the selenoprotein family, which may make the cells more susceptible to oxidative insult, including ferroptosis. These results may have implications for human diseases that are exacerbated by chronic stress, including neurodegenerative disease. Future studies will be necessary to elucidate the mechanisms through which glucocorticoids regulate the selenoproteome and the greater neurophysiological implications.

Disclosures: J. Nicholson: None. **M.W. Pitts:** None. **S. Remigio:** None. **L.A. Seale:** None. **M.J. Berry:** None. **D. Torres:** None.

Poster

140. Cellular Actions of Stress

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 140.03

Topic: F.03. Stress and the Brain

Support: NIH Grant MH108286
NIH Grant HD097093

Title: Extracellular vesicles as cellular communicators of stress-mediated allostasis

Authors: *N. R. MOON, J. CHAN, C. P. MORGAN, T. L. BALE;
Univ. of Colorado Anschutz Med. Campus, Aurora, CO

Abstract: Cellular reprogramming at reproductive tissues following chronic parental stress influences offspring neurodevelopment. In males, mechanistic studies identified lasting changes following chronic stress at epididymal epithelial cells (EECs) that provide sperm with essential maturation signals. While the inter- and intracellular mechanisms regulating the cellular allostatic set point following stress are unclear, the glucocorticoid receptor (GR) is a known intracellular regulator of the stress response and key target orchestrating allostasis. To examine the hypothesis that stress initiates GR-dependent cellular programming to influence offspring neurodevelopment, we reduced EEC GR expression in our model of chronic paternal stress. Remarkably, paternal EEC GR reduction normalized adult offspring stress responsivity. To determine GR dependent processes regulating the allostatic set point, we analyzed the EEC active translatome and detected two large clusters of co-regulated genes related to chromatin modifying and mitochondrial processes, over 400 and 1200 genes, respectively. Furthermore, using CUT&RUN sequencing, a high efficiency epigenetic profiling approach, we revealed that stress significantly increased binding by the ubiquitous transcriptional repressor, H3K27me3, at 7283 regions of the EEC genome. H3K27me3 bound regions were associated with mitochondrial processes by Gene Set Enrichment Analysis. As stress-responsive modulators of cellular energy, mitochondria are likely mediators of allostasis. Accordingly, we predicted that GR would function to reduce mitochondrial respiration. Using cell-based respirometry, we found that prior stress decreased basal mitochondrial respiration, and that GR knockdown protected against this effect. Our previous studies found that extracellular vesicles (EVs) secreted by EECs act as vehicles for transfer of cargo necessary for sperm maturation, and that stress alters EV content. Therefore, we next assessed the role of EVs as cellular coordinators of mitochondrial respiration. Amazingly, we found reduced EEC mitochondrial respiration following treatment with stress EVs. Together, these studies demonstrate a novel role of GR in programming the chromatin landscape after chronic periods of stress to impact cellular energy requirements, and of EVs to maintain this new cellular set point. These regulatory mechanisms of allostasis broadly apply to other stress-vulnerable cells, including neurons and glia, and are important to better understand the enduring pathophysiology of trauma and potential biological interventions.

Disclosures: **N.R. Moon:** None. **J. Chan:** None. **C.P. Morgan:** None. **T.L. Bale:** None.

Poster

140. Cellular Actions of Stress

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 140.04

Topic: F.03. Stress and the Brain

Support: NIEHS ES028202
NICHD HD097093
NIMH MH104184
MH108286

Title: DREADDing stress: using chemogenetics to bypass variability and go right to the source with CRF activation

Authors: *K. R. MONTGOMERY, M. S. BRIDI, L. M. FOLTS, R. MARX-RATTNER, V. MEADOWS, H. C. ZIERDEN, T. L. BALE;
Univ. of Maryland Sch. of Med., Baltimore, MD

Abstract: High lifetime stress experience is one of the strongest predictors of neuropsychiatric disease development. Understanding the mechanisms underlying this risk is essential for developing novel intervention and therapeutic strategies. Non-homeostatic stressors are perceived and processed by limbic structures that ultimately converge onto the paraventricular nucleus of the hypothalamus (PVN), where activation of corticotropin-releasing factor (CRF) neurons initiates hypothalamic-pituitary-adrenal (HPA) axis activation, ultimately resulting in glucocorticoid release. Current rodent stress models rely on various sensory modalities to induce a stress response; however, the use of differing paradigms presents challenges for consistency and reproducibility across labs and institutions. We hypothesized that direct activation of CRF neurons would mimic the experience of stress induced by these paradigms while bypassing the variability of experience and perception by working directly at the level of the neurons. To test this hypothesis, we developed a novel stress model using the Gq-coupled DREADD receptor hM3Dq to chemogenetically activate CRF neurons, providing an efficient and high-throughput method for studying acute and chronic stress. We found that the DREADD ligand clozapine-N-oxide (CNO) robustly activated the HPA response in hM3Dq/mCitrine × CRF-Cre mice and reproduced the significant sex difference in overall peak corticosterone levels in response to an acute stressor. To validate that chronic CNO administration induces a chronic stress state, we administered daily CNO for 4 weeks and monitored standard physiological changes indicative of chronic stress and a final HPA response following acute CNO injection. Both male and female hM3Dq-expressing mice had a blunted HPA response following chronic CNO administration, while hM3Dq-expressing males, but not females, had prolonged corticosterone release, suggesting that chronic CRF-neuron activation leads to sex-specific effects on HPA axis feedback. We next administered CNO daily for 10 weeks to examine the effects of long-term CRF-neuron activation on HPA axis reactivity and behavior. We found that hM3Dq-expressing males, but not females, had a significantly elevated HPA response to an acute restraint stress while both sexes displayed increased tactile sensitivity and higher fear memory, with females maintaining cued fear more robustly. The results from these studies demonstrate that direct CRF network activation successfully reproduces acute and chronic sensory stress and suggest that males and females have region-specific sensitivity to chronic stress.

Disclosures: K.R. Montgomery: None. **M.S. Bridi:** None. **L.M. Folts:** None. **R. Marx-Rattner:** None. **V. Meadows:** None. **H.C. Zierden:** None. **T.L. Bale:** None.

Poster

140. Cellular Actions of Stress

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 140.05

Topic: F.03. Stress and the Brain

Support: NIH Grant R00MH121355
BBRF Young Investigator Grant

Title: Chronic stress alters the intrinsic properties of parvalbumin-positive interneurons in the ventral hippocampus

Authors: A. M. MARRON[1], L. T. HEWITT[2], A. SANCHEZ[1], D. H. BRAGER[2], ***J. DONEGAN**[1];
[1]Dell Med. Sch. at UT Austin, Dell Med. Sch. at UT Austin, Austin, TX; [2]Univ. Texas at Austin, Univ. Texas at Austin, Austin, TX

Abstract: The ventral hippocampus (vHipp) regulates a diverse set of behaviors associated with motivation and emotion. Functional abnormalities in this region are observed in a variety of psychiatric disorders, including mood and anxiety disorders. We previously showed that restoring the function of parvalbumin (PV)-positive inhibitory interneurons in the vHipp of rodents alleviates physiological and behavioral deficits, including alterations in dopamine cell activity, reduced social interaction, and cognitive inflexibility. Chronic stress is a major risk factor for mood and anxiety disorders. The goal of the current experiments is to determine how chronic stress affects the synaptic connectivity and intrinsic membrane properties of PV-positive interneurons in the vHipp. To induce chronic stress, mice underwent chronic unpredictable stress (CUS), in which they were exposed to a total of 14 varied stressors, administered twice per day for 21 days. We used the mammalian GFP reconstitution across synaptic partners (mGRASP) technique to measure the synaptic connectivity between PV positive-interneurons and pyramidal cells in the vHipp. Our preliminary results suggest that CUS does not alter the number of synaptic contacts. We also used whole-cell current clamp to measure the intrinsic properties of PV-positive neurons in the vHipp. PV neurons from CUS mice had a significantly lower input resistance compared to control mice. Additionally, CUS PV neurons fired fewer action potentials and had a smaller afterhyperpolarization compared to control PV neurons. These results suggest that the activity of PV-positive interneurons is altered by chronic stress. Understanding how chronic stress affects PV-positive interneurons in the vHipp may lead to the development of new cellular targets for the treatment of psychiatric disorders associated with vHipp dysfunction.

Disclosures: A.M. Marron: None. **L.T. Hewitt:** None. **A. Sanchez:** None. **D.H. Brager:** None. **J. Donegan:** None.

Poster

140. Cellular Actions of Stress

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 140.06

Topic: F.03. Stress and the Brain

Support: NIMH R01MH062044
2CI Neurogenomics

Title: Time of day differences in BDNF effects on the behavioral response to social stress in hamsters and mice

Authors: *E. SHAUGHNESSY[1], A. M. ROSENHAUER[2], K. L. HUHMAN[3];
[1]Neurosci. Inst., Georgia State Univ., Atlanta, GA; [2]Dept. of Psychological Sci., Kennesaw State Univ., Kennesaw, GA; [3]Neurosci. Inst., Neurosci. Institute/Georgia State Univ., Atlanta, GA

Abstract: Social stress is a salient risk factor for developing mood and anxiety-disorders. Brain-derived neurotrophic factor (BDNF), which binds to its canonical receptor tropomyosin receptor kinase B (TrkB) and influences synaptic plasticity, learning, and memory, has been recognized as important for the etiology and treatment of stress-related mood and anxiety disorders. The existing data on the directionality of BDNF effects are inconsistent, however. Some labs have found that BDNF promotes behavioral responses to social stress (e.g., has a pro-depressant effect), while our lab has found that BDNF prevents behavioral responses to social stress (e.g., has an antidepressant effect). We use Syrian hamsters as a model for social stress, while many other labs use mice. We also perform all behavioral assays at the onset of the animals' active (dark) phase of the daily light-dark cycle, while many other labs perform behavioral tasks during the animals' inactive phase (in the light). We hypothesized that Syrian hamsters and mice respond to a TrkB agonist, 7,8-dihydroxyflavone (7,8-DHF), differently in the light and the dark. Animals from both species were defeated and their behavioral response to defeat was tested 24 hours later using a standard social interaction task. Both hamsters and mice displayed decreased social avoidance after social defeat when 7,8-DHF was administered systemically in the dark phase of the cycle. By contrast, hamsters defeated and then given 7,8-DHF during the light phase of the cycle showed an increase in social avoidance. Mice given 7,8-DHF in the dark also showed decreased social avoidance, an effect that was absent when 7,8-DHF was given during the light phase. These data indicate that there may be important chronopharmacological effects that generalize across species that will have to be taken into consideration when exploring whether novel BDNF-active treatments have therapeutic efficacy for social stress-related behavioral changes.

Disclosures: E. Shaughnessy: None. **A.M. Rosenhauer:** None. **K.L. Huhman:** None.

Poster

140. Cellular Actions of Stress

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 140.07

Topic: F.03. Stress and the Brain

Support: NCCIH
ODS
MIMH

Title: Chemokine receptor 5 mediates stress susceptibility in female social defeat stress

Authors: *H.-Y. LIN, F. CATHOMAS, L. LI, R. DURAND, K. CHAN, C. GUEVARA, L. PARISE, C. YUAN, F. GAAMOUCH, S. RUSSO, J. WANG;
Icahn Sch. of Med. at Mount Sinai, New York, NY

Abstract: Mounting evidence showing females generally are more susceptible to major depressive disorders (MDD) compared to males. However, the molecular mechanism underlying the sex difference in regulation of stress response remain poorly understood. Our previous study revealed complex patterns of sex dimorphism in peripheral system in response to stress. Here, we identified the CCL5 levels profoundly increase in susceptible (SUS) mice after female chronic social defeat stress (CSDS). Pharmacological blocking CCL5 signaling by intraperitoneal injection Met-CCL5 prior to defeat reverse social avoidance. Moreover, we identified elevated CC chemokine receptor 5 (*Ccr5*) expression in medial prefrontal cortex (mPFC) of female after CSDS. SUS mice show a primed or phagocytic microglia phenotype characterized by a ramified morphology, reduced branching length in mPFC region when compared to resilient (RES) and control (CTRL) mice. Altered Ccr5 expression in mPFC following defeat switch towards a pro-resilient microglia phenotype, behavior phenotype and firing rate. Together, our findings reveal the importance of studying sex-specific therapeutic approaches of CCL5-Ccr5 axis to combat stress-related disorders.

Disclosures: H. Lin: None. **F. Cathomas:** None. **L. Li:** None. **R. Durand:** None. **K. Chan:** None. **C. Guevara:** None. **L. Parise:** None. **C. Yuan:** None. **F. Gaamouch:** None. **S. Russo:** None. **J. Wang:** None.

Poster

140. Cellular Actions of Stress

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 140.08

Topic: F.03. Stress and the Brain

Support: NIH P50 MH096889
NIH NS28912

Title: A novel GABAergic CRH-expressing projection from basolateral amygdala to the nucleus accumbens

Authors: *Y. CHEN[1], M. BIRNIE[1], A. K. SHORT[1], G. DE CARVALHO[2], J. DAGLIAN[1], L. Y. CHEN[2], X. XU[2], T. Z. BARAM[3];
[1]Pediatrics, [2]Anat. & Neurobio., [3]Pediatrics, Anat. & Neurobio., Univ. of California-Irvine, Irvine, CA

Abstract: Background: Within the reward circuitry in the rodent, projections from basolateral amygdala (BLA) to the nucleus of accumbens (NAc) have been reported to modulate reward behaviors, and stimulation of BLA-NAc projection promotes selectively appetitive but not aversive behaviors. Projections connecting brain regions are composed of several cell types defined by their neurotransmitter and often by a co-expressed neuropeptide. The majority of the literature suggests that the BLA-NAc projection is glutamatergic. Unexpectedly, we report here on a GABAergic BLA-NAc projection expressing the neuropeptide corticotropin-releasing hormone (CRH). This neuropeptide has well-established roles in stress, addiction, and reward via specific cellular actions within NAc, providing impetus for the comprehensive characterization of this novel projection. Thus, the identify of such a cell-type specific projection is important. Methods: The cell identity and scope of this BLA-NAc CRH pathway was investigated by employing transgenic mice, anterograde and retrograde viral-genetic tracing, coupled with optogenetics. Results: Abundant CRH axon terminals and CRH receptors CRFR1 and CRFR2 reside in the NAc, particularly the medial shell. Anterograde tracing via injection of pAAV-FLEX-tdTomato into BLA of Crh-IRES-Cre mice identified CRH expressing projections from BLA to NAc. The use of rAAV2-retro DIO-CAG-tdTomato injected into the NAc shell identified a group of CRH cells in BLA, but not in the central amygdala. These NAc-projecting CRH cells are GABAergic as apparent from their expression of GABAergic but not glutamatergic markers. Optogenetic stimulation of the CRH+ fibers in the NAc yielded exclusively IPSCs. Conclusions: These data suggest that a group of CRH cells in BLA sends axonal projection to the NAc shell, and NAc-projecting CRH cells in BLA are GABAergic. The BLA-NAc CRH projection is involved in reward seeking behaviors.

Disclosures: Y. Chen: None. **M. Birnie:** None. **A.K. Short:** None. **G. de Carvalho:** None. **J. Daglian:** None. **L.Y. Chen:** None. **X. Xu:** None. **T.Z. Baram:** None.

Poster

140. Cellular Actions of Stress

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 140.09

Topic: F.03. Stress and the Brain

Support: Bench to Bedside Program Award #480670
NIH R21MH101409

Title: Differential Transcriptomic Signatures Before and After Allopregnanolone in Postpartum Depression Cell Lines

Authors: *S. A. RUDZINSKAS[1], M. MAZZU[2], A. GOFF[2], C. E. SCHILLER[3], S. MELTZER-BRODY[3], D. R. RUBINOW[3], D. GOLDMAN[2], P. J. SCHMIDT[1];
[1]Natl. Inst. of Mental Hlth., Bethesda, MD; [2]Natl. Inst. of Alcohol Abuse and Alcoholism, Rockville, MD; [3]Univ. of North Carolina, Chapel Hill, Chapel Hill, NC

Abstract: Given the health consequences, societal burden, and prevalence of postpartum depression (PPD), the recent FDA-approval of Brexanolone is an encouraging advance for its treatment. Allopregnanolone (ALLO), the steroid metabolite of progesterone that is chemically identical to Brexanolone, is thought to exert its anxiolytic- and antidepressant-like effects via positive allosteric modulation of $GABA_A$ receptors. However, ALLO's therapeutic mechanism of action at the molecular level, and its specificity for PPD, remains unclear. Using transcriptomics, we examined the consequences of ALLO exposure on lymphoblastoid cell lines (LCLs) derived from women with past PPD (n=9) compared to women with no history of PPD or other Axis 1 psychiatric illness (n=10, i.e., controls). All LCLs were treated for 60 hours total with either ALLO (three spikes, 100nM/spike) or DMSO vehicle. LCLs were then collected for Ampliseq RNA-sequencing. Quality control, unsupervised clustering, and differential expression analyses of RNA-seq data were performed in Transcriptome Analysis Console (TAC 4.0), and Weighted Gene Correlation Network Analysis (WGCNA) was performed in R. Differentially expressed genes (DEGs, $p_{nom}<0.05$) were detected both after ALLO treatment within control and PPD LCLs, and well as between PPD and control LCLs at vehicle baseline and after ALLO treatment. Regardless of ALLO treatment, diagnosis (i.e., control vs. PPD) was the primary driver of DEGs, in line with our previous findings demonstrating robust effects of past PPD on gene expression (Rudzinskas et. al, *under review*). Intriguingly, substantially more DEGs were induced following ALLO treatment within control LCLs as compared to within PPD LCLs (265 versus 98, respectively). Only 11 of these ALLO-responsive DEGs were overlapping, suggesting ALLO may induce or activate divergent cellular mechanisms or genetic pathways in PPD LCLs compared to controls. Correspondingly, WGCNA revealed statistically significant modules related to either ALLO treatment or PPD diagnosis; however, no modules significant for both PPD and ALLO were observed. These preliminary data highlight both ALLO -independent and -dependent molecular responses in PPD. Taken together, the striking lack of overlap in DEGs between diagnostic groups after ALLO treatment may suggest that ALLO's therapeutic and/or mechanistic response could be diagnosis-dependent.

Disclosures: S.A. Rudzinskas: None. **M. Mazzu:** None. **A. Goff:** None. **C.E. Schiller:** None. **S. Meltzer-Brody:** None. **D.R. Rubinow:** None. **D. Goldman:** None. **P.J. Schmidt:** None.

Poster

140. Cellular Actions of Stress

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 140.10

Topic: F.03. Stress and the Brain

Title: Sigma-1 Receptor regulation of steroid hormones at the adrenal gland

Authors: *N. SHARIKADZE, Y. YASUI, T. SU;
Cell. Pathobiology Section, Integrative Neurosci. Res. Branch, Intramural Res. Program, Natl. Inst. on Drug Abuse, NIH, Baltimore, MD

Abstract: A classic physiological stress response is the activation of HPA axis, which in turn regulates circulating levels of endogenous glucocorticoid hormones and provides a rapid response and defense against stress. The sigma-1 receptor (SIGMAR1) is a transmembrane protein residing in the ER-mitochondria interface and is highly expressed in adrenal gland and the brain regions involved in emotion and neuropsychiatric disorders. Some of SIGMAR1 agonists are a class of drugs for the treatment of depression and anxiety. The aim of our study is to investigate the role of SIGMAR1 in regulation of steroid hormones at the level of adrenal gland. We performed immunohistochemical studies and found that the SIGMAR1 is mainly localized in adrenal gland cortex zone which produces glucocorticoids. We used male and female wild type and SIGMAR1 knockout (KO) mice in different housing conditions and analyzed the plasma level of corticosterone as well as their metabolite as a non-invasive estimate of circadian glucocorticoid production. In multiple housing mice, the SIGMAR1 KO males have higher corticosterone than the WT males. Same effect was not seen in female mice. Single housing female mice exhibits much higher corticosterone concentrations compared to males in their fecal and serum samples. However, across the 4-day comparison the SIGMAR1 KO male mice show a tendency of increases in corticosterone. These results suggest that the SIGMAR1 is inhibiting the release or synthesis of corticosterone in male mice. We performed western blot analysis to evaluate SIGMAR1 expression under purportedly stressful single housing conditions. SIGMAR1 protein expression increases in female mouse adrenal glands after 4 days of single housing, suggesting a critical role of SIGMAR1 in female stress response system. We also examined corticosterone release per ACTH stimulation on either primary adrenal gland cells or the ex vivo intact adrenal glands from WT vs SIGMAR1 KO mice. SIGMAR1 KO primary adrenal gland cells showed higher corticosterone
release with 1nM ACTH stimulation. Same results were seen in ex vivo adrenal gland stimulation with 20nM ACTH. Both results thus confirm the SIGMAR1 inhibitory effect on corticosterone release in adrenal gland. We propose that SIGMAR1 receptor is involved in stress response through a regulation on adrenal corticosterone. This effect of SIGMAR1 however was seen only in male mice, suggesting a role of sex hormones in the SIGMAR1 regulation of stress response at the level of adrenal steroid hormones. This research was supported by the Intramural Research Program, NIDA, NIH.

Disclosures: **N. Sharikadze:** None. **Y. Yasui:** None. **T. Su:** None.

Poster

140. Cellular Actions of Stress

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 140.11

Topic: F.03. Stress and the Brain

Support: R01MH051399

Title: Transcriptome Profiles in the Locus Coeruleus and Nucleus Accumbens Associated with Resilience and Susceptibility to Single Prolonged Stress in Male Sprague-Dawley Rats

Authors: *R. J. NAHVI[1], A. TANELIAN[1], C. NWOKAFOR[1], A. GODINO[2], E. M. PARISE[2], M. ESTILL[2], L. SHEN[2], E. J. NESTLER[2], E. L. SABBAN[1];
[1]Biochem. and Mol. Biol., New York Med. Col., Valhalla, NY; [2]Nash Family Dept. of Neurosci. and Friedman Brain Inst., Icahn Sch. of Med. At Mount Sinai, New York, NY

Abstract: Although most people are subjected to traumatic stress in their lifetime, only a subset develop long-lasting, stress-triggered neuropsychiatric disorders, such as posttraumatic stress disorder (PTSD). The neurobiological factors predisposing individuals to the deleterious effects of stress is still unclear. Here we examined transcriptome profiles within the locus coeruleus (LC) and nucleus accumbens (NAc) that may contribute to stress susceptibility. Sprague-Dawley male rats were exposed to a single prolonged stress model used to study PTSD. Two weeks later they were tested for their anxiety/avoidance behavior on the elevated plus maze and were divided into high and low anxiety-like subgroups. Immediately after the behavioral test, the animals were euthanized and RNA (n=5 per group) was isolated from the LC and NAc and subjected to RNA sequencing analysis. Transcriptome analysis was used to identify differentially-expressed genes (DEGs) which differed by at least 50% with significance of $p \leq 0.01$. The results demonstrated that the LC had more than six times the number of DEGs than the NAc. Only one DEG (LOC100910446, encoding Syntaxin-7-like) was regulated similarly in both locations. Many of the DEGs in the LC were associated with morphological changes, including regulation of actin cytoskeleton, growth factor activity, regulation of cell size, brain development and memory with KEGG pathway regulation of actin cytoskeleton. The gene ontology of canonical pathways in LC revealed significant regulation of pathways involved in neurotransmitter regulation. Among them were tryptophan degradation VDR/RXR activation, anandamide degradation, actin cytoskeleton signaling and myo-inositol biosynthesis. The analysis identified *Mtpn* (myotrophin) and *Nr3c1* (glucocorticoid receptor; GR) as important upstream regulators of stress susceptibility in the LC, and *Grm5* (glutamate metabotropic receptor 5) as one the major DEGs downstream of GR. The DEGs in the NAc were related to DNA repair and synthesis and differential regulation of cytokine production, as confirmed by elevated *Il1a* mRNA in high anxiety group. Overall the study provides new insight into molecular pathways in the LC and NAc associated with susceptibility and resilience to stress-triggered anxiety.

Disclosures: R.J. Nahvi: None. **A. Tanelian:** None. **C. Nwokafor:** None. **A. Godino:** None. **E.M. Parise:** None. **M. Estill:** None. **L. Shen:** None. **E.J. Nestler:** None. **E.L. Sabban:** None.

Poster

140. Cellular Actions of Stress

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 140.12

Topic: F.03. Stress and the Brain

Support: University of Helsinki

Title: Atomoxetine dose-dependently shifts locus coeruleus excitation-inhibition balance and increases information in stimulus-evoked population activity

Authors: A. VREVEN, *N. K. TOTAH;
Helsinki Inst. of Life Sci., Univ. of Helsinki, Helsinki, Finland

Abstract: Locus Coeruleus (LC) neuronal population activity was recently shown to be decorrelated and to consist of subsets of coactive neurons (i.e., ensembles). The local connectivity that gives rise to such structured population activity may involve auto-inhibition and lateral inhibition mediated by volume transmission of locally released norepinephrine (NE). Here, we enhanced this local inhibition by systemically administering the NE reuptake inhibitor, atomoxetine (ATX, 0.3 mg/kg or 1.0 mg/kg) and recorded 242 single units (up to 65 simultaneously) from 10 urethane-anesthetized male rats. We recorded spontaneous and sensory stimulus-evoked spiking before and after ATX. Consistent with enhanced local inhibition, we found that ATX dose-dependently suppressed spontaneous spiking in 30% and 70% of units and suppressed evoked response magnitude in 42% and 67% of units (0.3 and 1.0 mg/kg, respectively). Unexpectedly, however, we also observed excitation of spontaneous and evoked activity. The lower dose allowed more LC neuronal activation (34% of units increased spontaneous spiking and 17% increased evoked responses), while the higher dose primarily promoted population suppression (only 12% increased spontaneous and 2% increased evoked). Surprisingly, units that were activated by ATX had low baseline activity prior to ATX administration, whereas suppressed units had high baseline activity. We next assessed spike count correlations among 3,672 and 6,048 unit-pairs (0.3 mg/kg and 1.0 mg/kg, respectively). ATX dose-dependently increased correlated pairwise spontaneous spiking. On the other hand, it decorrelated the evoked response between LC cell-pairs. Thus, systemic enhancement of NE volume neurotransmission adjusts LC population activity from a mixture of highly active and quiescent neurons to an overall intermediate level. In this ‘balanced’ population state, stimulus-related information content increases while spontaneous activity becomes more redundant.

Disclosures: A. Vreven: None. **N.K. Totah:** None.

Poster

140. Cellular Actions of Stress

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 140.13

Topic: F.03. Stress and the Brain

Support: NIH grant F31MH125541
NIH grant MH049698

Title: Impaired amygdala plasticity and salience evaluation following environmental enrichment loss in rats

Authors: *M. A. SMAIL[1], R. PARIKH[1], N. NAWREEN[1], J. B. CHAMBERS[1], R. E. MCCULLUMSMITH[2], J. P. HERMAN[1];
[1]Pharmacol. and Systems Physiol., Univ. of Cincinnati, Cincinnati, OH; [2]Neurosciences, Univ. of Toledo, Toledo, OH

Abstract: Psychological loss can erode well-being and precipitate depression. We can emulate loss by exposing rats to protracted environmental enrichment and subsequent removal to an impoverished environment. Previously, multi-omics analyses revealed that enrichment removal (ER) dysregulates cell-matrix communication in the basolateral amygdala (BLA). Here, we further investigate the role of these phenotypes in loss.
All studies featured 3 groups of adult male rats: environmentally enriched (EE), enrichment removed (ER), and standard housed controls (SH). EE and ER animals were housed in groups of 10 in large, multi-level cages with toys. After 4 weeks, ER animals were moved to single-housing, simulating the experience of loss. In one cohort, brains were collected two weeks after removal for analysis of BLA matrix-related endpoints. A second cohort received behavioral testing focused on BLA-related functions.
ER increased the total amount of extracellular matrix (ECM) in the BLA. A major component of the ECM is perineuronal nets (PNNs), which primarily surround inhibitory parvalbumin (PV) interneurons. ER also increased the number of PNNs surrounding PV. Increased ECM and PNNs is typically indicative of decreased synaptic plasticity; thus, these findings suggest that ER impairs BLA plasticity. Furthermore, PNNs can influence PV phenotypes. Here, ER decreased inhibitory synaptic input onto PV and increased PV FOS activation following fear conditioning, indicating that PV interneurons are more active following ER. Behaviorally, ER rats exhibited impaired fear recall, startle responses, and flexibility, suggesting a blunted capacity for salience evaluation (i.e., the ability of the animal to properly take in, evaluate, and select appropriate responses for various stimuli). It is likely that the decreased plasticity and increased inhibition observed in the BLA following ER plays a key role in these behavioral impairments. We are presently testing this link by enzymatically digesting BLA matrix following ER to determine if blocking the ER-related increase in matrix can attenuate ER behavioral phenotypes.
Altogether, these results suggest that ER increases BLA ECM, decreasing plasticity, altering PV phenotypes, and ultimately blunting the ability of the BLA to properly evaluate and respond to environmental challenges. This notion aligns well with human loss, in which emotional blunting is a common symptom. As such, these results represent an important step in understanding the molecular effects of psychological loss and developing novel therapeutics to help those suffering from loss.

Disclosures: M.A. Smail: None. **R. Parikh:** None. **N. Nawreen:** None. **J.B. Chambers:** None. **R.E. McCullumsmith:** None. **J.P. Herman:** None.

Poster

140. Cellular Actions of Stress

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 140.14

Topic: F.03. Stress and the Brain

Support: R00DA045795
P30DA033934

Title: Histone H1x in the Ventral Hippocampus Drives Susceptibility to Social Stress

Authors: *R. K. KIM, N. L. TRUBY, G. M. SILVA, J. A. PICONE, X. CUI, P. J. HAMILTON;
Dept. of Anat. and Neurobio., Virginia Commonwealth Univ., Richmond, VA

Abstract: Chronic stress is a risk factor for developing many neuropsychiatric syndromes including post-traumatic stress disorder and major depressive disorder. A better understanding of the neurobiological mechanisms that engender vulnerability to chronic stress may guide the development of novel therapeutics. Here, we characterize the role of linker histone H1x in modulating behavioral adaptations to social stress. H1x has been shown to be differentially expressed within the ventral hippocampus (vHipp) of stress susceptible and resilient mice (Hamilton et al, 2020). Therefore, we hypothesize that elevated levels of H1x in the vHipp potentiates function of this brain area and drives susceptibility to social stress. Male C57BL/6J mice were randomly assigned to stressed and unstressed groups. Stressed animals underwent a 10-day chronic social defeat stress (CSDS) paradigm (Golden et al, 2011), while unstressed animals were single housed for the same period. Following CSDS, animals were defined as susceptible versus resilient by social interaction (SI) testing. One cohort of animals (n=30 stressed, n=15 unstressed) were sacrificed, and 14-guage bilateral punches of vHipp were collected for a targeted Western blot of H1x. A second cohort (n=25 stressed, n=10 unstressed) was randomly divided following behavior stratification to receive bilateral 1 µl injections of HSV-H1x or HSV-GFP virus to the vHipp. Behavior was re-tested on day 3 post-surgery, and paired data comparing SI and elevated plus maze (EPM) behavior before and after virus delivery is reported. Susceptible mice had increased H1x protein in the vHipp compared to unstressed and resilient mice ($p=0.001$); resilient and unstressed mice had no difference in H1x protein levels. Resilient animals were similarly affected by intra-vHipp treatment with HSV-H1x and HSV-GFP; conversely only susceptible animals treated intra-vHipp with HSV-H1x developed further social deficits. In sum, we present that linker histone H1x protein levels are differentially regulated within the vHipp of stress susceptible and stress resilient mice. Additionally, we demonstrate that delivering H1x protein to the vHipp of stress exposed mice exacerbates stress-related behaviors specifically in the stress susceptible cohort. We plan to probe the molecular consequences of H1x expression in the vHipp and how H1x-regulated functions differ in stress susceptible versus stress resilient brains using bioinformatics techniques.

Disclosures: R.K. Kim: None. **N.L. Truby:** None. **G.M. Silva:** None. **J.A. Picone:** None. **X. Cui:** None. **P.J. Hamilton:** None.

Poster

141. Dynamic Neurovascular and Activity Changes in the Brain

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 141.01

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: ZIA-MH002783
ZIC-MH002968

Title: How conscious in-scanner thoughts modulate functional connectivity during resting-state fMRI

Authors: M. A. SPURNEY, J. GONZALEZ-CASTILLO, K. LAM, D. HANDWERKER, J. TEVES, F. PEREIRA, *P. BANDETTINI;
Natl. Inst. of Mental Hlth., Natl. Inst. of Mental Hlth., Bethesda, MD

Abstract: Previous research suggests that patterns of functional connectivity (FC) during resting-state fMRI (rsfMRI) are modulated by what subjects experience during the scan, even when no external stimuli is presented. Yet, to what extent those experiences constitute a significant source of inter-subject and inter-population variability in rsfMRI remains unknown. Quantifying the magnitude and spatial extent of these effects is desirable because it will help us to better understand what rsfMRI functional connectivity represents and to segregate state-related effects (e.g., those associated with a particular mental state) from intrinsic phenotypes (e.g., those that are state independent and may reflect a clinical condition). Here, we seek to better understand this relationship using 463 pre-processed low-motion rsfMRI scans from the publicly available MPI-Leipzig Mind-Brain-Body dataset. All scans are accompanied by responses to the Short New York Cognition Questionnaire (SNYCQ), 11 Likert-scale questions regarding the content and form of one's in-scanner thoughts, which subjects complete immediately upon exiting the scanner. First, we cluster scans using responses to the SNYCQ. This procedure results in two groups of scans with distinct reported in-scanner experiences: Group 1, comprised scans that are described as being accompanied by negative thoughts about one's surroundings in the form of words, and Group 2, comprised scans that are described as being accompanied by positive thoughts about other people in the form of images. Next, we looked for significant differences in FC across scan groups. We found that scans described by subjects as containing more externally focused thoughts (Group 1) showed stronger FC between attentional and sensory networks, while scans described by subjects as containing more internally focused thoughts (Group 2) showed stronger FC between the default mode network and other known resting-state networks, such as the control network. In addition, we searched for relationships between individual SNYCQ scores and brain regions associated with the corresponding surveyed functions. We found that higher scores on questions related to thinking in the form of images correlate with more activity in brain regions previously shown to be involved in processes of mental imagery. In sum, using multiple metrics, we found that in-scanner experiences modulated rsfMRI in meaningful ways. Consequently, state-level phenomena (i.e., in-scanner experience) might explain parts of trait-level FC signatures that

otherwise could inadvertently be interpreted as differences in inherent connectivity patterns between clinical populations.

Disclosures: M.A. Spurney: None. **J. Gonzalez-Castillo:** None. **K. Lam:** None. **D. Handwerker:** None. **J. Teves:** None. **F. Pereira:** None. **P. Bandettini:** None.

Poster

141. Dynamic Neurovascular and Activity Changes in the Brain

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 141.02

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: NIH R01-AG010735
NIH R00-MH111748
McKnight Scholar Award
Pew Biomedical Scholars Award

Title: Uncovering non-linear relationships in multimodal neuroimaging data with deep learning

Authors: *L. P. L. JACOB, L. D. LEWIS;
Boston Univ., Boston Univ., Boston, MA

Abstract: Functional magnetic resonance imaging (fMRI) is a powerful tool for neuroscience, enabling non-invasive neuroimaging with high spatial resolution. However, analyzing fMRI's hemodynamic data can be challenging, as it displays variable and non-linear relationships to the underlying neural activity. A promising solution lies in deep neural networks, which can learn complex, non-linear mappings from input to output. Deep learning has many successful applications in the classification of resting-state fMRI data, but few have used it for 'sequence-to-sequence' problems such as continuous cross-modal predictions. If deep learning can translate fMRI data to neurophysiological EEG, it could become a promising method for uncovering relationships between hemodynamic changes and neural activity. To explore this, we used deep learning to predict EEG power in the sleep delta band (1.2-4 Hz) from simultaneous resting-state fMRI. Model input (predictors) was 11s sequences of fMRI signals from parcellated regions of interest (ROIs) across the whole brain; output (predictions) was EEG delta (1.2-4Hz) power. Training was done on a hold-one-run-out basis, with validation performed on the held-out run (14 total runs across 12 subjects; 10 subjects had a single run and were thus held-out subjects). Our model successfully predicted delta power (r=.22 correlation between predictions and ground truth). This performance was significantly higher than a control condition in which fMRI data was shifted by 1101s, breaking the true relationship between EEG and fMRI (r=.01 correlation between control predictions and truth). To assess the relationship between different brain networks and delta power, we also obtained predictions using only cortical regions (r=.20), only subcortical regions (r=.12), and only 'physiological' regions (white matter and ventricles; r=.16). All three were significantly better at predicting delta power than control (Tukey's HSD), but the

subcortical and physiological regions performed significantly worse than predictions using all regions. To examine if the model learned non-linear relationships rather than simple linear correlations, we calculated cross-correlations between each fMRI ROI and the EEG delta power. We found that the correlations between gray matter fMRI and EEG (r=.13 at the highest) were lower than the deep learning's model predictions, suggesting that the model learned non-linear relationships to translate fMRI to EEG delta power. Our results highlight the potential of deep learning to identify complex relationships between hemodynamic fMRI and EEG neural activity that cannot be detected with traditional linear analyses.

Disclosures: L.P.L. Jacob: None. **L.D. Lewis:** None.

Poster

141. Dynamic Neurovascular and Activity Changes in the Brain

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 141.03

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

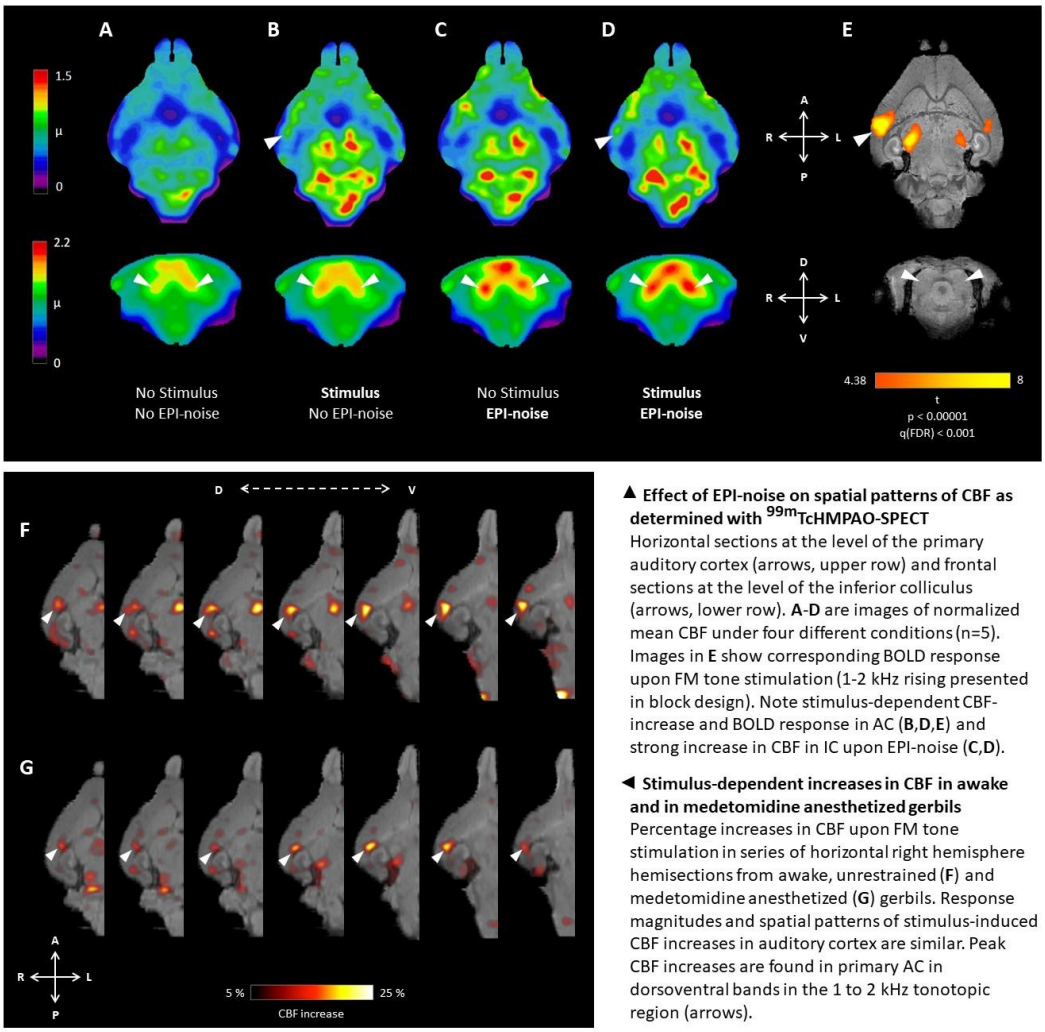
Support: LIN Special Project 2018

Title: Effects of medetomidine anesthesia and EPI-noise in BOLD-fMRI on auditory-evoked activation patterns - a CBF SPECT imaging study in Mongolian gerbils

Authors: A. MICHALEK[1], L. HESSEL[1], A. M. OELSCHLEGEL[2], P. WENK[1], N. ANGENSTEIN[1], *E. BUDINGER[1,3], J. GOLDSCHMIDT[1,3];
[1]Combinatorial NeuroImaging Core Facility, [2]Neuroplasticity, Leibniz Inst. for Neurobio. Magdeburg, Magdeburg, Germany; [3]Ctr. for Behavioural Brain Sci., Magdeburg, Germany

Abstract: One of the most widely used approaches for BOLD-fMRI studies in rodents is echoplanar imaging (EPI) in medetomidine anesthetized animals. The effects of anaesthesia and EPI-noise on brain activation patterns, particularly on auditory-evoked patterns, are largely unknown. We here use cerebral blood flow (CBF) SPECT with ^{99m}TcHMPAO for imaging, in Mongolian gerbils, frequency-modulated (FM) tone induced brain activation patterns under awake unrestrained conditions outside the MR scanner and under medetomidine anesthesia (0.4 mg/kg/h) inside the MR scanner in the presence or absence of EPI-noise during simultaneous BOLD-fMRI. CBF-SPECT images showed a clear right-lateralized increase in CBF in the primary auditory cortex (AC) under FM tone-stimulation conditions (1-2 kHz rising), consistent with right-lateralized BOLD-responses to the same stimulus in the same region. Inside a Bruker 9.4 T horizontal MR scanner, the EPI-noise under medetomidine anesthesia without FM tone stimulation lead to a strong bilateral increase of CBF (>45%) in the inferior colliculus (IC) but only moderately increased CBF in AC. FM tone stimulation did not further increase CBF significantly in IC, and significant BOLD-responses in IC were not detected on group level. CBF response magnitudes to FM tone stimulation in AC were remarkably similar in awake and medetomidine anesthetized gerbils peaking at ca. 25%. In the presence of EPI-noise the response

was ca. 5% lower. Subcortical auditory pathways were more clearly delineated in medetomidine anesthetized as compared to awake gerbils. To the best of our knowledge, our study is the first study that disentangles potentially confounding effects of EPI-noise and medetomidine anesthesia on brain-wide activation patterns in rodent BOLD-fMRI. Auditory cortical activation patterns during medetomidine anesthesia closely mimic those in the awake state. Interfering effects on the auditory system in BOLD-fMRI can arise from EPI-noise and most strongly affect the IC.



▲ **Effect of EPI-noise on spatial patterns of CBF as determined with ^{99m}TcHMPAO-SPECT**
Horizontal sections at the level of the primary auditory cortex (arrows, upper row) and frontal sections at the level of the inferior colliculus (arrows, lower row). **A-D** are images of normalized mean CBF under four different conditions (n=5). Images in **E** show corresponding BOLD response upon FM tone stimulation (1-2 kHz rising presented in block design). Note stimulus-dependent CBF-increase and BOLD response in AC (**B**,**D**,**E**) and strong increase in CBF in IC upon EPI-noise (**C**,**D**).

◀ **Stimulus-dependent increases in CBF in awake and in medetomidine anesthetized gerbils**
Percentage increases in CBF upon FM tone stimulation in series of horizontal right hemisphere hemisections from awake, unrestrained (**F**) and medetomidine anesthetized (**G**) gerbils. Response magnitudes and spatial patterns of stimulus-induced CBF increases in auditory cortex are similar. Peak CBF increases are found in primary AC in dorsoventral bands in the 1 to 2 kHz tonotopic region (arrows).

Disclosures: A. Michalek: None. **L. Hessel:** None. **A.M. Oelschlegel:** None. **P. Wenk:** None. **N. Angenstein:** None. **E. Budinger:** None. **J. Goldschmidt:** None.

Poster

141. Dynamic Neurovascular and Activity Changes in the Brain

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 141.04

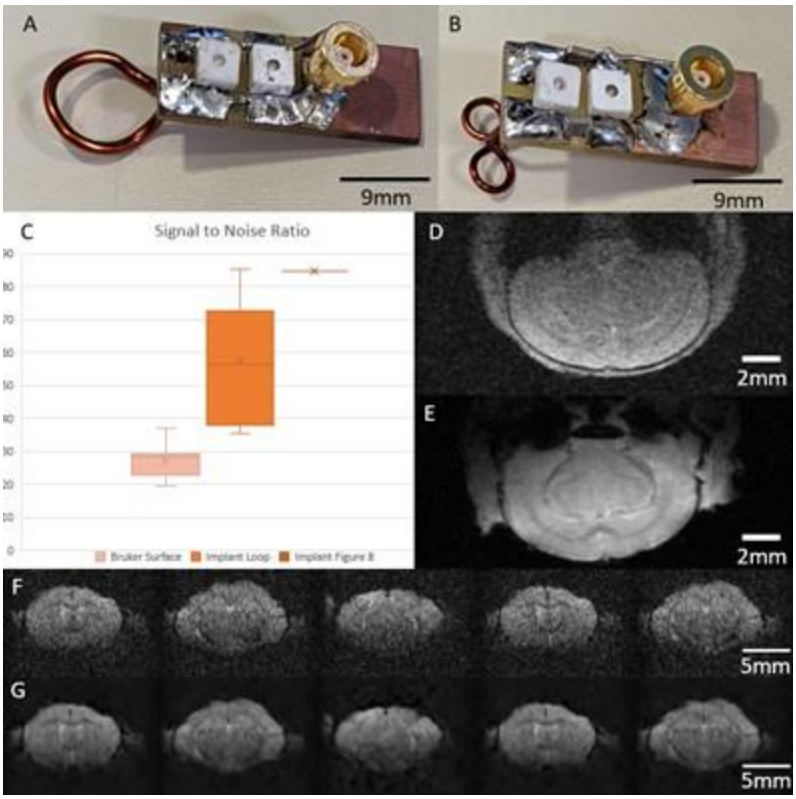
Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: NSF-239346
NSF-2123971
R01NS122904
RF1-RF1NS113278

Title: Implanted RF coils enable 100µm isotropic resolution of EPI-fMRI images in ultra-high field preclinical MRI

Authors: *D. HIKE[1], A. MURSTEIN[1,2], Z. XIE[1,3], X. LIU[1], S. CHOI[1], B. ZHANG[1], Y. JIANG[1], X. YU[1];
[1]Radiology, Massachusetts Gen. Hosp., Boston, MA; [2]Neurosci., Boston Univ., Boston, MA; [3]Sch. of Traditional Chinese Med., Southern Med. Univ., Guangzhou, China

Abstract: High resolution functional magnetic resonance imaging (fMRI) presents a unique advantage to other preclinical imaging modalities. This noninvasive mapping scheme presents a great opportunity to bridge the mechanistic brain dynamic studies preclinically with translational and clinical studies. However, achieving a high signal-to-noise ratio (SNR) with ultra-high spatiotemporal resolution fMRI, approaching the scales of the other optical or acoustic imaging methods, remains to be improved. Here, we developed an implantable MRI coil to significantly improve the SNR in mouse MRI and push the spatial resolution of echo planar imaging (EPI) fMRI toward 100um isotropic in awake mice. First, we compared implantable single-loop coil vs. non-implantable 4-array commercial surface coils for *in vivo* mouse brain imaging to determine the SNR improvement. Male C57BL/6J mice underwent a surface coil implantation (used to fix the head and minimize motion). Scans were run on a 9.4T horizontal MRI system. Coils were designed and build as a single loop 11mm in diameter (Fig 1A), or an "∞" shape spanning 11mm across for cortex imaging (Fig 1B) and miniaturized to weigh less than 2.5g before attaching to the mice. High resolution T1-weighted anatomical images (100x100um in-plane resolution & 500 µm slice thickness) were acquired (Fig 1D - Non-implant & Fig 1E - Implant). Figure 1C shows the much-improved SNR measured at the cortex using a total of 12 mice (~2x for single loop, and ~3x for figure 8). Second, we imaged the whole mouse brain using a horizontal 14T scanner with implanted coils. The SNR improved ~2x over the comparable 9.4T scan. Also, we performed 2D gradient-echo EPI fMRI to achieve the 100um isotropic resolution (TE=7ms, TR=1s, 2 segments, Matrix: 144x96x30, bandwidth=400kHz, NR=200, ~ 6 min acq. time). Fig 1 F&G, shows multiple coronal slices of EPI images in awake mice after applying the VST denoising tool (X. Ma. NeuroImage, 2020). This work allows us to further explore the brain-wide neurovascular dynamic changes in normal and genetically engineered mouse models of a broad spectrum of diseases.



Disclosures: **D. Hike:** None. **A. Murstein:** None. **Z. Xie:** None. **X. Liu:** None. **S. Choi:** None. **B. Zhang:** None. **Y. Jiang:** None. **X. Yu:** None.

Poster

141. Dynamic Neurovascular and Activity Changes in the Brain

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 141.05

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Title: The effect of anesthetic agents on the evoked-BOLD fMRI signal in Yucatan minipigs

Authors: ***A. H. NETZLEY**[1], K. A. MUNOZ[2], L. C. KLEYN[3], J. HUANG[4], G. PELLED[5,3,4]; [1]Biomed. Engin., [2]Col. of Vet. Med., [3]Neurosci. Program, [4]Radiology, [5]Mechanical Engin., Michigan State Univ., East Lansing, MI

Abstract: Intro/Background The advancement of translational, large animals imaging procedures is essential for the study of various diseases in a non-invasive, quantitative, and replicable way, leading to improved quality of life for millions of patients worldwide. To date, the majority of preclinical imaging studies, including those in pigs, administer either inhaled isoflurane or sevoflurane for the maintenance of general anesthesia (GA). Although inhalational anesthetics are easy to administer, evidence from preclinical studies showed that they

significantly diminish fMRI signals through altered neurovascular coupling. Human imaging studies have suggested that propofol may have a lesser effect on cerebral hemodynamics, therefore propofol has become a preferred substance for the maintenance of GA in pediatric fMRI studies. It remains critical to identify the optimal anesthetic regime to obtain accurate information about brain function. In this study we compared tactile-evoked fMRI responses in the sensorimotor cortex of Yucatan minipigs under sevoflurane versus propofol anesthesia. **Methods** Six-month-old Yucatan minipigs were imaged in a large-bore 1.5 Tesla Siemens MRI (n=4). Pigs were anesthetized, intubated, and placed on the MRI bed in the supine position. General anesthesia was maintained using either sevoflurane in oxygen or a constant rate infusion (CRI) of propofol (10-20mg/kg/hr) intravenously. Functional images were acquired with a GE-EPI pulse sequence (TE/TR = 37/2000 ms, FOV = 172 mm, FA = 90°, voxel size = 2.7×2.7×2.7 mm^3, and slice number = 38). Tactile stimulation was delivered to both hind limbs in four 20 s cycles, with 20 s rest in between. Analysis was conducted using Analysis of Functional Neuroimages (AFNI). The number of activated voxels above a threshold of $z > 1.97$, and $p < 0.05$ was used to calculate the extent of the response. Single-subject ROI analysis was conducted to quantify the number of voxels active in the sensorimotor area of each pig. **Results** Propofol anesthesia resulted in a significantly higher number of activated voxels 26.75 ±11.67 in the sensorimotor cortex compared to sevoflurane 56.25 ±20.07 ($p < 0.05$). **Conclusions** The type of anesthetic agent used to maintain general anesthesia for fMRI studies can have a significant impact on the result on the measurement of activity of neural circuits. Our results suggest that propofol produces a robust and reproducible activity in the pig brain.

Disclosures: **A.H. Netzley:** None. **K.A. Munoz:** None. **L.C. Kleyn:** None. **J. Huang:** None. **G. Pelled:** None.

Poster

141. Dynamic Neurovascular and Activity Changes in the Brain

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 141.06

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: ERC: #DISCONN; no.802371

Title: Chemogenetic stimulation of oxytocinergic neurons dynamically modulates fMRI connectivity

Authors: C. MONTANI[1], ***A. HAYWARD**[1], D. GUTIERREZ-BARRAGAN[1], G. MORELLI[2], F. G. ALVINO[1], L. COLETTA[1,3], A. GALBUSERA[1], M. PASQUALETTI[4], L. CANCEDDA[2], A. GOZZI[1];
[1]Functional Neuroimaging Lab., Inst. Italiano di Tecnologia, Rovereto, Italy; [2]Brain Develop. and Dis. Lab., Inst. Italiano di Tecnologia, Genoa, Italy; [3]CIMeC - Ctr. for Mind/Brain Sci., Univ. of Trento, Rovereto, Italy; [4]Unit of Cell and Developmental Biology, Dept. of Biol., Univ. of Pisa, Pisa, Italy

Abstract: Oxytocin (OXT) is a key modulator of complex socio-affective behaviors. However, the brain-wide networks endogenously modulated by OXT remain poorly understood.
Here, we combine chemogenetics and fMRI to map the topography and dynamics of brain networks engaged by endogenously-released OXT in the mammalian brain. To remotely stimulate endogenous OXT release, we crossed mice harboring a double-floxed DREADD activator hM3Dq with OXT-specific *Cre*-recombinase mice, leading to cell-type specific expression of hM3Dq in OXT-producing neurons. Stimulation of DREADD receptors with the selective JHU37160 actuator in OXT-hM3Dq mice produced physiologically-relevant release of OXT, an effect that was associated with increased grooming behavior as previously reported. fMRI mapping of OXT-evoked activity in OXT-hM3Dq (n=20) vs. control (n=21) mice revealed sustained fMRI (cerebral blood volume) activation of parietal cortical areas, hypothalamus and dorsal hippocampal regions. These effects were associated with a dramatic reconfiguration of fMRI connectivity as assessed with resting state fMRI. Specifically, chemogenetic stimulation of OXT-producing neurons robustly increased functional connectivity between hypothalamic regions and prefrontal areas, and by inverse coupling between insular and amygdala regions of the rodent salience network, and between the hippocampus and fronto-cortical areas. Notably, these changes were paralleled by a distinct reorganization of the temporal structure of rsfMRI connectivity, with a robustly increased occurrence of dynamics states encompassing the rodent salience network, which were configured as network attractors.
Taken together, these results show that endogenous OXT can rapidly and robustly alter interareal communication between key components of the social brain via temporal re-organization of fMRI dynamics.

Disclosures: C. Montani: None. **A. Hayward:** None. **D. Gutierrez-Barragan:** None. **G. Morelli:** None. **F.G. Alvino:** None. **L. Coletta:** None. **A. Galbusera:** None. **M. Pasqualetti:** None. **L. Cancedda:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; IAMA Therapeutics. **A. Gozzi:** None.

Poster

141. Dynamic Neurovascular and Activity Changes in the Brain

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 141.07

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: NIH R01DK102794

Title: Insulin Sensitivity and Resting-State Network Functional Connectivity in Limbic and Reward Networks

Authors: *H. LIU[1,2], B. ANGELO[1,2], S. PRATHAP[3,2], S. B. MURRAY[4], K. A. PAGE[1,2], K. JANN[5];

[1]Div. of Endocrinology, Dept. of Medicine, Keck Sch. of Med., [2]Diabetes and Obesity Res. Institute, Keck Sch. of Med., [3]Neurosci. Grad. Program, [4]Dept. of Psychiatry & Behavioral Sciences, Keck Sch. of Med., [5]USC Stevens Neuroimaging and Informatics Institute, Keck Sch. of Med. of USC, USC, Los Angeles, CA

Abstract: Insulin resistance is a key feature of obesity and type 2 diabetes, and has been associated with various cognitive impairments in attention, memory, and emotional salience. Thus, insulin resistance may serve as a biological link between metabolic and cognitive dysfunctions. While prior work has shown that both obesity and type 2 diabetes are associated with altered brain resting-state functional connectivity (rs-FC), few studies have examined how insulin sensitivity, independent of adiposity or type 2 diabetes, is associated with rs-FC. To this end, we examined how insulin sensitivity, independent of BMI, is associated with functional connections in brain networks involved in reward/salience, memory, and glucose regulation in healthy adults without diabetes.

Participants were 58 healthy young adults (26 males; 22.91 ± 3.31 years; BMI 26.97 ± 4.84 kg/m^2; whole-body insulin sensitivity index (ISI) 3.96 ± 3.30). Study visits were performed in the morning after an overnight fast. A 2-hour oral glucose tolerance test was performed, and ISI was derived using the Matsuda ISI. A 3 Tesla Siemens Prisma scanner was used to acquire resting state functional MRI (rs-fMRI) images and structural T1 images, which were used for anatomical registration. rs-fMRI data were analyzed in CONN Toolbox. A seed-based approach was used to examine 9 seeds in limbic (amygdala, hippocampus) and reward (putamen, insular cortex) networks using a seed-to-seed analysis and secondary seed-to-voxel analysis.

Seed-to-seed results ($p < 0.05$, p-FDR corrected, $\alpha < 0.05$) showed that insulin sensitivity, adjusted for age, sex and BMI, was positively associated with FC between the hippocampus and amygdala (z-score = 3.526, $p < 0.0014$) and negatively associated with FC between the putamen and insula (z-score = -3.136, $p < 0.0028$). Seed-to-voxel results (cluster threshold $p < 0.05$, cluster-size p-FDR corrected) further corroborated these findings and revealed that insulin sensitivity was associated with greater FC between the amygdala (seed) and temporal lobe and hypoconnectivity between the putamen (seed) and insula, anterior cingulate cortex, precentral gyrus, and cuneal cortex.

The results show that in young adults without diabetes, higher insulin sensitivity, independent of BMI, is associated with stronger FC in limbic regions involved in memory and glucose homeostasis and weaker FC in reward-related regions. These findings support the role of insulin sensitivity in promoting the functional synergy of brain networks involved in glucose regulation and reducing reward-related network connectivity.

Disclosures: H. Liu: None. **B. Angelo:** None. **S. Prathap:** None. **S.B. Murray:** None. **K.A. Page:** None. **K. Jann:** None.

Poster

141. Dynamic Neurovascular and Activity Changes in the Brain

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 141.08

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: National Institutes of Health including MD015904 (AG)
K23 DK106528 (AG)
ULTR001881/DK041301 (UCLA CURE/CTSI Pilot and Feasibility Study (AG)
pilot funds provided for brain scanning by the Ahmanson-Lovelace Brain Mapping Center

Title: Brain-gut microbiome profile of neuroticism predicts food addiction in obesity: a transdiagnostic approach

Authors: *X. ZHANG[1], R. BHATT[2], S. TODOROV[3], A. GUPTA[4];
[1]David Geffen Sch. of Medicine, UCLA, Los Angeles, CA; [2]USC, Los Angeles, CA; [3]UCLA, Los Angeles, CA; [4]David Geffen Sch. of Med., Oppenheimer Family Ctr. For Neurobio. of Stress, UCLA, Los Angeles, CA

Abstract: Background: Neuroticism is one of the most robust risk factors for psychiatric, and addictive disorders, although the associated mechanisms are not well understood. Due to the role of brain-gut-microbiome interactions in obesity, a transdiagnostic approach was used to identify the neuroticism-related neuropsychological and gut metabolomic patterns associated with food addiction (key contributor to obesity). **Methods**: Predictive modeling of neuroticism was implemented using multimodal features (23 clinical, 13531 resting-state functional connectivity (rsFC), and 336 gut metabolomic) in 114 high body mass index (BMI) participants (BMI>=25 kg/m^2). Synthetic Minority Over Sampling Technique was applied to balance the class distribution of food addiction. The most important features were identified using gradient boosting machines. Logistic regression models were used to evaluate classification performance for food addiction. **Results:** Neuroticism was significantly associated with food addiction (P<0.001). Neuroticism-related features predicted food addiction with high performance [area under the curve (AUC) = 0.89]. Multimodal models performed better than single-modal models in predicting food addiction. Across all models, transdiagnostic alterations corresponded prominently to rsFC involved in key brain regions from the emotion regulation, reward, and cognitive control and self-monitoring networks, and the metabolite 3-(4-hydroxyphenyl)propionate, as well as anxiety symptoms. Neuroticism moderated the relationship between BMI and food addiction. **Conclusion**: Neuroticism-related brain-gut-clinical features accurately predicts food addiction in high BMI individuals. Neuroticism drives neuropsychological and gut microbial signatures implicated in dopamine synthesis and inflammation, anxiety, and food addiction. Such transdiagnostic models are essential in identifying the core maladaptive mechanisms that underlie the presentation of food addiction in obesity, as it can help develop multiprong interventions to improve symptoms.

Disclosures: X. Zhang: None. **R. Bhatt:** None. **S. Todorov:** None. **A. Gupta:** None.

Poster

141. Dynamic Neurovascular and Activity Changes in the Brain

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 141.09

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: Natural Sciences and Engineering Research Council of Canada Discovery Grant

Title: Spontaneous Functional Connectivity Increased with Gestational Age: A Functional Near-Infrared Spectroscopy Study in Healthy Newborns

Authors: *H. VAHIDI[1,2], A. KOWALCZYK[7], K. STUBBS[3], M. MUSABI[7], S. ROYCHAUDHURI[7], S. BHATTACHARYA[7], S. DE RIBAUPIERRE[7,4], K. ST. LAWRENCE[4], Y. MOHSENZADEH[2,5], E. DUERDEN[2,6];
[1]Schulich Sch. of Med. and Dent., [2]Western Inst. for Neurosci., [3]BrainsCAN, [4]Dept. of Med. Biophysics, [5]Dept. of Computer Sci., [6]Fac. of Educ., Western Univ., London, ON, Canada; [7]Div. of Neonatal-Perinatal Medicine, Dept. of Pediatrics, London Hlth. Sci. Ctr., London, ON, Canada

Abstract: Evidence from functional magnetic resonance imaging (fMRI) studies in preterm and term-born neonates suggests that functional connectivity increases with gestational age. Specifically, resting-state networks are thought to begin as unilateral (intra-hemispheric) components and later become bilateral (interhemispheric). While fMRI has provided the basis for understanding the development of functional networks, much of this work has been conducted while infants are either sedated or asleep in unnaturalistic environments, which may unduly influence these networks. Functional near-infrared spectroscopy (fNIRS) is an emerging neuroimaging technique that uses near infrared light to measure changes in oxygenated (HbO) and deoxygenated hemoglobin (HbR) concentrations, an indirect assessment of neural activity. fNIRS can facilitate the study of neural activity in a more naturalistic manner, particularly in infants as they can be scanned while awake. Therefore, we aimed to extend previous findings concerning functional network development in awake preterm and term born neonates using fNIRS. As part of a multi-cohort study, 33 neonates (36+0 - 40+6 weeks gestational age) underwent fNIRS at bedside in the Mother Baby Care Unit within 48 hours of birth while extensive demographic information was collected. fNIRS was used to record sensorimotor networks in both hemispheres using 8 LED sources and 8 detectors. After correcting for motion artifacts, datasets that did not meet quality assessment thresholds were excluded from further analysis. The remaining data (n=24, 11 females) were first converted to optical density and the modified Beer-Lambert Law was then used to calculate HbO, HbR, and total hemoglobin (HbT; combined HbO and HbR). Lastly, HbT was filtered using a nuisance regression algorithm and resampled to 1 Hz for spontaneous functional connectivity (sFC) analysis. Our results indicate that as gestational age increased, there was a significant increase in sFC in the right hemisphere (Pearson's $R = 0.56$, $p = 0.005$). This is consistent with previous fMRI findings that have shown increased intra-hemispheric connectivity in the sensorimotor network in infants. While still preliminary, our results help corroborate previous findings on the development and lateralization of neonatal brain networks.

Disclosures: H. Vahidi: None. **A. Kowalczyk:** None. **K. Stubbs:** None. **M. Musabi:** None. **S. Roychaudhuri:** None. **S. Bhattacharya:** None. **S. de Ribaupierre:** None. **K. St. Lawrence:** None. **Y. Mohsenzadeh:** None. **E. Duerden:** None.

Poster

141. Dynamic Neurovascular and Activity Changes in the Brain

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 141.10

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

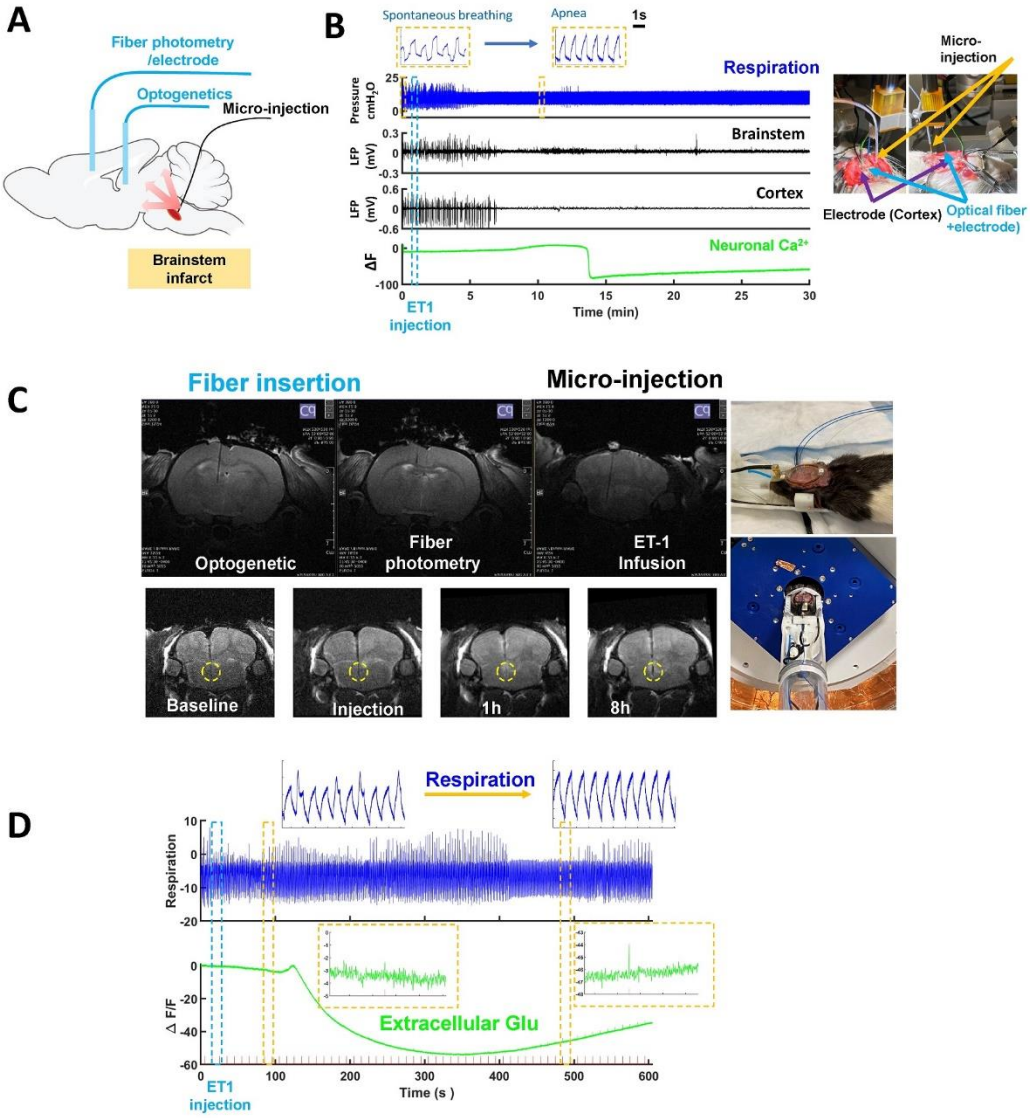
Support: NIH Grant R01NS122904
NIH Grant R21NS121642
NIH Grant RF1NS113278
NSF Grant 2123971
NIH Grant R01NS120594
NIH Grant S10MH124733
NIH Grant R01MH111438

Title: Real-time brainstem coma induction model for neuro-glio-vascular (NGV) signaling with multi-modal fMRI platform

Authors: *Z. XIE[1,3], Y. JIANG[1], B. ZHANG[1], A. LIU[1,4], P. D. A. P. CARNEIRO[1], B. L. EDLOW[1,2], X. YU[1];
[1]Martinos Ctr. for Biomed. Imaging, Massachusetts Gen. Hosp., Charlestown, MA; [2]Dept. of Neurol., Massachusetts Gen. Hosp., Boston, MA; [3]Sch. of Traditional Chinese Med., Southern Med. Univ., Guangzhou, China; [4]Dept. of Neurosci., Boston Univ., Boston, MA

Abstract: Previously, our lab developed a robust coma rat model by dorsomedial brainstem injection of endothelin-1 (ET-1) into the tegmentum, which provides an acute 12-hour time window to study coma recovery[1]. Here, we report a novel real-time brainstem coma induction scheme to measure neuro-glio-vascular (NGV) signaling using a 14T MRI scanner from coma induction through acute recovery of consciousness. We implemented microinjection of ET-1 with peek capillary (ID, 0.1mm) into the brainstem tegmentum through the ventral surface of the brain (**Fig 1A**). As shown in **Fig 1B**, apnea was observed after coma induction, indicating the apnea was caused by the brainstem injury. Cortical and brainstem activity, as measured by local field potentials (LFP), abruptly vanished following a spreading depression-like event after ET-1 injection and the withdrawal of the anesthetics (isoflurane). We combined optical fiber photometry for glutamate (Glu sensor: iGluSnFR) signal recording with genetically encoded sensors. We also targeted the central thalamus with optogenetic stimulation and performed simultaneous whole-brain MR imaging (**Fig 1C)**. The T_2-weighted Rapid Acquisition with Relaxation Enhancement (RARE) sequence images were able to identify lesions (i.e. cytotoxic edema) at the approximate point of the injection site. Following coma induction, extracellular glutamate recording showed first increased extracellular Glu level (possibly indicating spreading depression-like events), then presented decreased signal related to the iso-electric lines (or dramatic suppression of the neuronal activity) following coma induction (**Fig 1D)**. In summary, we optimized a brainstem coma induction model with real-time monitoring of the LFP, whole-brain anatomical and functional MRI, fiber photometry-based NGV dynamic signal recording,

and optogenetic stimulation during coma induction and acute coma recovery. In particular, we observed that spreading depression-like events occurred during coma induction, causing massive neuronal activity depression (as evidenced by iso-electric lines).



Disclosures: **Z. Xie:** None. **Y. Jiang:** None. **B. Zhang:** None. **A. Liu:** None. **P.D.A.P. Carneiro:** None. **B.L. Edlow:** None. **X. Yu:** None.

Poster

141. Dynamic Neurovascular and Activity Changes in the Brain

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 141.11

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: NIH R01 MH125931

Title: Age prediction with physiologically-induced resting-state fMRI BOLD variability

Authors: *S. WANG[1], K. K. ROGGE-OBANDO[2], C. G. MARTIN[3], R. YANG[4], R. W. SONG[4], C. CHANG[1,4,3];
[1]Dept. of Biomed. Engin., [2]Neurosci. Grad. Program, [3]Dept. of Electrical and Computer Engin., [4]Dept. of Computer Sci., Vanderbilt Univ., Nashville, TN

Abstract: The temporal variability of blood oxygen level-dependent (BOLD) signal changes has been shown to be a good predictor of age[1]. While some portion of BOLD signal variability is driven by fluctuations in neural activity, physiological factors like respiratory variation (RV) and heart rate (HR) contribute to BOLD signal independently of neural activity by introducing alternations in cerebral blood flow, cerebral blood volume and arterial CO_2 concentration[2,3]. Therefore, the physiologically-induced fMRI BOLD signal is directly linked to vasculature, and may contain valuable information about age-related vascular changes[2]. Here, we investigated the relationship between the fMRI physiological component and age by exploring whether physiologically-induced fMRI BOLD variability itself is predicative of age. We included the resting-state fMRI scans of 515 subjects from the Nathan Kline Institute Rockland Sample [4] (mean age of 48.4 years, standard deviation of 17.2). We used the basis functions proposed by Chen et al. to derive the combined RV and HR ("RVHR")-induced fMRI BOLD component based on subjects' respiration and heart rate recordings [5]. The RVHR-induced fMRI variance map was then calculated by taking the standard deviation of the fMRI RVHR component time series on the voxel level. The fMRI RVHR variance maps were then fed into a support vector regression (SVR) model with previously reported hyperparameters (a linear kernel with C=Inf and epsilon=0.00001)[6]. We performed a 5-fold cross validation to verify the model's performance on the test set. We achieved an average Pearson Correlation Coefficient (PCC) of 0.6738 between the predicted and target age across the 5 test sets, and an overall PCC of 0.6697 when pooling the test sets of all 5 folds together. A permutation test was carried out by randomly selecting another subject's physiological recording to derive the fMRI RVHR component, and using the same SVR model to carry out the age prediction 100 times with the same 5-fold split. Our results showed significantly better prediction on both the averaged PCC ($p<0.01$) and the overall PCC ($p<0.01$). Our finding suggests that the fMRI physiological component is indicative of age and contains useful information regarding aging-related brain vasculature changes. Further investigation is needed to better understand how brain aging affects physiologically-induced fMRI BOLD signal. 1 Garrett, D. D., et al, Sci. Rep. *7*(2017)2 Abdelkarim, D., et al, Neurosci. Biobehav. Rev., *107*(2019)3 Camandola, S., & Mattson, M. P., EMBO J., *36*(2017)4 Nooner, K. B., et al, Front. Neurosci., *6(2012)*5 Chen, J. E., et al, *NeuroImage*, *213(2020)*6 Millar, P. R., et al., Cereb. Cortex, *30*(2020)

Disclosures: S. Wang: None. **K.K. Rogge-Obando:** None. **C.G. Martin:** None. **R. Yang:** None. **R.W. Song:** None. **C. Chang:** None.

Poster

141. Dynamic Neurovascular and Activity Changes in the Brain

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 141.12

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: NARSAD
ERC 802371

Title: Cortical excitatory/inhibitory balance critically controls brain-wide fMRI coupling

Authors: *D. SASTRE YAGÜE[1,3], F. ROCCHI[1,3], A. STUEFER[1,3], S. NOEI[2,3], L. COLETTA[1], F. ALVINO[1], A. GALBUSERA[1], S. PANZERI[4], A. GOZZI[1];
[1]Functional Neuroimaging Lab., [2]CNCS, Inst. Italiano di Tecnologia (IIT), Rovereto, Italy; [3]Cimec, Univ. of Trento, Rovereto, Italy; [4]Ctr. for Mol. Neurobio. Hamburg (ZMNH), Hamburg, Germany

Abstract: Resting-state fMRI (rsfMRI) is widely used to map intrinsic brain network organization in the healthy, as well as in psychiatric and neurological disorders, where evidence of disrupted or abnormal rsfMRI functional coupling has been largely documented. However, the neural underpinnings and dynamic rules governing brain-wide rsfMRI coupling remain unclear. Neocortical excitatory/inhibitory (E/I) balance critically affects local and long-range information processing and can conceivably bias brain-wide network coupling as measured with rsfMRI. This notion would be consistent with the emerging evidence of neocortical imbalance and altered interareal communication in multiple brain disorders such as Autism Spectrum Disorder or Schizophrenia. Here we combine chemogenetic manipulations, rsfMRI, electrophysiology and behavioral measurements to causally probe how neocortical excitatory-inhibitory balance affects brain-wide fMRI and neural coupling in the mouse brain. We used DREADD-based chemogenetics to remotely alter E/I balance in the mouse prefrontal cortex (PFC) by increasing pyramidal neuron excitability, or by reducing the activity of subclasses of inhibitory interneurons. For each of the employed manipulations, we recorded rsfMRI network activity, and the underlying neural rhythm via in-vivo multielectrode electrophysiology before and after CNO administration. We found that increasing PFC excitability via DREADD activation of CamkII-expressing pyramidal neurons dramatically desynchronized brain-wide rsfMRI functional connectivity in the mouse default network, an effect that was associated with increased gamma activity and reduced low frequency interareal coherence. Notably, analogous connectivity and neural desynchronization was observed upon chemogenetic inhibition of fast-spiking parvalbumin positive interneurons, but not somatostatin-positive cells. Importantly, all connectivity-affecting perturbations were associated with socio-communicative deficits as assessed in a three-chamber sociability test, hence underscoring the behavioral relevance of the employed manipulations. Our results show that excitatory/inhibitory balance critically biases brain-wide fMRI coupling and point at a possible unifying mechanistic link between E/I imbalance and connectivity disruption in brain disorders.

Disclosures: **D. Sastre Yagüe:** None. **F. Rocchi:** None. **A. Stuefer:** None. **S. Noei:** None. **L. Coletta:** None. **F. Alvino:** None. **A. Galbusera:** None. **S. Panzeri:** None. **A. Gozzi:** None.

Poster

141. Dynamic Neurovascular and Activity Changes in the Brain

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 141.13

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

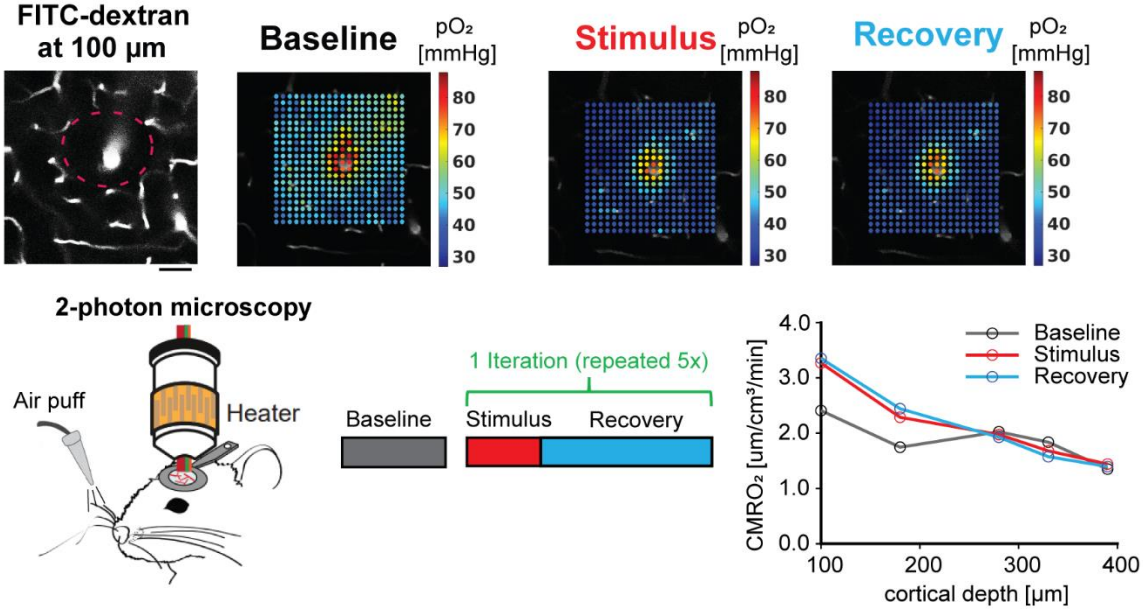
Support: NIH Brain Initiative R01MH111359
NIH Brain Initiative R01DA050159
NIH Brain Initiative R01NS108472
NIH Brain Initiative U19NS123717
NIH Brain Initiative K99MH120053
Swiss National Science Foundation (P2ZHP3_181568)
U24 EB028941

Title: High oxygen metabolism in layer I revealed with two-photon phosphorescence lifetime microscopy in awake mice under rest and stimulation

Authors: *N. FOMIN-THUNEMANN[1], P. MÄCHLER[2], M. THUNEMANN[1], M. J. SAETRA[4], M. DESJARDINS[5], K. KILIÇ[1], T. VAYISOGLU[1], P. DORAN[1], J. JIANG[1], E. MARTIN[1], I. SENCAN[6], B. LI[7,6], P. SAISAN[2], Q. CHENG[2], K. L. WELDY[2], D. A. BOAS[1], R. B. BUXTON[3], G. T. EINEVOLL[8,4], A. M. DALE[2,3], S. SAKADŽIć[6], A. DEVOR[1,6];
[1]Biomed. Engin., Boston Univ., Boston, MA; [2]Dept. of Neurosciences, [3]Dept. of Radiology, Univ. of California San Diego, San Diego, CA; [4]Dept. of Physics, Univ. of Oslo, Oslo, Norway; [5]Dept. de physique, de génie physique et d'optique, Univ. Laval, Québec, QC, Canada; [6]Athinoula A. Martinos Ctr. for Biomed. Imaging, Massachusetts Gen. Hospital, Harvard Med. Sch., Charlestown, MA; [7]Shenzhen Inst. of Advanced Technology, Chinese Acad. of Sci., Shenzhen, China; [8]Dept. of Physics, Norwegian Univ. Life Sci., Aas, Norway

Abstract: Quantifying oxygen availability and metabolism in cortical tissue offers a crucial physiological parameter in health and disease. According to a common notion, cortical layer IV has a higher oxygen consumption than other layers due to higher mitochondrial density. We tested this hypothesis using direct measurements of the partial pressure of O_2 (pO_2) around diving arterioles across cortical layers obtained with 2-photon phosphorescence lifetime microscopy (2PLM) in awake mice. We estimated $CMRO_2$ from pO_2 gradients around diving arterioles using a modified Krogh model of O_2 diffusion from a cylinder. Our results show that, contrary to the common notion, the baseline $CMRO_2$ in layer I was higher than that in other layers. In addition, we observed the same effect under stimulation. Stimulus-induced $CMRO_2$ increase outlasted the stimulus duration, likely indicating higher metabolic demands of an active brain state. We hypothesize that the higher $CMRO_2$ in layer I could be explained, at least in part, by ascending inputs targeting apical pyramidal dendrites. In our study, the pO_2 probe Oxyphor

2P was microinjected into the cortical tissue 1-2 hours before the measurements. To control for potential adverse effects of this procedure on cortical physiology, experiments are underway using alternative methods of the probe delivery. Our results question the use of mitochondrial density to quantify oxidative metabolism. Understanding the laminar profile of $CMRO_2$ is important for interpretation of high resolution Blood Oxygen Level Dependent (BOLD) functional Magnetic Resonance Imaging (fMRI) studies.



Disclosures: **N. Fomin-Thunemann:** None. **P. Mächler:** None. **M. Thunemann:** None. **M.J. Saetra:** None. **M. Desjardins:** None. **K. Kiliç:** None. **T. Vayisoglu:** None. **P. Doran:** None. **J. Jiang:** None. **E. Martin:** None. **I. Sencan:** None. **B. Li:** None. **P. Saisan:** None. **Q. Cheng:** None. **K.L. Weldy:** None. **D.A. Boas:** None. **R.B. Buxton:** None. **G.T. Einevoll:** None. **A.M. Dale:** None. **S. Sakadžić:** None. **A. Devor:** None.

Poster

141. Dynamic Neurovascular and Activity Changes in the Brain

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 141.14

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: NIH Grant R00-MH111748
McKnight Foundation
NIH Grant R01-AG070135
The Pew Charitable Trusts

Title: Introducing EEG-LLAMAS, a low-latency EEG-fMRI neurofeedback and artifact removal application

Authors: *J. LEVITT, L. D. LEWIS;
Biomed. Engin., Boston Univ., Boston, MA

Abstract: Real-time EEG-fMRI has the potential to be a powerful neuroimaging tool, as it would enable multimodal neurofeedback experiments and image the neural consequences of EEG-guided paradigms. Since EEG and fMRI offer complementary temporal and spatial resolutions, their use in tandem can offer greater information than either can independently. However, the presence of scanner-induced noise in the EEG has been a substantial barrier to EEG-fMRI neurofeedback research, as it must be removed from EEG signals in real time to make these experiments possible. Here we introduce EEG-LLAMAS (EEG Low-Latency Artifact Mitigation Acquisition Software), an open-source application for removing ballistocardiogram (BCG) and gradient artifacts with low latency during EEG-fMRI experiments. Previous techniques for removing BCG artifacts have relied upon methods that require higher latency, or on methods that have limited efficacy. EEG-LLAMAS uses a technique similar to reference layer artifact subtraction (RLAS), adapted for real-time applications using a Kalman filter. We evaluated the efficacy of this software in terms of its ability to remove BCG artifact and recover a steady-state visual evoked response (SSVEP), as well as its latency. We collected EEG-fMRI data from 10 healthy adult subjects who were shown a visual flickering checkerboard stimulus, to induce an EEG signal with known frequency characteristics. We compared three methods for removing gradient and BCG artifacts: real time removal using LLAMAS, and offline using RLAS and a widely-used Optimal Basis Sets method. We compared this cleaned EEG data from inside the MR scanner to EEG collected outside the scanner. Although no method was able to recover an SSVEP of the same magnitude as was collected outside the scanner, LLAMAS performed as well as the high-latency alternatives. Additionally, to assess the latency added by LLAMAS compared to EEG recorded with no artifact removal or digital filters, we measured the mean time from the acquisition of a sample to the completion of processing, and found that mean latency was between 44ms and 58ms, depending upon the graphical settings. This speed, coupled with artifact removal that matches the best available offline techniques, will allow for EEG-fMRI neurofeedback experiments that have been previously unfeasible. This method can now be used to improve our understanding of the mechanisms of neuromodulation, with greater spatiotemporal resolution than has previously been possible.

Disclosures: J. Levitt: None. **L.D. Lewis:** None.

Poster

141. Dynamic Neurovascular and Activity Changes in the Brain

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 141.15

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: MOST Grant 110WFA0910064
MOST Grant 110WFA0112268

Title: Exploring a biomarker of psychological resilience by measuring DMN stability in rsfMRI

Authors: *C.-W. HSU[1,2], J. GOH[1,2], S. HSIEH[3], C.-T. YANG[3], S.-H. LIN[4], M.-C. TSAI[5], Y.-H. CHANG[6], K.-P. SU[7], Y.-T. CHANG[1,2], W.-R. LIN[1,2];
[1]Natl. Taiwan Univ., Taipei, Taiwan; [2]Grad. Inst. of Brain and Mind Sci., Taipei, Taiwan; [3]Psychology, [4]Inst. of Clin. Med., Natl. Cheng Kung Univ., Tainan, Taiwan; [5]Pediatrics, Natl. Cheng Kung Univ. & Hosp., Tainan, Taiwan; [6]Psychology, Asia Univ., Taichung, Taiwan; [7]An-Nan Hosp., China Med. Univ., Taichung, Taiwan

Abstract: Globalization and modernization have increased the frequency and complexity of mental challenges that people experience in their lives. Thus, promoting mental health is one of the greatest of current global challenges. Psychological resilience, the ability to mentally bounce back in face of adversity, reflects the maintenance of normative brain function under challenging circumstances. In this study, we explore a biomarker of psychological resilience using resting-state functional magnetic resonance imaging (rs-fMRI). Importantly, psychological resilience is an abstract concept presently operationally defined based on self-report questionnaires. We suggest a general definition of resilience as a dynamic state of mind that fluctuates due to external circumstances but returns to homeostasis and maintains a stable level of psychological functioning. In this light, we considered that the stability of psychological states should be reflected in neural activity, especially in the default mode network (DMN), which is implicated in mental representations of self-states. Based on this, higher levels of mental stability should be represented by smaller variation of DMN activity. To quantify DMN resting state stability, the multivariate signals in all DMN voxels at each time point were projected in two-dimensional space using multidimensional scaling (MDS). The average distances between state coordinates between consecutive time points were extracted as individual indices of DMN stability. 233 healthy subjects (108 males, 125 females, mean age (SD) = 26.6 (13.64)) completed a rs-fMRI scan, the Connor-Davidson Resilience Scale (CD-RISC), Brief Resilience Scale (BRS), and Resilience Scale for Adults (RSA). Individuals with higher DMN stability showed higher resilience in CD-RISC (r = -.18, $p(FDR)$ < .05) and BRS (r = - .18, $p(FDR)$ < .05). We are continuing to evaluate DMN stability as a neural-based objective definition of mental state dynamics toward a novel biomarker of resilience. This technique might be a more accurate and reliable physiological assessment of mental health that can be applied in the development of targeted interventions to maintain normal psychological functioning under adversity that promotes mental health.

Disclosures: C. Hsu: None. **J. Goh:** None. **S. Hsieh:** None. **C. Yang:** None. **S. Lin:** None. **M. Tsai:** None. **Y. Chang:** None. **K. Su:** None. **Y. Chang:** None. **W. Lin:** None.

Poster

141. Dynamic Neurovascular and Activity Changes in the Brain

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 141.16

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: NIH Grant R01 NS095933
NIH Grant R56 NS095933

Title: The impact of sex on hemodynamic response function across the majority of human cerebral cortex

Authors: *N. J. FESHARAKI, A. TAYLOR, J. KIM, D. RESS;
Baylor Col. of Med., Houston, TX

Abstract: In functional magnetic resonance imaging (fMRI), vascular and metabolic responses to neural activity evoked by a short stimulus create the hemodynamic response function (HRF). Assuming linearity, the HRF is used as an impulse response for analysis of fMRI experiments, which permits inferences about neural activity. Yet, there is a lack of knowledge on the impact of sex on the HRF. In particular, there have been observations of sex differences in resting cerebral blood flow and oxygen metabolism, as well as various metrics of cortical activation. Thus, it is of great interest to explore through measurements and modeling how neurovascular and neurometabolic coupling during brain activation differs between the two sexes. Here, we recruited a cohort of 20 healthy subjects, ages 22-64 years, balanced evenly between the two sexes. Use was made of a simple event-related paradigm consisting of brief (2-s) speeded audiovisual tasks to evoke strong HRFs across the majority of cerebral cortex (Taylor et al., 2018). HRFs were evaluated using a model-free parameterization to measure amplitudes and dynamics. In terms of HRF amplitudes, ~80% of activated cortex showed similarity between the two sexes, while the remainder had significant differences (Figure). Amplitude differences (A) were largely in auditory and language areas. A smaller fraction (~8%) of cortex exhibited differences in dynamics (B—D). Note the overlap between regions of amplitude and onset time (D). To further assess physiology, HRFs were also modeled as in our previous work (Kim and Ress, 2016). Model-based predictions indicated that sex differences can be caused by both CBF and $CMRO_2$ dynamics. We conclude that HRFs are primarily similar between the sexes, but there are a few regions of significant differences.

References: Taylor, A.J., Kim, J.H., Ress, D., 2018. Characterization of the hemodynamic response function across the majority of human cerebral cortex. Neuroimage 173: 322-331.Kim, JH, Ress, D., 2016. Arterial impulse model for the BOLD response to brief neural activation. Neuroimage. 124(Pt A):394-408.

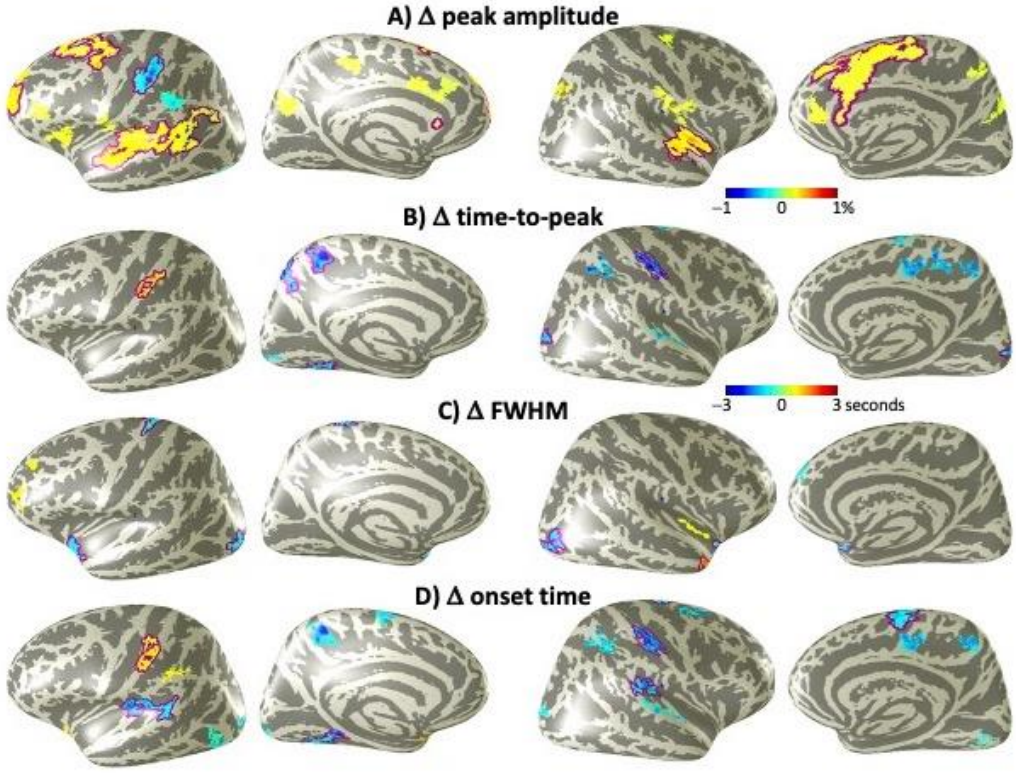


Figure: significant ($p < 0.05$) clusters (>1 cm^2) of sex differences in MNI-152 space for four parameters: A) peak amplitude; B) time-to-peak; C) FWHM; and D) onset time. Colored overlay shows differences; hot colors for male parameter larger, cool colors for female parameter larger.

Disclosures: **N.J. Fesharaki:** None. **A. Taylor:** None. **J. Kim:** None. **D. Ress:** None.

Poster

141. Dynamic Neurovascular and Activity Changes in the Brain

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 141.17

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Title: Combined Functional Ultrasound and Photoacoustic Imaging of Brain Activity

Authors: *H. CHEN[1,2], S. AGRAWAL[1], Q. LI[1], W. TU[3], N. ZHANG[1,2], B. J. GLUCKMAN[1,2,3,4], S. R. KOTHAPALLI[1,2,5];

[1]Biomed. Engin., [2]Ctr. for Neural Engin., [3]Engin. Sci. and Mechanics, Pennsylvania State Univ., University Park, PA; [4]Dept. of Neurosurg., [5]Penn State Cancer Inst., Pennsylvania State Univ., Hershey, PA

Abstract: Combining functional ultrasound (fUS) and photoacoustic (PA) imaging provides complementary deep brain hemodynamic information. fUS provides hemodynamic neuronal activity of deep rodent brain based on relative changes in cerebral blood volume (CBV) with high spatiotemporal resolution, while PA imaging exploits the local cerebral oxygen saturation up to 1 cm inside the brain based on differential light absorption between oxy- (HbO) and deoxy- (HbR) hemoglobin. Therefore, a platform combining fUS and PA imaging modalities into a portable and wearable form is favorable to derive a multiparametric awake brain activity. Towards this goal, we developed a light-weight and portable fUS+PA imaging device that can be mounted on top of a freely moving rat. Ultrasound coupling is significantly minimized by optimizing the light delivery system around the ultrasonic transducer using acrylic lenses. The combined fUS+PA imaging capabilities were first tested using wire target, blood flow and blood oxygenation phantoms. Wire phantom revealed a US imaging lateral resolution of 0.14 mm and axial resolution of 0.18 mm and PA imaging lateral resolution of 0.1 mm and axial resolution of 0.12 mm. In addition, by inducing 5% CO_2 to the animal (N = 3), we quantitatively assessed the hemodynamic changes by simultaneously acquiring time-locked fUS and PA imaging frames during hypercapnia. The increased intensity in fUS images and reduction in blood oxygenation revealed by PA images faithfully validated the imaging system as the results corresponded to the physiological changes of increased blood flow and HbR during hypercapnia. In the future, the fUS+PA multimodal imaging platform can be used on a freely moving rodent to study neurovascular coupling and brain connectivity in naturally behaving animals under normal conditions as well as diseased, such as epilepsy.

Disclosures: H. Chen: None. **S. Agrawal:** None. **Q. Li:** None. **W. Tu:** None. **N. Zhang:** None. **B.J. Gluckman:** None. **S.R. Kothapalli:** None.

Poster

141. Dynamic Neurovascular and Activity Changes in the Brain

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 141.18

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: 1U54MH091657

Title: Association between Higher Blood Pressure and Lower Hippocampal Functional Connectivity in Healthy Younger Adults

Authors: *I. MERMILLIOD[1,2], J. WON[2,3], R. ZHANG[2,3];
[1]Southern Methodist Univ., Dallas, TX; [2]Inst. for Exercise and Envrn. Medicine, Texas Hlth. Presbyterian Hosp., Dallas, TX; [3]Neurol., Univ. of Texas Southwestern Med. Ctr., Dallas, TX

Abstract: Objective and Rationale: High blood pressure (BP) in mid-aged and older adults is associated with hippocampal atrophy. However, we know little about the association between BP and functional network connectivity (FC) of the hippocampus in younger adults which is the aim of the present study. **Methods:** 751 younger adults (28.6±3.7 years) from the Human Connectome Project were included for the analyses. Brachial systolic (SBP) and diastolic (DBP) BP were assessed using semi-automatic BP monitor. Structural and functional magnetic resonance imaging (MRI) data were analyzed to assess hippocampal volume and FC.Fluid and crystalized cognitive composite scores were obtained through comprehensive neuropsychological tests. Linear regression models were used to test the associations between BP and hippocampal FC (whole brain voxel-wise $p < 0.0001$, FDR correction $p < 0.05$, $k \geq 27$) adjusting for age, sex, education, body mass index (BMI), smoking history, and alcohol consumption frequency. We also assessed the association between BP quartile (1st, < 120 SBP and < 80 mmHg DBP; 2nd, 120-129 SBP and < 80 mmHg DBP; 3rd, 130-139 SBP or 80-89 mmHg DBP; and 4th, ≥ 140 SBP or ≥ 90 mmHg DBP) and hippocampal FC to examine a potential dose-response relationship. Association between BP and caudate FC was computed as a control. **Results:** The mean BMI of the participants was 26.0±4.9 kg/m^2 (16-45 kg/m^2), mean SBP was 122.5±12.8 mmHg (93-159 mmHg), and the mean DBP was 75.7±9.6 mmHg (51-102 mmHg). Higher SBP was associated with lower FC between the hippocampus and the right precentral gyrus. Similarly, there were associations between higher DBP and lower FC between the hippocampus and the superior temporal gyrus, insula, fusiform gyrus, medial frontal gyrus, and parahippocampal gyrus. There was a dose-response relationship between BP and hippocampal FC, such that higher BP quartile was associated with lower hippocampal FC in the superior temporal gyrus and right fusiform gyrus. Higher pulse pressure was associated with lower FC between hippocampus and right culmen and right precuneus. No significant associations were found between BP and caudate FC, bilateral hippocampal volume, and cognitive functioning. **Conclusions:** The present study suggests that higher BP is associated with lower hippocampal FC even in healthy and young age. Our findings shed light on the importance of implementing early intervention to control high BP for sustained brain health throughout the adulthood.

Disclosures: I. Mermilliod: None. **J. Won:** None. **R. Zhang:** None.

Poster

141. Dynamic Neurovascular and Activity Changes in the Brain

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 141.19

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: ERC DisConn 802371

Title: Evolutionarily conserved fMRI coactivation dynamics in the human, macaque and mouse brain

Authors: *D. GUTIERREZ-BARRAGAN[1], J. S. B. RAMIREZ[2], S. PANZERI[3], T. XU[2], A. GOZZI[1];
[1]Functional Neuroimaging Lab., Inst. Italiano di Tecnologia, CNCS, Rovereto, Italy; [2]Ctr. for the Developing Brain, Child Mind Inst., New York, NY; [3]Ctr. for Mol. Neurobiology, Dept. of Excellence for Neural Information Processing, Univ. Hamburg, Hamburg, Germany

Abstract: Evolutionarily relevant networks of spontaneous brain activity have been consistently mapped in humans, primates and rodents using resting-state fMRI (rsfMRI). It is however unclear whether the dynamic rules that govern rsfMRI network dynamics are species-invariant, or if they instead have evolved across the phylogenetic tree. Here, we used frame-wise clustering of rsfMRI timeseries acquired in awake mice, macaques, and humans, to map and compare the topography and dynamic properties of rsfMRI co-activation patterns (CAPs) across species. We report that rsfMRI dynamics in the mammalian brain are characterized by recurrent transitions between fluctuating BOLD co-activation patterns (CAPs), whose topography and dynamics follow evolutionarily-conserved principles. Specifically, in all species rsfMRI activity could be reliably partitioned in a small number (k= 6, mouse: n=51; k=8, macaque: n=8 x 2 sessions, k = 8, human: n=10 x 5 sessions) of stable and reproducible CAPs across independent datasets and sessions, explaining a substantial fraction of rsfMRI variance ($R^2 > 0.6$ in all species). Moreover, mouse, macaque and human CAPs could be paired into spatially opposing topographies, indicative of peaks and throughs of fluctuating fMRI network activity. Spectral analyses revealed that CAPs fluctuate with centered power in the infraslow range (0.01-0.04Hz), and that CAPs exhibited preferential occurrence within Global fMRI Signal (GS) cycle that in all species, indicative of species-invariant relationship between CAP emergence and fMRI global signal cycles. Evolutionarily-conserved CAP topographies were also apparent, with evidence of a competing engagement of default-mode network (DMN) and somatosensory regions (CAPs 1-2), as well as the presence of pan-cortical patterns of fMRI coactivation (CAPs 3-4) in all species. In keeping with cortical expansion along the phylogenetic tree, one CAP pair was instead reliably identified only in human and macaque, exhibiting primate-specific features in high-order regions of dorsal-attention and executive-networks. Taken together, our results reveal a set of fundamental, evolutionarily-conserved principles underlying rsfMRI network dynamics in the awake mammalian brain.

Disclosures: D. Gutierrez-Barragan: None. **J.S.B. Ramirez:** None. **S. Panzeri:** None. **T. Xu:** None. **A. Gozzi:** None.

Poster

141. Dynamic Neurovascular and Activity Changes in the Brain

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 141.20

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Title: Spontaneous and task-evoked brain activity do not interact in an event-related fmri task

Authors: *S. NAYAK, S. HOJJATI, S. OZORIA, F. FEIZ, J. SHTEINGART, A. FERNANDEZ GUERRERO, A. MODARESSI, Q. R. RAZLIGHI;
Radiology, Quantitative Neuroimaging Laboratory, Brain Hlth. Imaging Institute, Weill Cornell Med. Col., New York, NY

Abstract: The brain activities can be categorized into at least two distinct groups; spontaneous and task-evoked. To date, there is no consensus in the field about the roles of each brain activity and whether there is an interaction between them. One of the most well-studied networks of spontaneous brain activity is the Default mode network (DMN), where the strongest task-evoked negative BOLD response is also observed. Using 36 young (27.72 ± 5.49 years) cognitively normal participants performing an event-related perceptual speed task inside fMRI scanner, we aimed to show that there is no interaction between functional connectivity (an fMRI measurement of spontaneous activity) and the task-evoked negative BOLD response in the DMN. Independent component analysis (ICA) and general linear model (GLM) were used to obtain the DMN's functional connectivity and the task-evoked response in each participant. The time courses of FC and TE are orthogonalized to quantify their unique fMRI associations. A univariate second-level multiple regression analysis is performed to model the effects of task-evoked (TE), functional connectivity (FC), and their interaction on the fMRI signal ($fMRI = \beta_0 + \beta_1 TE + \beta_2 FC + \beta_3 (TE * FC) + \varepsilon$). Voxels within DMN (green masks) with strong negative response ($t<-6$, $p<10^{-5}$; Fig. 1a) and functional connectivity ($t>6$, $p<10^{-5}$; Fig. 1b) are selected. The mean amplitude of the BOLD response in the selected voxels is $\beta_{1\_ave}=-14$ and for functional connectivity is $\beta_{2\_ave}=39$; However, no significant cluster of voxels was found with interaction within DMN (Fig. 1c) and the mean amplitude of interaction is $\beta_{3\_ave}=0.69$ in the selected voxel. Our results indicate that spontaneous and task-evoked activity each account for a unique portion of the fMRI signal variance whereas they do not show any significant interaction. These results suggest that the presence or absence of the coherent spontaneous activity in the DMN has almost no effect on the amplitude of the BOLD response and vice versa.

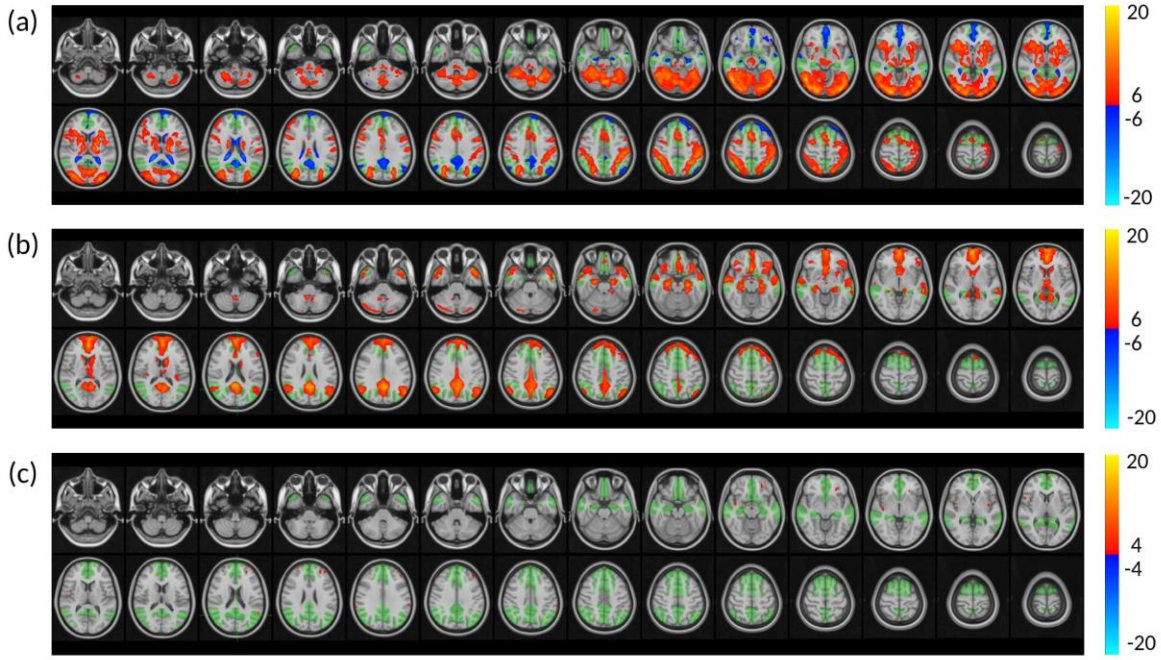


Figure 1: The spatial pattern of the significance (t statistics) of the voxels a) representing activated/deactivated during the perceptual speed task, b) showing functional connectivity during the same fMRI scan within the DMN, and c) their interaction overlaid on 40 axial slices of the MNI template. The t statistics are color coded with heatmap and the DMN mask is shown in green.

Disclosures: **S. Nayak:** None. **S. Hojjati:** None. **S. Ozoria:** None. **F. Feiz:** None. **J. Shteingart:** None. **A. Fernandez Guerrero:** None. **A. Modaressi:** None. **Q.R. Razlighi:** None.

Poster

141. Dynamic Neurovascular and Activity Changes in the Brain

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 141.21

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: MOST, Taiwan Grant 110-2321-B-A49A-502
MOST, Taiwan Grant 110-2628-B-A49A-509
MOST, Taiwan Grant 110-2634-F-075-001
MOST, Taiwan Grant 110-2634-F-A49-005
Mt. Jade Young Scholarship Award from Ministry of Education, Taiwan
National Yang Ming Chiao Tung University and the Ministry of Education (Aim for the Top University Plan), Taipei, Taiwan

Title: Association between abnormal functional connectivity and autonomic dysfunction in major depressive disorder

Authors: *C.-H. LEE[1], A.-C. YANG[2];
[1]Inst. of Brain Science, Natl. Yang Ming Chiao Tung Univ., Taipei, Taiwan; [2]Inst. of Brain Science/Digital Med. Ctr., Natl. Yang Ming Chiao Tung Univ., Taipei, Taiwan

Abstract: MDD patients are often accompanied by autonomic dysfunction. However, the impacts of autonomic changes on the brain in MDD are still unclear. We aimed to investigate the relationship between autonomic nervous system changes and brain functional abnormalities in MDD patients. This study selected 33 MDD and 132 HC according to similar age and gender distribution. All participants received a resting-state functional MRI scan and Electrocardiography measurement simultaneously. We used a generalized linear model combined with a voxel-based functional connectivity method and heart rate variability(HRV) to identify brain regions that could be associated with MDD and autonomic dysfunction. The results showed that the right hippocampus and bilateral parahippocampal gyrus were hyper-connectivity in MDD. Furthermore, the high frequency was associated with reduced functional connectivity in the middle frontal in the HRV effect. This study found the relationship between brain function and autonomic dysfunction in MDD patients. Our findings provide a more comprehensive understanding of the brain mechanism of autonomic dysfunction in MDD.

Disclosures: C. Lee: None. **A. Yang:** None.

Poster

141. Dynamic Neurovascular and Activity Changes in the Brain

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 141.22

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: NIH Grant 5R00MH111748-05

Title: Swadee: a gui-based tool for slow wave activity detection via eeg and eyetracking

Authors: *Z. YANG[1], S. D. WILLIAMS[2], N. TACUGUE[2], Z. VALDIVIEZO[2], T. LY[2], M. AON[2], J. HUA[3], N. LEONARD[2], R. S. HUANG[2], D. ZIMMERMAN[2], J. YEE[2], L. D. LEWIS[2];
[1]Biomed. Engin., Boston Univ. Grad. Program For Neurosci., Boston, MA; [2]Biomed. Engin., [3]Computer Engin., Boston Univ., Boston, MA

Abstract: Slow waves in the EEG are a prominent feature of non-rapid eye movement (NREM) sleep and are characterized by widespread synchronized hyperpolarization and depolarization of neurons. Slow-wave activity (EEG power between 0.5 and 4 Hz) is often used as an electrophysiological marker of sleep pressure accumulation during sleep deprivation. However, spectral power measures lack the sensitivity and specificity needed to investigate the coordination of slow waves across the cortex and potential alterations to individual slow waves

due to sleep deprivation. Manual identification of slow waves by experienced researchers can be time-consuming and lack high inter-rater reliability. Multiple techniques have therefore been developed for the automatic detection of slow waves. However, while existing techniques can be very effective for sleep EEG, a challenge with awake sleep deprivation is the presence of eye blinks that can interfere with automated slow wave detection. We created a simple Matlab-based GUI for selecting and choosing parameter estimates commonly used for slow wave detection that are based on frequency modulation, amplitude, and duration. We also incorporate a novel eye blink artifact detection algorithm based on optimally selected EEG features. The average correlation coefficient between electrooculogram (EOG) activity and pupillometry is applied for feature optimization evaluation, and simultaneously recorded eye video is used for the validation of blinks detected. We collected eyes-open resting-state EEG data from 15 healthy human participants undergoing a full night of sleep deprivation. Consistent with prior studies, spectral power analysis of the resting state EEG demonstrated that the low frequency (0.1 - 5 Hz) power increased after sleep deprivation. We then applied multiple slow-wave detection methods to identify individual slow waves, and calculated the number of false positives due to eye blinks. We found that some eye blinks could be misidentified as slow waves if only a frequency threshold or duration-based method was used to detect slow waves. A combination of several methods (filter parameter optimization, peak-to-peak amplitude threshold, negative half-wave duration and canonical wave selections) yielded the lowest rate of false positives. Our software also graphically displays single and group average slow waves, trajectories of each individual slow wave detected by different EEG channels, and the globality of individual slow wave. The software and example code will be made freely available to facilitate the analysis of sleep EEG recordings for the neuroscience community.

Disclosures: **Z. Yang:** None. **S.D. Williams:** None. **N. Tacugue:** None. **Z. Valdiviezo:** None. **T. Ly:** None. **M. Aon:** None. **J. Hua:** None. **N. Leonard:** None. **R.S. Huang:** None. **D. Zimmerman:** None. **J. Yee:** None. **L.D. Lewis:** None.

Poster

141. Dynamic Neurovascular and Activity Changes in the Brain

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 141.23

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: NIMH: 1K08MH121757-01A1

Title: Functional ultrasound imaging reveals theta-frequency stimulation of the mouse medial septum increases hippocampal and medial prefrontal cortical blood flow in an NMDA-dependent manner

Authors: *L. M. CROWN[1], K. AGYEMAN[2], W. CHOI[1], V. N. CHRISTOPOULOS[2], D. J. LEE[1];

[1]Keck Sch. of Med., USC, Los Angeles, CA; [2]Bioengineering, Univ. of California, Riverside, Riverside, CA

Abstract: Deep Bran Stimulation (DBS) has shown remarkable success in treating neurological and, more recently, neuropsychiatric disorders such as major depression and obsessive-compulsive disorder. A variety of groups, including our own, are now investigating the potential of DBS to improve functional outcomes and cognition in other psychiatric conditions. However, the underlying mechanism of action remains unknown. While most DBS treatments for movement disorders require continuous stimulation, there is evidence that DBS may have long-lasting effects beyond the period of stimulation. This suggests that DBS alters brain activity in ways beyond its acute electrical effects, necessitating a broader exploration of how of DBS alters brain networks, such as through cerebral blood flow. In this study we utilize functional ultrasounds imaging (fUSI) in mice to investigate how stimulation of the medial septal nucleus (MSN) impacts neurovascular activity in the septo-hippocampal network and its afferents. To determine the relationship between MSN stimulation and cerebral blood volume (CBV), 60 male mice were anesthetized with isoflurane and given either MSN theta (7.7Hz) frequency, gamma frequency (100Hz) or no stimulation for 5 minutes, 40 minutes following either saline or 1mg/kg MK-801 administration (i.p.). Across a sagittal plane we imaged the hippocampus, medial prefrontal cortex, thalamus, hypothalamus, pallidum and striatum. We first found that MK-801 reduces blood perfusion across all regions of interest, but at different rates. To determine the impact of DBS on blood perfusion, we then compare CBV before, during, and after stimulation. We found that relative to pre-stimulation, theta-frequency stimulation increased CBV in the hippocampus and medial prefrontal cortex to a greater degree in saline-treated than MK-801-treated mice. These results suggest that MSN theta-frequency stimulation may increase septo-hippocampal and prefrontal cortical blood flow in an NMDA-dependent manner.

Disclosures: L.M. Crown: None. **K. Agyeman:** None. **W. Choi:** None. **V.N. Christopoulos:** None. **D.J. Lee:** None.

Poster

141. Dynamic Neurovascular and Activity Changes in the Brain

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 141.24

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: NIMH Grant: MH103366 (BSNIP2)

Title: Neural and behavioral effects of long-term exposure to the antisaccade task

Authors: *B. S. JACKSON[1], L.-Y. HUANG[1], S. S. KEEDY[3], M. S. KESHAVAN[4], C. A. TAMMINGA[5], G. D. PEARLSON[6], B. A. CLEMENTZ[2], J. E. MCDOWELL[1];
[1]Psychology, [2]Departments of Psychology and Neurosci., Univ. of Georgia, Athens, GA; [3]Psychiatry and Behavioral Neurosci., Univ. of Chicago, Chicago, IL; [4]Psychiatry, Harvard Med.

Sch., Boston, MA; [5]Psychiatry, UT Southwestern Med. Ctr., Dallas, TX; [6]Dept Psychiatry & Behav Sci., Johns Hopkins Hosp., Baltimore, MD

Abstract: Antisaccade tasks require high levels of cognitive control and are utilized to study cognitive deficits in people with psychotic disorders. Psychosis is associated with deficits to cognitive processes including inhibition, attention, and working memory, reflected by increased error rates and decreased neural activation for the antisaccade task. Previous work has shown that short-term, repeated exposure to the antisaccade task has resulted in improvements to both brain and behavioral function in psychotic samples, however, transdiagnostic longitudinal studies are rare. The current study utilized functional magnetic resonance imaging (fMRI) and saccadic eye-movement tasks to explore the neural and behavioral impacts to cognitive control processes after long-term exposure to antisaccade tasks (measured six months apart) in people with psychosis (schizophrenia, schizoaffective, psychotic bipolar) and healthy controls. Behavioral tasks were administered in the MR environment and contained an event-related antisaccade run with 32 total trials. Behavioral data demonstrated practice effects in the psychosis group, such that psychosis probands had decreased error rates on the antisaccade task from baseline to 6-months, while healthy controls demonstrated marginally increased error rates. A 2-way ANOVA of group (psychosis vs. healthy) and time (baseline vs. 6-months) showed a significant interaction ($p<0.05$) in neural activation in a cluster including the parahippocampus, thalamus, and cerebellum. In this cluster, healthy controls displayed decreased activation from baseline to 6-months, while psychosis probands demonstrated increased activation from baseline to 6-months. These findings replicate previous work demonstrating impacted hippocampal regions as a biomarker for psychosis. Contrast tests for group demonstrated overall neural attenuation in the psychosis group (decreased activation from baseline to 6-months) while healthy controls did not differ across time, highlighting markedly different patterns of neural activation for groups across time. In sum, for the group by time interaction, psychosis probands demonstrated increased neural activation and lower error rates on the antisaccade task at 6-months compared to baseline, indicating improved performance and neural efficiency (specifically in an area affected at baseline and in previous literature) after task exposure. Results from this study highlight the impact of long-term exposure to cognitive control tasks in psychotic and healthy samples and the potential role for practice-induced improvements to neural functioning in groups with known cognitive impairments.

Disclosures: B.S. Jackson: None. **L. Huang:** None. **S.S. Keedy:** None. **M.S. Keshavan:** None. **C.A. Tamminga:** None. **G.D. Pearlson:** None. **B.A. Clementz:** None. **J.E. McDowell:** None.

Poster

141. Dynamic Neurovascular and Activity Changes in the Brain

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 141.25

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Title: Functional implication of the sensorimotor network in post-Cov19 children, a rs-fMRI study

Authors: *Y. ROJAS-LEMUS[1], D. E. ALVAREZ-AMADO[2], E. BARRAGAN[3], P. DIES-SUAREZ[4], B. DE CELIS ALONSO[7], J. C. GARCIA[2], C. MAURICIO[5], S. BONILLA[6], M. C. ROMERO-FLORES[2], S. HIDALGO-TOBON[8];
[1]Physics, Univ. Autonoma Metropolitana Iztapalapa, Iztapalapa, Mexico; [2]Neurol., Hosp. Infantil de Mexico Federico Gomez, Cuidad de México, Mexico; [3]Neurol., Hosp. Infantil de Mexico Federico Gomez, CIUDAD DE MEXICO, Mexico; [4]Imagenology, Hosp. Infantil de Mexico Federico Gomez, Ciudad de Mexico, Mexico; [5]COVID, Hosp. Infantil de Mexico Federico Gomez, Cuidad de México, Mexico; [6]COVID, Hosp. Infantil de Mexico Federico Gomez, CIUDAD DE MEXICO, Mexico; [7]Benemerita Univ. Autonoma De Puebla, Puebla, Mexico; [8]Fisica, UAM-Hospital Infantil de Mexico Federico Gomez, Ciudad DE Mexico, Mexico

Abstract: The COV19 pandemic left many reports of neurological sequels in adults, known as "long COVID". Although there are plenty reports about adulthood sequels (Asadi-Pooya A. A., 2022), there is little knowledge about sequels in children. Therefore, we decided to perform tests on a population of children who survived COV19 (n=14, age (11.5 [10,13])) looking for any functional variation using resting-state functional Magnetic Resonance Imaging (Rs-fMRI). Functional images were obtained in a SIEMENS Skyra 3 Tesla scanner at the Hospital Infantil de México Federico Gómez (HIMFG) with a 32-channel head coil, using a BOLD contrast and an EPI 2D sequence with SMS technology, of TR=1500ms, TE=30ms. Obtaining 240 cerebral volumes build by 44 2D slices, FOV=250*250 mm, and matrix size of 94*94 pixels for each subject. The hospital's ethics committee approved this study following international practice, including procedures from the Helsinki Declaration. The study cohort was selected from Hospital records, exclusion criteria included previous comorbidities. Functional images were acquired some months (7.5[4,15]) after COV19 symptom onset. The control cohort(n=35) was selected from a group of volunteers with no diagnosis of COV19 or other adjacent neurological diagnoses at the functional images acquisition date. The functional images from both cohorts were processed and compared using CONN toolbox to find any functional difference among them; only nodes that met the condition p-FDR < 0.05 were accepted. The results showed higher temporal correlations in 3 clusters; one of them included bilateral activation of nodes in the Precentral and Postcentral Gyrus (PostCG l&r, PreCG l&r), which associates with sensory processing and execution regulation(Agarwal N., 2018), as well as bilateral activation of the Supplementary Motor Area (SMA l&r), which is associated to the planning of complex movements(Agarwal N., 2018), in anticorrelation with the Sensorimotor Superior Network, which integrates intentional movements(Podgórski P., 2021). These results indicate that Post COV19 children may be presenting higher demands of resources when these regions perform this anticorrelation pattern compared to Controls. However, the symptomatology associated with these functional variations is still under observation.[1] Agarwal, N. Neuroimaging. Springer. (2018)[2] Asadi-Pooya, A. A., et al. *J. Med. Virol.*, *94*(3), 979-984. (2022)[3] Podgórski, P., et. al. Front. Neurol. (2021)[4] S. Whitfield-Gabrieli, et al. *(*2012) *Conn.*

Disclosures: Y. Rojas-Lemus: None. **D.E. Alvarez-Amado:** None. **E. Barragan:** None. **P. Dies-Suarez:** None. **B. De Celis Alonso:** None. **J.C. Garcia:** None. **C. Mauricio:** None. **S. Bonilla:** None. **M.C. Romero-Flores:** None. **S. Hidalgo-Tobon:** None.

Poster

141. Dynamic Neurovascular and Activity Changes in the Brain

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 141.26

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: NIH / NCCIH Grant R01 AT008563

Title: Cerebral blood flow changes evoked by repeated transcranial direct current stimulation at the right dorsolateral prefrontal cortex

Authors: *V. SACCA, N. MALEKI, S. HODGES, J. KONG;
Dept. of Psychiatry, Massachusetts Gen. Hosp., Boston, MA

Abstract: Aim: Transcranial direct current stimulation (tDCS) produces physiological changes that allow examining the relationship between brain and behavior. This study aims to investigate the effects of tDCS on the cerebral blood flow (CBF). **Method:** 81 healthy subjects were randomized to three groups: 1) anodal at the right dorsolateral prefrontal cortex (rDLPFC) and cathodal at the left orbitofrontal cortex (lOFC); 2) cathodal at the rDLPFC and anodal at the lOFC; and 3) sham tDCS. tDCS was applied at 2 mA for 20 min using the StarStim system (Spain) in three consecutive days. Arterial spin labeling (ASL) scans were collected in the first (day 1) and third (day 3) sessions. ASL scans were applied before, during and after tDCS in day 1 and before and during tDSC in day 3. ASL data were preprocessed using FSL (v6.0.1). A mixed-effects model was used to examine group-level differences in CBF across the whole brain using the following contrasts: (i) pre-tDCS vs during tDCS (days 1 and 3 separately); (ii) pre-tDCS vs post-tDCS (day 1). Cluster-based thresholding at $p<0.05$ corrected based on Gaussian Random Field Theory was applied. **Results:** For within-group comparison between the pre- and during tDCS, we found that the anodal tDCS led to increased CBF in the bilateral thalamus and right insula in day 1, and increased CBF in the bilateral thalamus in day 3. No significant results were found in the cathodal and sham groups.For within-group comparison between the pre- vs post- tDCS, we found that both cathodal and sham were associated with increased CBF in the right insula, yet anodal tDCS was associated with CBF increase in the cerebellum and occipital lobe. The between-group comparisons (among the three groups) on the differences of pre- and post-tDCS showed that anodal tDCS produced greater CBF increase in the bilateral medial prefrontal cortex (MPFC) and lateral prefrontal cortex (LPFC) compared to sham in day 1. **Discussion and summary:** We found that 1) during the anodal tDCS, the CBF significantly increased in the bilateral thalamus and insula, 2) increased CBF in the bilateral MPFC and LPFC after anodal tDCS compared to the sham group, and 3) both cathodal and sham were associated with increased CBF in the right insula. Literature suggests that both the insula and thalamus are anatomically connected to the DLPFC and involved in sensory processing (including pain). In addition, studies showed that the MPFC and LPFC play a crucial role in the pain modulation. The above results suggest that different tDCS modalities may be associated with different CBF changes. Our findings may shed light on understanding the potential therapeutic effects of tDCS, particularly for pain management.

Disclosures: **V. Sacca:** None. **N. Maleki:** None. **S. Hodges:** None. **J. Kong:** None.

Poster

142. Neurovisceral Physiology I

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 142.01

Topic: F.06. Autonomic Regulation

Support: NIH SPARC OT2OD024908
Craig H. Neilsen Foundation – 476681

Title: High-resolution spinal cord stimulation evokes micturition and continence reflexes in anesthetized and chronically-implanted awake behaving animals.

Authors: *C. GOPINATH[1], M. K. JANTZ[2], R. KUMAR[2], A. MCCUMBER[3], C. CHIN[4], T. M. SIMPSON[3], D. M. WEIR[3], B. MCLAUGHLIN[5], L. E. FISHER[3], R. A. GAUNT[3];
[2]Bioengineering, [3]Rehab Neural Engin. Labs, Physical Med. and Rehabil., [1]Univ. of Pittsburgh, Pittsburgh, PA; [4]Micro-leads Neuro, Somerville, MA; [5]Micro-Leads, Somerville, MA

Abstract: Epidural spinal cord stimulation (SCS) is used clinically to manage pain, but has also been effective in improving locomotion and improving bladder dysfunction in people with spinal cord injury (SCI). Our previous work found that high-resolution SCS can recruit lower urinary tract nerves selectively and here we asked whether stimulation could evoke functional continence and micturition reflexes in both anesthetized and awake behaving cats.
We implanted high-resolution SCS electrodes over the sacral spinal cord of cats and monitored lower urinary tract function in terminal experiments under alpha-chloralose anesthesia (n=6) and also after a chronic implant to test performance in awake behaving animals (n=3). In 3 terminal experiments, a complete spinal transection at T10 was performed after initial tests to evaluate the effects of supraspinal pathways on SCS-evoked function. We first tested low (3 Hz) and high-frequency (33 Hz) stimulation (300-800 µA, 200 µs pulsewidth, 30-60s trains) at a constant bladder volume on each channel while monitoring changes in bladder pressure to identify responsive electrodes. We then evaluated these electrodes during both bladder filling and voiding. In the chronically implanted cats, we tested electrodes under dexmedetomidine anesthesia on a bimonthly basis to identify responsive electrodes, with all other testing occurring without anesthesia in a regular and an automated caging setup.
Micturition and continence reflexes were evoked on responsive electrodes (53 bipolar channels; 6 cats) simply by altering the stimulus frequency. In terminal experiments, 33 Hz stimulation on at least one electrode generated voiding pressures (27±5 cmH2O) with incomplete voiding in all animals. Voiding evoked by 33 Hz stimulation was abolished after a complete thoracic spinal transection in all animals. Stimulation at 3 Hz caused robust continence effects characterized by a suppression of non-voiding contractions and decreases in bladder pressure in all animals (ΔP = -14±3 cmH2O). These stimulation-evoked inhibitory effects remained intact after the thoracic spinal transection. We also observed frequency-dependent continence and micturition effects in

chronically implanted cats, although they appeared in different ways. Stimulation at 3 Hz produced a decrease in bladder pressures while stimulation at 33 Hz had minimal effects in awake animals, possibly due to voluntary inhibition. It is yet to be seen if the frequency-dependent neural circuits seen in spinal intact cats are preserved after chronic spinal cord injury. Future efforts will focus on investigating the effects of SCS after chronic spinal cord injury.

Disclosures: **C. Gopinath:** None. **M.K. Jantz:** None. **R. Kumar:** None. **A. McCumber:** None. **C. Chin:** A. Employment/Salary (full or part-time):; Micro-leads Neuro LLC. **T.M. Simpson:** None. **D.M. Weir:** None. **B. McLaughlin:** A. Employment/Salary (full or part-time):; Micro-leads Neuro LLC. **L.E. Fisher:** None. **R.A. Gaunt:** F. Consulting Fees (e.g., advisory boards); Braingrade GmbH, NeuroWired LLC, Blackrock Microsystems.

Poster

142. Neurovisceral Physiology I

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 142.02

Topic: F.06. Autonomic Regulation

Support: NIH SPARC OT2OD025297

Title: Soft silicone-based neural interface to modulate bladder function

Authors: *R. KUMAR[1,2], C. GOPINATH[1,3], T. SIMPSON[1,3], D. WEIR[1,3], A. MCCUMBER[1,3], A. THIESSEN[4], D. MCDONNALL[4], R. A. GAUNT[1,3,2];
[1]Rehab Neural Engin. Labs, [2]Dept. of Bioengineering, [3]Physical Med. and Rehabil., Univ. of Pittsburgh, Pittsburgh, PA; [4]Ripple, Salt Lake City, UT

Abstract: Direct bladder wall stimulation (DBWS) has been attempted for decades to restore bladder function in people with spinal cord injury and other voiding dysfunctions. However, these efforts were limited by mechanical incompatibilities between the rigid electrodes and bladder tissue, especially during large volume changes, as well as stimulation-induced co-activation of the urethra, legs and other pelvic organs. We designed a stretchable silicone net that can be placed around the bladder body to anchor a soft electrode array directly to the surface of the bladder base, which we had previously determined to be the most sensitive location to stimulate. We created implantable versions of these electrode nets and tested them in 7 chronically implant cats (4 females, 3 males) with and without anesthesia for 2-3 months. Bladder wall stimulation through various electrode configurations (monopolar, bipolar), temporal patterns (single electrode, sequential stimulation of multiple electrodes) and stimulus intensities was able to generate complete bladder emptying up to 15 weeks in both anesthetized and awake trials. To understand the mechanisms contributing to these results we conducted terminal experiments in 6 anesthetized cats. First, we compared the stimulation-evoked bladder pressure responses under isoflurane (suppressed reflexes) and α-chloralose anesthesia (active reflexes) and found that bladder pressures under α-chloralose were significantly higher than

those under isoflurane. We then used hexamethonium to block ganglionic transmission in the bladder wall and found that even in the presence of a ganglionic blocker, significant bladder contractions could be generated through DBWS. Next, we transected the pelvic nerves bilaterally to eliminate reflex activity with its afferent arm in the pelvic nerve that might be activated by stimulation and found that robust bladder contractions could still be generated at higher stimulus intensities (3-4 mA, 10-30 Hz) but were suppressed at lower stimulus intensities (1-2 mA, 3-10 Hz), indicating the role of pelvic reflexes in generating bladder contractions. Chronic experiments demonstrated that these electrodes are an effective neural interface to generate comfortable, complete bladder emptying in awake animals. Further, the mechanistic data suggests that robust bladder contractions can be generated by stimulating the bladder wall even in absence of inputs from the central nervous system and without presynaptic activation of the pelvic ganglia, mimicking the case of pelvic nerve denervation, which can occur in conditions such as diabetic neuropathy and sacral spinal cord injury.

Disclosures: **R. Kumar:** None. **C. Gopinath:** None. **T. Simpson:** None. **D. Weir:** None. **A. McCumber:** None. **A. Thiessen:** None. **D. McDonnall:** None. **R.A. Gaunt:** F. Consulting Fees (e.g., advisory boards); Braingrade GmBh, Neurowire LLC, Blackrock Microsystems.

Poster

142. Neurovisceral Physiology I

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 142.03

Topic: F.06. Autonomic Regulation

Support: VIEP-SEP 511-6/2019.-11812

Title: Low-level laser therapy in the regeneration of the dorsal nerve of the clitoris in rat

Authors: *N. MIRTO AGUILAR, A. ALBARADO-IBAÑEZ, C. MORAN;
Inst. de Ciencias, Benemérita Univ. Autónoma de Puebla, Puebla, Mexico

Abstract: The process of releasing urine, referred to as micturition, serves an essential physiological function to expel waste and maintain water balance. Storage and periodic expulsion of urine are regulated by the neural control system in the brain, spinal cord, and peripheral nerves that coordinate the reciprocal activity of two functional units in the lower urinary tract. In pathological conditions, urination control is lost and the frequency of urine expulsion is significantly increased. In an animal model, the lesion of the dorsal nerve of the clitoris (DNCl) induces the main signals of urinary incontinence. To find a treatment that recovers urinary function, several clinical and preclinical studies have been carried out that have allowed us to know the physiology of the urinary system and the etiology of urinary dysfunctions. The most common treatments for urinary incontinence are surgical, pharmaceutical, and neurostimulations, but the results have not been very positive. Aim: To study the effect of Low-level Laser Therapy (LLLT) in the DNCl injury model in the rat.

Methods: In 28 Wistar Adult females rats were distributed into three groups; Control (n=4), Injury (Left Crushing and Right Neurectomy (Nx); 4, 8, and 15 days), and Injury+LLLT (Left Crushing and Right Nx; 4, 8 and 15 days). Irradiation doses every 3 days of LLLT (10 J/cm2) The NDCl and perigenital skin were removed and prepared for histological analysis. Results: Animals with treatment has a reduction in the number of leukocyte cells and an increase in Schwann cells, compared to groups without LLLT ($p<0.05$). While the Nx+LLLT has a reduction in the thickness of nerve fibers. On the other hand, perigenital skin with LLLT has an increased stratum corneum. Conclusion: LLLT enhances the regeneration and recovery of the DNCl, as produced alterations of the perigenital skin. In this research protocol, a multidisciplinary integration effort is proposed to address a health problem, integrating lasers into biomedical applications.

Disclosures: N. Mirto aguilar: None. **C. Moran:** None.

Poster

142. Neurovisceral Physiology I

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 142.04

Topic: F.06. Autonomic Regulation

Support: NIH K12 DK100024
Pratt School of Engineering Faculty Discretionary Fund

Title: Glycinergic neural pathways mediate stimulation-evoked inhibition of the bladder in urethane-anesthetized rats

Authors: *E. M. ABBOTT, E. J. GONZALEZ, W. M. GRILL;
Biomed. Engin., Duke Univ., Durham, NC

Abstract: Pudendal sensory nerve (PSN) stimulation may be an effective treatment for overactive bladder as PSN stimulation increases bladder capacity. The objective of this study is to identify the neurotransmitters responsible for bladder inhibition by PSN stimulation. We investigated two candidate neurotransmitters, $GABA_A$ and glycine, during single-fill cystometric trials. Female Wistar rats were anesthetized with urethane and paralyzed with gallamine. Through a midline abdominal incision, we placed a catheter into the bladder dome to measure pressure and an electromyography paddle on the external urethral sphincter to measure muscle activity. We exposed the PSN through a dorsal incision and placed a cuff electrode around the isolated PSN to deliver electrical stimulation. We exposed the S1 spinal segment with a laminectomy of the L1-L2 vertebrae and created a small incision in the dura mater to deliver neurotransmitter antagonist drugs intrathecally. During a single-fill cystometric trial, we infused the bladder with saline at a constant rate (4-9 ml/hr) until a distension-evoked bladder contraction voided urine. Following six baseline cystometric trials, we performed eight trials after intrathecal administration of either $GABA_A$ antagonist drugs (bicuculline, 0.1µg, n=5;

picrotoxin, 0.1 μg, n=6) or a glycine antagonist drug (strychnine, 0.1μg, n=5). All trial blocks were randomized so that half of the trials received continuous electrical stimulation of the PSN (10Hz, 50-200uA). Statistical significance was determined with a two-way ANOVA to analyze the effect of neurotransmitter antagonist and stimulation on bladder capacity. In all baseline trials, electrical stimulation of the PSN increased bladder capacity (bicuculline group: 42% ($p < 0.0001$); picrotoxin group: 37% ($p < 0.0005$); strychnine group: 30% ($p < 0.0001$)). After administration of $GABA_A$ antagonists, there remained an increase in bladder capacity with electrical stimulation (bicuculline group: 24%; picrotoxin group: 21%) which was not different compared to pre-drug ($p > 0.1$). After administration of strychnine, there was only a 6% increase in bladder capacity with electrical stimulation which was significantly lower than pre-drug ($p < 0.05$). If a specific neurotransmitter is involved in stimulation-evoked bladder inhibition, we would expect that there would be no increase in bladder capacity after administration of the neurotransmitter antagonist with electrical stimulation. Our results in rats suggest that glycinergic pathways and not GABAergic pathways mediate PSN stimulation-evoked inhibition of the bladder.

Disclosures: E.M. Abbott: None. **E.J. Gonzalez:** None. **W.M. Grill:** None.

Poster

142. Neurovisceral Physiology I

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 142.05

Topic: F.06. Autonomic Regulation

Support: Craig H. Neilsen Foundation Award 647332
International Society for the Study of Women's Sexual Health
NIH Award T32NS115724

Title: Peripheral neuromodulation of vaginal blood flow: a potential treatment for female sexual dysfunction

Authors: *E. C. BOTTORFF[1,4], G. I. LANE[2], M. B. MOORE[1], G. M. RODRIGUEZ[3], P. GUPTA[2], T. M. BRUNS[1,4];
[1]Dept. of Biomed. Engin., [2]Dept. of Urology, [3]Dept. of Physical Med. and Rehabil., Univ. of Michigan, Ann Arbor, MI; [4]Biointerfaces Inst., Ann Arbor, MI

Abstract: Female sexual dysfunction (FSD) is a potentially life altering condition that impacts an estimated 40% of women. Unfortunately, the few treatment options available have limited success due to their high incidence of adverse events and inability to improve subjective arousal. One potential treatment option, peripheral neuromodulation, has been successful in improving female sexual function index scores. However, the underlying mechanisms of how neuromodulation improves FSD are still largely unknown. We hypothesize that improvements in FSD symptoms are due to improvements in genital hemodynamics.

We developed a clinical study to investigate changes in vaginal blood flow (VBF) in response to dorsal genital nerve (DGN) and tibial nerve stimulation in three cohorts of women: healthy controls, women with FSD, and women with spinal cord injury (SCI). Incorporating women with SCI allows us to investigate which neural pathways contribute to genital sexual arousal. Each participant attends two study visits: one for each nerve target, randomly ordered. At each visit, a vaginal photoplethysmography (VPP) sensor is used to measure blood flow during a 5-minute baseline, 20 minutes of nerve stimulation, and a 5-minute washout period. The VPP signals are filtered in the neurogenic energy frequency spectrum (0.076 - 0.200 Hz) for analysis.
Seven out of eight participants reported genital sensations due to nerve stimulation, three of whom have SCI. One participant with a complete SCI had increases in their VPP neurogenic energy during dorsal genital nerve stimulation (Fig. 1). An animal study is being planned to investigate the VBF response observed in complete SCI. This work provides further support for neuromodulation as a treatment for neurogenic and non-neurogenic FSD.
Funding: Craig H. Neilsen Foundation and International Society for the Study of Women's Sexual Health

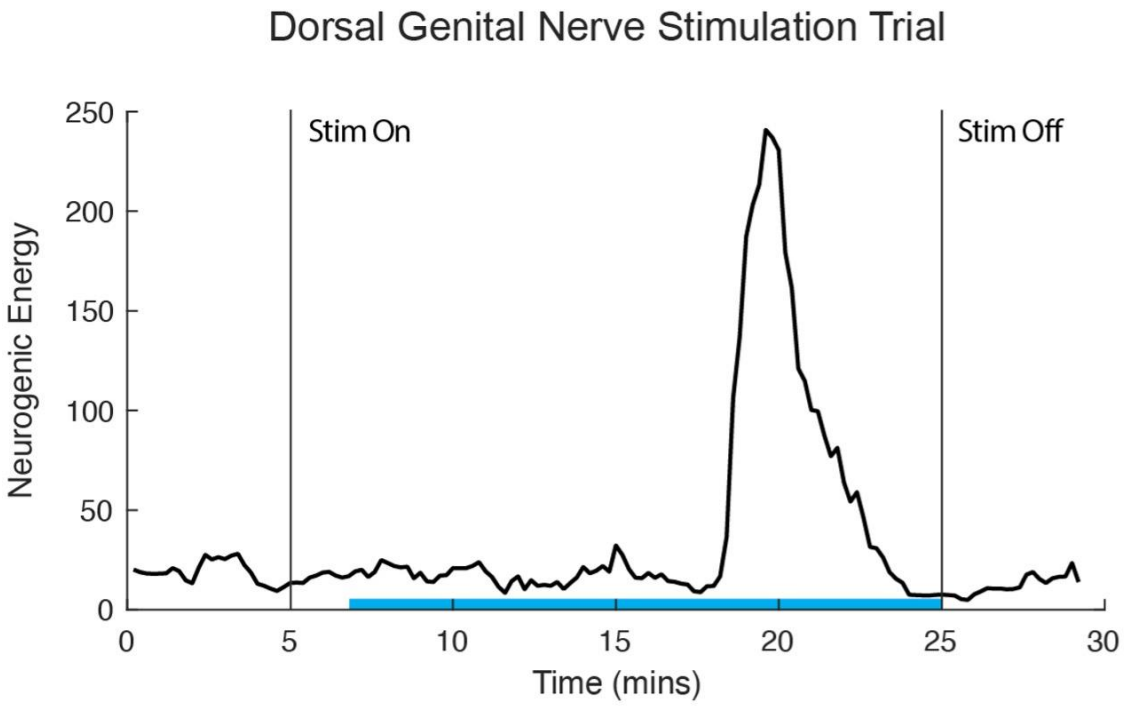


Figure 1. VPP neurogenic energy and reported arousal (blue line) for one participant during DGN stimulation.

Disclosures: E.C. Bottorff: None. **G.I. Lane:** None. **M.B. Moore:** None. **G.M. Rodriguez:** None. **P. Gupta:** None. **T.M. Bruns:** None.

Poster

142. Neurovisceral Physiology I

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 142.06

Topic: F.06. Autonomic Regulation

Support: Missouri Spinal Cord Injuries grant (David Schulz, PI)

Title: mRNA expression profiles of ion channels and neurotransmitters during postnatal development of mouse major pelvic ganglion

Authors: *B. R. BERIGAN, K. M. LETT, C. W. KYI, V. B. GARCIA, M. L. GARCIA, D. J. SCHULZ;
Univ. of Missouri, Columbia, MO

Abstract: During postnatal development, bladder circuits undergo functional changes from reflex voiding to voluntary control, presumably in part as a result of differences in underlying autonomic inputs. Mouse bladder circuitry provides an ideal system to study bladder function as parasympathetic and sympathetic signals are functionally and anatomically distinct in peripheral ganglia. Moreover, there is little known about the role of peripheral ganglia such as the major pelvic ganglion (MPG) in determining bladder circuit output during postnatal development. Therefore, to better understand the complex processes underlying postnatal development of bladder circuitry in mice, we used quantitative polymerase chain reaction (qPCR) to measure 47 functionally relevant ion channels and neurotransmitter receptors from whole MPGs collected at four different postnatal time points (P5, P11, P17, juvenile (P28-42)). Using Principal Component Analysis (PCA) and hierarchical clustering analysis (HCA), we find that there are distinct expression profiles within each age group. To determine the effects of age on each gene tested, non-parametric Kruskal-Wallis tests reveal that 45/47 genes are significantly different ($p < 0.05$) across postnatal development. These results suggest that the expression of ion channels and neurotransmitter receptors in MPG neurons is dynamic during postnatal development. Moreover, we find that functionally related ion channel and receptor genes exhibit strong correlations across age. In rodent MPG, nicotinic cholinergic transmission is the major system in synaptic transmission, and in mouse MPGs, we find that correlations of peripheral nicotinic acetylcholine receptor (nAChR) subunits α3-β4 maintain strong positive correlations throughout postnatal development. In summary, these data provide insight into the expression profile of MPG neurons and the cellular excitability of MPG cells at different timepoints during postnatal development. Electrophysiological recording from MPG cells during postnatal development would elucidate whether these changes in expression profiles translate to functionally distinct neuronal outputs of MPG cells.

Disclosures: B.R. Berigan: None. **K.M. Lett:** None. **C.W. Kyi:** None. **V.B. Garcia:** None. **M.L. Garcia:** None. **D.J. Schulz:** None.

Poster

142. Neurovisceral Physiology I

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 142.07

Topic: F.06. Autonomic Regulation

Support: Clinical and Translational Pilot Projects

Title: Innervation of the ovine pelvic floor muscles by levator ani and perineal nerves

Authors: *Z. YOUSUF[1], K. L. VINCENT[2], M. I. ROMERO-ORTEGA[1];
[1]Bioengineering and Biomed. Sci., UNIVERSITY OF HOUSTON, Houston, TX; [2]Dept. of Obstetrics & Gynecology, Univ. of Texas Med. Br., Galveston, TX

Abstract: Background and Aim: Characterized by uncontrolled urine leakage during increased intra-abdominal pressure, Stress Urinary Incontinence (SUI) affects approximately 35% of the adult female population in the US. It is predominantly caused by pelvic floor neuro-musculature injuries during childbirth, aging or menopause. Conventional therapies have low patient compliance or are associated with post-treatment complications. To test novel therapies such as pelvic floor neuromodulation (PFNM), suitable animal models for SUI are needed. Sheep are potentially suitable preclinical models for SUI due to similarities in pelvic and reproductive anatomy as well as similar risk factors for pelvic floor dysfunction as women. However, there is a lack of anatomical and functional studies on the pelvic floor innervation in these animals. The goal of this study is to anatomically map and functionally characterize the ovine pelvic floor innervation to develop an ovine nerve crush injury model for SUI. **Methods:** An adult female yearling sheep was used to determine the gross anatomy of the pelvic neuromuscular system. Post-euthanasia, the pelvic area was dissected, and the innervation pattern and morphometry of the perineal and coccygeal nerves was described. **Results and Discussion:** After passing through the Alcock canal, the pudendal nerve (diameter: 1.18 mm) branched into medial (diameter: 0.5 mm) and lateral (diameter: 0.8 mm) divisions, where the lateral nerve superficially innervated the skin over the perineal region. The levator ani nerve (LAN) arose from spinal levels S4 and S5 and innervated the levator ani muscle (LAM) prior to innervating the perineal musculature surrounding the clitoris, vagina and rectum. Evoked muscle activity will be measured next to confirm the pelvic floor muscle and perineal muscle innervation (to be completed by November). This study will be instrumental in the development of the ovine nerve crush injury model for SUI and pelvic floor dysfunction.

Disclosures: Z. Yousuf: None. **K.L. Vincent:** None. **M.I. Romero-Ortega:** None.

Poster

142. Neurovisceral Physiology I

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 142.08

Topic: F.06. Autonomic Regulation

Support: NIH R01DK129194

Title: Gender differences in spinal neural circuits in the control of external urethral sphincter (EUS) function and lower urinary tract dysfunction after spinal cord injury (SCI) in mice

Authors: M. HASHIMOTO[1], *N. YOSHIMURA[1], J. M. BECKEL[2], W. C. DE GROAT[2], S. KARNUP[2];
[1]Dept. Urology, [2]Dept. Pharmacol. and Chem. Biol., Univ. of Pittsburgh Sch. of Med., Pittsburgh, PA

Abstract: The lower urinary tract has two main functions, the storage and voiding of urine. During the voiding phase, the EUS relaxes and the bladder contracts to promote efficient release of urine through supraspinal and spinal mechanisms. SCI rostral to the lumbosacral level results in LUTD such as detrusor overactivity (DO) and detrusor sphincter dyssynergia (DSD). This study aims to identify gender differences in neural circuits controlling the EUS function and LUTD following SCI in mice because such data have yet to be available. C57BL/6 mice of both sexes at 9-10 weeks old were used. First, retrograde tracing of EUS-related spinal circuits in male and female mice was conducted using pseudorabies virus with red fluorescent protein (PRV614-RFP) injected into the EUS of male and female mice. Periods between inoculation and spinal tissue removal ranged from 2 to 5 days. Second, in another group of mice, SCI was produced by complete transection of the Th 8-9 level of spinal cord. Cystometry was conducted under a conscious condition at 6 weeks after SCI, and cystometric parameters were compared between male and female SCI mice. Labeling of EUS-motoneurons takes on average 3 days in males and 4 days in females. However, interneurons in the lumbar spinal coordinating center (LSCC) of L4/L3 segments were traced later, namely on day 4 in males and day 5 in females. Retrograde viral tracing of the EUS spinal circuits has shown lower numbers of the EUS-related motoneurons and interneurons presynaptic to them in females than in males. This correlated with the thinner striated EUS muscle layer in females compared to males, and probably with a lower number of motor units in the female EUS. Awake cystometry showed that DO evident as non-voiding bladder contractions during the storage phase occurred with a greater frequency in male SCI than in female SCI mice (0.99±0.32/min and 0.61±0.18/min, respectively; $p<0.05$). In male SCI mice, urine elimination occurred during the oscillation period of voiding bladder contractions, which is known to be induced by EUS bursting activity, whereas urine elimination in female SCI mice was observed during notch-like reductions in bladder pressure, which are known to be induced by periodic relaxations of tonic EUS contraction, during voiding bladder contractions. Overall, these results suggest that there is the sexual dimorphism in spinal neural control circuits innervating the EUS that could contribute to gender differences in LUTD with different EUS behaviors (i.e., EUS bursting in males and EUS relaxation in females during voiding) after SCI.

Disclosures: M. Hashimoto: None. **N. Yoshimura:** None. **J.M. Beckel:** None. **W.C. de Groat:** None. **S. Karnup:** None.

Poster

142. Neurovisceral Physiology I

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 142.09

Topic: F.06. Autonomic Regulation

Support: CONACYT 840925
VIEP 100-310-955-UALVIEP-19
VIEP NSS525517-VIEP2021

Title: Effect of vagotomy on neurotransmitter synthesis in prevertebral ganglia during the estrous cycle of the female rat

Authors: *M. RIVERA CASTRO[1], C. PASTELÍN[2], N. MIRTO AGUILAR[3], C. MORÁN[4]; [1]Inst. de Investigaciones Cerebrales, Univ. Veracruzana, Xalapa de Enriquez, Mexico; [2]Facultad de Medicina Veterinaria y Zootecnia, [3]Inst. de Ciencias, Benemérita Univ. Autónoma de Puebla, Puebla, Mexico; [4]Inst. de Ciencias, Benemérita Univ. Autonoma de Puebla, Puebla, Mexico

Abstract: The aim of this work was to analyze the neuronal pathway that communicates the right vagus nerve (RVN) with prevertebral ganglia (celiac ganglions (CG), adrenals (AG) and superior mesenteric), this parasympathetic pathway has been described that influence on the celiac plexus, abdominal organs and ovaries. In this study cyclic adult female rats of the CIIZV strain were used during the estrous cycle (240 -350 g); were divided into three groups for proestrus (P) and estrus (E) (n=4): control, sham and experimental: neuroectomy of RVN (Vx). After 24 hours, the animals were sacrificed and the prevertebral ganglia (PG) was removed and analyzed by immunofluorescence for anti-tyrosinehydroxylase (TH), anti-choline acetyltransferase (ChAT) and anti-tryptophan hydroxylase (TPH) antibodies. The results show that RVN has two identifiable organizations in the subdiaphragmatic zone towards the celiac plexus, in one of them a new ganglion has been identified. Regarding enzymatic reactivity, results are presented between sham and Vx to remove factor of surgery; the right celiac ganglion (RCG) is the mainly affected by Vx, showing less number of neurons positive for TH (E: s 2448 ± 258, Vx 1689±287), TPH (P: s 2259 ± 135, Vx 1145 ± 129; E: s 1863 ± 196, Vx 1050 ± 113) and ChAT (P: s 2271 ± 577, Vx 1582 ± 191; E: s 1990± 165, Vx1670 ± 139); the left CG had differences in TH (P:s 2115 ± 166, Vx 1109; E: s 1967 ± 228, Vx 1161 ± 74) and ChAT (just P: s 1785 ± 194, Vx 859 ± 334); the neurons in superior mesenteric ganglion were decreased in E with ChAT antibody (s 829 ± 29, Vx 441 ± 51). The suprarenal ganglia do not present modifications after neuroectomy of RVN, but the surgery itself influences on the expression for TH and ChAT for the right AG in P and E; In left AG were modified the neurons for ChAT in E. Additionally, a different number of positive neurons was observed for each neurotransmitter in both days in all the PG. These results suggest that the RVN is mainly communicated with RCG and the variation in enzymatic expression may be associated with the lost of nerve signal by the absence of this vagal pathway, which corroborates the communication with the prevertebral ganglia plexus.

Disclosures: M. Rivera Castro: None. **C. Pastelín:** None. **N. Mirto aguilar:** None. **C. Morán:** None.

Poster

142. Neurovisceral Physiology I

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 142.10

Topic: F.06. Autonomic Regulation

Title: Pudendal nerve stimulation to prevent urinary leakage using multi-contact cuff electrodes

Authors: *M. A. ORTIZ-LOPEZ, A. LAGUNAS, P. R. PATEL, T. M. BRUNS;
Univ. of Michigan, Ann Arbor, Univ. of Michigan, Ann Arbor, MI

Abstract: Stress urinary incontinence (SUI) is a medical condition that affects life quality, particularly for women, and is characterized by urine leakage due to increased abdominal pressure from physical activities such as jumping, laughing, or exercising. Electrical stimulation of the pudendal nerve has been studied for SUI in females, with promising outcomes when compared against standard treatments. Pudendal nerve stimulation for SUI targets efferent axons that contract the external urethral sphincter (EUS) and prevent urinary leakage. However, the pudendal nerve also innervates the external anal sphincter (EAS) and has afferent axons that relay sensory information from the genitalia and urethra. Methods for selectively activating fibers that control the EUS while reducing off-target activation are needed. We hypothesize that multi-contact cuff electrodes have the potential to selectively activate fascicles that innervate the EUS and reduce off-target stimulation effects in the pudendal nerve. In this study, we are using 20-micron thick Parylene C multi-contact cuff electrodes with 4 or 8 platinum electrode contact pads (0.77 or 1.0 mm^2). The electrode contacts have an average impedance of 1.01 ± 0.20 kOhms (n=35) at 1 kHz. In chloralose-anesthetized felines we place a multi-contact cuff electrode and a bipolar cuff electrode on one pudendal nerve, a bipolar cuff electrode on the contralateral pudendal nerve, supra-public catheters in the bladder for volume control and pressure monitoring, and electromyography (EMG) needle electrodes in the bulbourethral sphincter (BUS) and EAS. The data collection starts by recording EMG and pressure responses for all two-contact combinations for a range of amplitudes. Selectivity of each contact combination is measured by the relative BUS/EAS EMG ratio and compared to the responses for standard bipolar cuff electrodes. The contact combination that evokes consistent EUS contractions is selected to evaluate pudendal nerve stimulation to prevent urine leakage caused by increased intra-abdominal pressures at a full bladder. This study is the first to quantify lower urinary tract (LUT) responses to multi-contact stimulation on the pudendal nerve. Furthermore, this approach could lead to selective treatment for LUT dysfunctions and give insight into selectivity and stability that can be achieved through extraneural interfaces for peripheral nerves.

Disclosures: M.A. Ortiz-Lopez: None. **A. Lagunas:** None. **P.R. Patel:** None. **T.M. Bruns:** None.

Poster

142. Neurovisceral Physiology I

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 142.11

Topic: F.06. Autonomic Regulation

Support: NIH SPARC OT2028191

Title: Changing pudendal neuromodulation settings shifts patient sensations and pelvic floor responses

Authors: *A. LAGUNAS[1], P.-J. CHEN[1], P. GUPTA[2], T. BRUNS[1];
[1]Biomed. Engin., [2]Urology, Univ. of Michigan, Ann Arbor, MI

Abstract: Millions of people in the United States have lower urinary tract problems like overactive bladder and incontinence. These disorders will become increasingly prevalent as the population continues to age. Unfortunately, if current treatments like lifestyle changes, pharmaceuticals, or sacral neuromodulation fail, individuals are left with few options. Pudendal neuromodulation is a promising off-label treatment for pelvic pain and bladder dysfunction that can fill this need. While pudendal neuromodulation has promise as an effective treatment for bladder problems, little is known about how it modulates lower urinary tract function clinically. The goal of this study is to measure the physiological effects of clinical pudendal neuromodulation on the lower urinary tract and the pelvic floor in participants with an implanted stimulation lead at the pudendal nerve. We utilize a high-density pressure sensing catheter placed in the urethra and bladder along with an abdominal catheter in the rectum and electromyogram electrodes around the anus. Participant sensations during stimulation are recorded. The bladder is filled with fluid until we reach bladder capacity. During bladder filling we turn on stimulation with the implanted lead to observe how bladder volume impacts stimulation outcomes. Bladder pressure changes, urethral pressure changes, and patient sensations in response to stimulation have varied across the first twelve patients (ten female). In most participants, activation of the stimulator led to reduced urgency sensations and increased bladder capacities. Increasing stimulation amplitude resulted in movement of the sensation area for some participants, such as causing sensation to drift to the leg from the urethra. For others, changing the cathodic electrodes position could make sensations of paresthesia turn into pain. These results showcase the heterogeneity of patient responses and hint at the importance that the relative electrode-pudendal nerve location may play in treatment outcomes. Continued patient recruitment and data analysis will improve our understanding of the role that urethral and bladder activation play in pudendal neuromodulation for the treatment of lower urinary tract dysfunction. Funding: NIH SPARC OT2028191.

Disclosures: A. Lagunas: None. **P. Chen:** None. **P. Gupta:** None. **T. Bruns:** None.

Poster

142. Neurovisceral Physiology I

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 142.12

Topic: F.06. Autonomic Regulation

Support: Canada Foundation for Innovation
Government of Ontario

Title: Overflow incontinence is evoked by low-amplitude saphenous nerve stimulation in anesthetized rodents

Authors: Z. MOAZZAM[1], ***P. B. YOO**[1,2,3];
[1]Inst. of Biomed. Engin., [2]Electrical and Computer Engin., Univ. of Toronto, Toronto, ON, Canada; [3]KITE Res. Inst., UHN, Toronto, ON, Canada

Abstract: Electrical stimulation of the saphenous nerve (SN) is a novel approach to modulating bladder function. Earlier animal studies have shown that bladder-inhibitory responses can be evoked by low-amplitude (25 μA) current pulses applied is short duration trials (10 minute), where stimulation frequencies between 10 Hz and 20 Hz were found to be most effective. In the current study, we further explored this bladder-inhibitory reflex by examining both the duration and frequency of SN stimulation as factors in modulating bladder function. Anesthetized rats were separated into 3 groups: intravesical saline infusion + SN stimulation (group A), intravesical 0.1% acetic acid infusion + SN stimulation (group B), and intravesical saline infusion + no SN stimulation (group C). Changes in bladder function – basal bladder pressure (P_{base}), contraction amplitude (ΔP) and inter-contraction interval (T_{ICI}) – were measured in response to stimulation trials applied at different frequencies (10 and 20 Hz) and durations (10, 20, and 40 min). In group A, we found that longer-duration (40 min) stimulation trials applied at 10 Hz evoked the strongest inhibitory effects. Overflow incontinence (OI) episodes were observed in 5 of 8 animals and were associated with significant changes in P_{base} (122.7 ± 9.1%, p=0.026), ΔP (-60.8 ± 12.8%, p=0.044), and T_{ICI} (-43.2 ± 13.0%, p=0.031). In contrast, no significant changes in bladder function were observed in groups B or C. Our findings indicate that the inhibitory effects of SN in urethane-anesthetized rats (a) exhibit a dose-dependent response and (b) are tuned to stimulation pulses applied at 10 Hz.

Disclosures: Z. Moazzam: None. **P.B. Yoo:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); EBT Medical Inc.

Poster

142. Neurovisceral Physiology I

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 142.13

Topic: F.06. Autonomic Regulation

Support: National MS Society Grant PP-1804-30731 (David Schulz, PI)

Title: Lower Urinary Tract Dysfunction in Experimental Autoimmune Encepalomyelitis: The Effects of Central Demyelination on the Properties of Neurons in Major Pelvic Ganglia

Authors: *S. L. HENDERSON, V. GARCIA, M. L. GARCIA, D. J. SCHULZ;
Univ. of Missouri- Columbia, Columbia, MO

Abstract: Lower urinary tract (LUT) dysfunction is a common sequela of neurological pathologies like Multiple Sclerosis (MS). We hypothesize that changes in the peripheral neural pathways of the LUT following central demyelination are in part responsible for the emergence of LUT dysfunction. In rodents, the MPG (major pelvic ganglion) is composed of 70% parasympathetic and 30% sympathetic neurons that act as the final common pathway between the central nervous system and LUT target organs. Since these autonomic neurons provide a portion of the final nervous output to the bladder, it is imperative to investigate how the properties of these neurons change in disease. Utilizing the current clamp technique, we characterized the excitability, active, and passive properties of autonomic MPG neurons in experimental autoimmune encephalomyelitis (EAE) - the most common model of relapsing remitting MS. We also sampled the mRNA abundances of 21 voltage gated ion channel genes via whole ganglion q-PCR to develop an understanding of potential mechanisms underlying changes in the properties of MPG neurons. Finally, we collected void spot assays (VSAs) and cystometrograms (CMGs) to determine the onset and severity of LUT dysfunction. Our results indicate no significant change to the passive properties of resting membrane potential, input resistance, tau, or capacitance as compared to controls (p= 0.686, 0.884, 0.984, and 0.714, respectively). However, EAE does impact aspects of neuronal excitability such as negative rheobase (p=0.049) and maximum firing frequency (p=0.031). MPG action potential properties such as half-width, max rise slope, max decay slope, and decay slope (p=0.004, 0.042, 0.014, and 0.031, respectively) are altered in EAE. We also report differences in the mRNA abundances of Scn2a1 (p=0.0007), Scn3a (p=0.001), Kcnn3 (p=0.006), and Kcna1-4 (p=0.0002, 0.003, 0.03, and 0.001, respectively). These changes in mRNA abundances suggest these ion channels may underly changes in MPG neuron excitability and firing properties.For the first time, these findings indicate that the properties of efferent MPG neurons are impacted by EAE. Moreover, changes in these neurons in the micturition pathway could in part contribute to the development of LUT dysfunction.

Disclosures: S.L. Henderson: None. **V. Garcia:** None. **M.L. Garcia:** None. **D.J. Schulz:** None.

Poster

142. Neurovisceral Physiology I

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 142.14

Topic: F.06. Autonomic Regulation

Support: NIH Grant OT2OD030524

Title: The bladder accommodates to vast differences in filling rate to maintain constant pressure and volume micturition reflex thresholds

Authors: *D. J. JASKOWAK, Z. C. DANZIGER;
Florida Intl. Univ., Florida Intl. Univ., Miami, FL

Abstract: In cystometric investigations of lower urinary tract (LUT) function fluid is infused into the bladder at supraphysiological rates to study LUT behavior across many voiding cycles; however, the infusion rate itself is a potential experimental confound if it activates LUT voiding and storage reflexes in aphysiological ways. The activation of the micturition reflex, for example, results from a complex interaction of viscoelastic and neural elements in the bladder. Understanding how the bladder reacts to increasing rates of bladder filling will give insight into the nuanced interactions of the neural and viscoelastic responses to a full range of mechanical stretch. In this work we explore the effect of filling rate on the activation of the micturition reflex. We conducted single fill cystometry in female urethane-anesthetized Sprague-Dawley rats (250-350g) using 10 flow rates that range 0.92 to 65.5 ml/hr. This range incorporates the so-called physiological range, and flows that are outside of what would typically be observed in cystometry experiments. We found no relationship between bladder infusion rates and the volume and pressure thresholds which trigger a distention evoked reflex bladder contraction. The intervoid interval had a reciprocal relationship with infusion rate. Taken together, these results suggest that the micturition reflex is triggered irrespective of the rate of stretch of the bladder wall. This could mean that the elasticity of the bladder wall is extremely accommodating to high rates of stretch, reflecting the bladder wall's ability to manage the afferent response. It is similarly feasible that a sensation of fullness drives the reflex response at higher rates of stretch particularly if the physiological afferent propagation pathways (i.e., cell signaling, umbrella cell and collagen organization) are overloaded. This surprising result led us to investigate whether the guarding reflex onset and duration was affected by infusion rates. During filling, an increase in the electromyographic (EMG) activity of the external urethral sphincter (EUS) represents the passive guarding reflex to prevent leakage of urine during continence. The EMG activity would typically increase with increasing bladder pressure until the bladder starts to contract.

Disclosures: D.J. Jaskowak: None. **Z.C. Danziger:** None.

Poster

142. Neurovisceral Physiology I

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 142.15

Topic: F.06. Autonomic Regulation

Support: NIH OT2-OD023867
NIH P41-EB015896
NIH P01-AT006663
NIH R21-DK116029
NIH U01-DJ112193
NIH S1-0RR023043

Title: Faster gastric peristalsis and meal emptying during transcutaneous auricular vagus nerve stimulation in functional dyspepsia - A 4D cine-MRI study

Authors: *R. SCLOCCO[1], H. FISHER[2], A. BOLENDER[2], K. HAN[2], J. COLL-FONT[2], C. NGUYEN[2], N. KETTNER[4], B. KUO[3], V. NAPADOW[1];
[1]Spaulding Rehabil. Hospital, Harvard Med. Sc, Spaulding Rehabil. Hospital, Harvard Med. Sc, Charlestown, MA; [2]Massachusetts Gen. Hospital, Harvard Med. Sch., Charlestown, MA; [3]Massachusetts Gen. Hospital, Harvard Med. Sch., Boston, MA; [4]Logan Univ., Chesterfield, MO

Abstract: The vagus nerve controls both sensory and motor aspects of gastric physiology, thus vagal neuromodulation may be promising to regulate gastric function in disorders of gut-brain interaction such as functional dyspepsia (FD) or gastroparesis. Transcutaneous auricular vagus nerve stimulation (taVNS) targets the nucleus tractus solitarii (NTS) in the brainstem, and we showed that NTS response is enhanced by stimulating during exhalation, via Respiratory-gated Auricular Vagal Afferent Nerve Stimulation (RAVANS). Here, we use abdominal 4D cine-Magnetic Resonance Imaging (MRI) to assess the effect of RAVANS taVNS on velocity of gastric peristalsis and meal emptying in FD subjects and controls. We enrolled 15 FD patients (13F, 29.1±13.2y/o) and 15 healthy controls (10F, 32.1±7.7y/o). MRI followed ingestion of a food-based contrast meal (pineapple-based for high manganese content). Each subject was scanned 15, 45 and 70 minutes post-meal (T0, T1, T2), while experiencing active RAVANS ("A", 1.5s stimulation trains delivered at 100Hz in left cymba concha) or Sham ("S", no current) on two separate visits (randomized order). Abdominal MRI images were semi-automatically segmented to isolate gastric meal content, and peristaltic propagation velocity in the antrum was calculated using cross-sectional area time series. Effects of RAVANS on gastric function were assessed using mixed-effects linear models. RAVANS taVNS did not modulate gastric function in healthy controls. In FD, peristaltic velocity was on average 0.7mm/s faster during RAVANS compared to sham (β =0.67, SE=0.28, t=2.39). Since there was no significant effect of time, data were averaged across post-meal time points, and follow-up comparison confirmed significantly higher velocity during active RAVANS (A: 5.1±0.3mm/s (mean±SEM); S: 3.7±0.4mm/s; p=0.017). The increase in peristaltic velocity was accompanied by a trend towards faster meal emptying during RAVANS (β =-4.15, SE=1.94, t=-2.14). Post-hoc tests using Tukey correction for multiple comparisons suggested faster emptying during active RAVANS at T1/T0 (A: -17.8±3.4%; S: -9.5±3.6%; p=0.032) and at T2/T0 (A: -30.7±3.4%; S: -22.4±3.6%; p=0.032). Our analysis found that RAVANS taVNS can successfully modulate gastric function in FD patients, suggesting therapeutic applicability in disorders of gut-brain interaction. Further, our 4D cine MRI approach allowed for a fully non-invasive evaluation of gastric function. Future work focusing on the central circuitry underlying gastric response to RAVANS taVNS will inform applicability of this therapy for FD patients.

Disclosures: R. Sclocco: None. **H. Fisher:** None. **A. Bolender:** None. **K. Han:** None. **J. Coll-Font:** None. **C. Nguyen:** None. **N. Kettner:** None. **B. Kuo:** None. **V. Napadow:** None.

Poster

142. Neurovisceral Physiology I

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 142.16

Topic: F.06. Autonomic Regulation

Support: NIH/NINDS OD010996

Title: Central pathways involved in the control of sympathetic innervation of the kidneys in mice

Authors: *G. CANO[1], S. L. HERNAN[1], S. D. STOCKER[2], A. F. SVED[1];
[1]Neurosci., Univ. of Pittsburgh, Pittsburgh, PA; [2]Neurobio., Univ. of Pittsburgh Sch. of Med., Pittsburgh, PA

Abstract: Renal sympathetic nerves regulate many aspects of renal function. Elevated renal sympathetic nerve activity (SNA) is associated with prevalent pathologies such as hypertension and chronic kidney disease. Animal models are extensively used to study the central control of renal SNA, including transgenic mice. The central neural pathways controlling the kidneys have been extensively described in rats, but not that well in mice. We sought to characterize this circuitry in mice using viral transynaptic tracing with Pseudorabies virus (PRV). Mice (n=4) were injected with a PRV expressing GFP (PRV-152) into the left kidney. Additional mice (n=3) were injected with 0.5% FluoroGold i.p. to label SPNs in the spinal cord, followed by injection of a PRV expressing RFP (PRV-614) into the left kidney. Other mice (n=4) were injected simultaneously with PRV-614 and PRV-152 into the left and right kidneys, respectively. Mice were perfused at different survival times (40-96 hrs); brains, spinal cords, and dorsal root ganglia (DRG) were removed and processed immunohistochemically and with RNAScope to detect infected neurons and their phenotypes. At 40 hrs survival time, infected neurons were observed in the DRG of T7-13, whereas infected sympathetic preganglionic neurons (SPNs) were located ipsilaterally in the intermediolateral column (IML), with few in the intercalatus nucleus (IC) of segments T5-11, with T8-10 containing the most infected SPNs. At 72 hrs survival time, infection extended from T3-T13, but in the most caudal segments infected neurons were in IC. Infected interneurons were found dorsal and ventral to IML, whereas numerous infected small neurons and few motorneurons were in the dorsal and ventral horn, respectively. Infection was mainly ipsilateral, but some infected IML clusters were observed contralaterally. The first infected brain neurons (72 hrs) were in the dorsal, ventral, and posterior subdivisions of the paraventricular hypothalamic nucleus (PVN), A5 region, Barrrington's nucleus, locus coeruleus, gigantocellular nuclei, caudal raphe, and rostroventrolateral medulla (RVLM); the lateral paragigantocellular nucleus contained the highest number of infected neurons. Most infected neurons in PVN were glutamatergic; very few contained oxytocin. Early infected neurons in RVLM were non-C1 cells (in contrast to the early labeling of C1 cells in rats). At longer survival times, numerous brain nuclei became infected. In mice injected in both kidneys, all infected brain areas contained single- and double-infected neurons. Though the central pathways

controlling the kidneys in rats and mice share most elements, some subtle differences were observed.

Disclosures: G. Cano: None. **S.L. Hernan:** None. **S.D. Stocker:** None. **A.F. Sved:** None.

Poster

142. Neurovisceral Physiology I

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 142.17

Topic: F.06. Autonomic Regulation

Support: NIH Grant 1OT2OD030535-01

Title: Compartmental modeling of the GI system to simulate retrograde contractions with potential application to modeling of emesis

Authors: *S. Q. FERNANDES[1], M. V. KOTHARE[2], C. C. HORN[3], B. MAHMOUDI[4]; [1]Dept. of Chem. and Biomolecular Engin., [2]Chem. & Biomolecular Engin., Lehigh Univ., Bethlehem, PA; [3]Med., Univ. of Pittsburgh, Pittsburgh, PA; [4]Emory Univ., Alpharetta, GA

Abstract: In prior work (SFN 2021), a compartmental model (CM) of gastric emptying was reported, which was computationally cheap with approximately 90 ordinary differential equations of time compared to complex finite element methods (FEM) models. The stomach's spatial geometry was decomposed into seven compartments: fundus, pacemaker, lower corpus, proximal/middle/terminal antrum, and pyloric sphincter. By stimulating the interstitial cells of Cajal (ICC) neural network, an electro-chemo-mechanical coupling (ECMC) model converted the ICC stimulation to active stress in the muscle tissues. The electrical activity is captured by a 'Leaky Integrate and Fire' Model with time dependent capacitor. The intrallecular calcium concentration equation in the smooth muscle cells (SMC) is given by Fukuta et al., 2002. Active stress is generated in the muscle tissue which is compared to the activation of myosin light chain kinase enzyme. Michaelis-Menten kinetics along with a Hai-Murphy four state model is used to develop a relation between intracellular calcium concentration and the stress in the muscle tissue. A non-linear viscoelastic model was used to convert stress to stretch values, giving rise to muscle contractions in each compartment by using a stretch-contraction transformation equation. The gastric liquid volume was computed with a transient Bernoulli's, circulation fluid jet and Shapiro's equation. The model is solved with differential equation solvers in MATLAB. Results were in close agreement with other simulation and experimental data: (1) CFD study of gastric emptying (Li & Gin, 2020); (2) FEM ECMC model (Klemm et al., 2020); and (3) experimental data (Vella &Camilleri, 2017) on response to nutrient ingestion. In the present research, we report the extension and use of this model to capture retrograde contractions as prodromal responses of emesis. Retrograde contractions of the gastrointestinal (GI) tract and movement GI luminal contents from the intestine to the stomach is a well-known response occurring prior to the expulsion phase of emesis; however, to date, there is no computational model of this process.

By using CM, functioning of conditions like emesis were studied with a compartment for the duodenum where the giant retrograde contraction is stimulated that propagates to the pacemaker region of the stomach. The model computes membrane voltage for ICC, SMC, intracellular calcium concentration, stress and stretch values during muscle contraction. Importantly, this model provides a framework for developing insights into mechanisms of emesis through simulation studies, which could prove critical for determining approaches to treat GI disease.

Disclosures: S.Q. Fernandes: None. **M.V. Kothare:** None. **C.C. Horn:** None. **B. Mahmoudi:** None.

Poster

142. Neurovisceral Physiology I

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 142.18

Topic: F.06. Autonomic Regulation

Support: R01NS111929
University of Texas at Dallas

Title: Transcriptomics of Lateralized Vagal Sensory Pathways

Authors: *H. F. WELCH[1], I. SANKARANARAYANAN[1], R. A. MORRISON[1], J. BROUGHER[2], A. C. SHEMBEL[1,3], T. J. PRICE[1], C. A. THORN[1];
[1]Univ. of Texas at Dallas, Richardson, TX; [2]Doloromics, Menlo Park, CA; [3]Otolaryngology - Head & Neck Surgery, UT Southwestern Med. Ctr., Dallas, TX

Abstract: The nodose ganglia contain the cell bodies of the sensorimotor neurons of the vagus nerves, which convey autonomic signals between the viscera and the brain. Recent research has further revealed a lateralized sensory pathway within the nodose ganglia that activates reward circuits in the central nervous system. Electrical stimulation of the right, but not left, vagus nerve, or optogenetic stimulation of the axon terminals of right nodose ganglion neurons, have been found to increase neural activity in midbrain dopaminergic nuclei and to drive appetitive behaviors. In the current experiment, we build on recent genetic sequencing studies that have revealed extraordinary cellular diversity of vagal sensorimotor neurons. We aimed to determine whether differences in gene expression between the right and left nodose ganglia may contribute to the striking lateralization of vagal reward-related signaling. Right and left ganglia of young adult (8-11-week) male (n=8) and female (n=8) rats were dissected, and single-cell RNA sequencing (scRNA-seq) was performed. Here, we compare sex- and side-specific expression profiles of genes encoding known mechanoreceptors and chemoreceptors to begin to identify candidate sensory pathways that may contribute to vagal reward-related signaling. Understanding the differential molecular expression of right and left nodose ganglia neurons will inform mechanistic and functional studies into appetitive viscero-central signaling.

Disclosures: **H.F. Welch:** None. **I. Sankaranarayanan:** None. **R.A. Morrison:** None. **J. Brougher:** A. Employment/Salary (full or part-time):; Doloromics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Doloromics. **A.C. Shembel:** None. **T.J. Price:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Doloromics. **C.A. Thorn:** None.

Poster

142. Neurovisceral Physiology I

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 142.19

Topic: F.06. Autonomic Regulation

Support: Aligning Science Across Parkinson's ASAP-000375 through the Michael J. Fox Foundation for Parkinson's Research (MJFF)
National Institutes of Health (GM007616 and DK078938)
Department of Defense (PD160030)
Caltech Center for Environmental and Microbial Interactions (CEMI)

Title: Neuronal activation of the intestinal tract of mice shapes the microbiome and alters gut physiology

Authors: *J. A. GRIFFITHS, B. B. YOO, S. K. MAZMANIAN;
Biol. and Biol. Engin., Caltech, Pasadena, CA

Abstract: The enteric nervous system (ENS) coordinates complex responses that regulate gut motility, secretion, and immunity. Intrinsic and extrinsic neurons innervate the gastrointestinal (GI) tract, which harbors a diverse gut microbiome that interacts with the ENS in ways that remain poorly understood. Herein, we activated gut-associated neurons in mice to determine effects on intestinal microbial communities and their metabolites, as well as on host physiologic responses. Recombinant adeno-associated viral (rAAV) vectors with enhanced tropism for the gut, and no targeting to the brain, were used to deliver chemogentic receptors to activate choline acetyltransferase (ChAT+)-expressing neurons, which are implicated in gut motility, or tyrosine hydroxylase (TH+)-expressing neurons. Targeted activation of ChAT+ or TH+ neurons strikingly alters the mouse and microbial proteomes, metagenome, and fecal metabolome. We reveal previously unknown and broad roles for ChAT+ neurons in modulating microbiome structure, and provide evidence for novel ENS functions such as regulating fungal colonization and shaping of bile acid profiles in the gut. In terms of GI physiology, ChAT+ neuronal activation upregulates transcriptional pathways for muscle cell proliferation, angiogenesis, and muscle development, among others. Accordingly, mice display increased fecal production and diarrhea-like symptoms following activation of gut-associated ChAT+ cells compared to tyrosine hydroxylase-expressing neurons. These findings suggest that specific subsets of neurons

differentially regulate the gut microbiome and GI physiology in mice following peripheral (non-brain) activation.

Disclosures: J.A. Griffiths: None. **B.B. Yoo:** None. **S.K. Mazmanian:** None.

Poster

142. Neurovisceral Physiology I

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 142.20

Topic: F.06. Autonomic Regulation

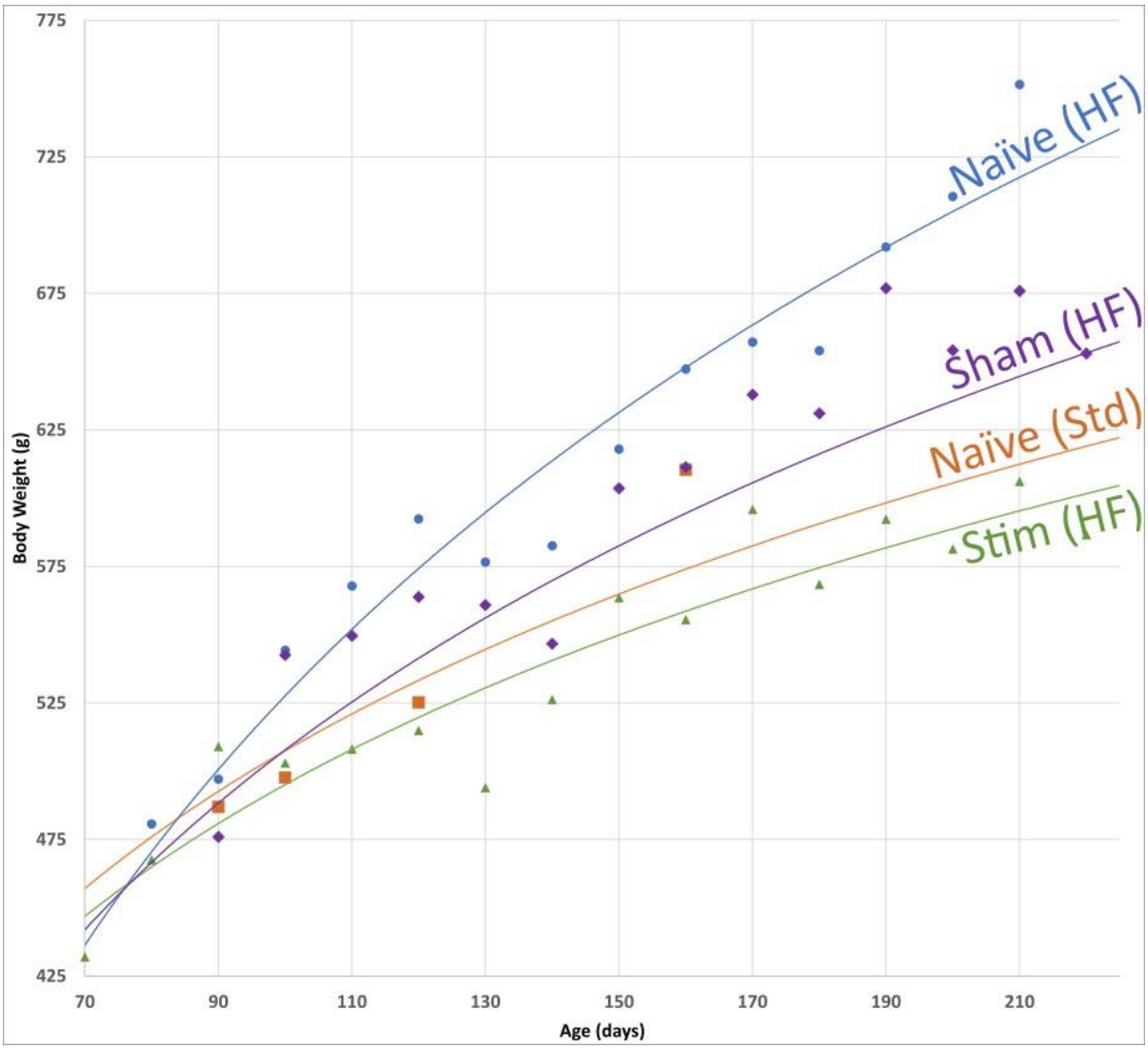
Support: Department of Veterans Affairs Career Development Award Level 2 (CDA2) Grant IKRX001817
Brain Rehabilitation Research Center (BRRC) at the MRVAMC
Rehabilitation Research and Development Service (RR&D) at the MRVAMC
dvanced Platform Technology (APT) Center at the LSCVAMC
The VA Foundation at the LSCVAMC

Title: Bilateral subdiaphragmatic vagal nerve stimulation (sVNS) using intermittent pulse width modulation reduces weight gain in obesity-prone Sprague Dawley rats exposed to a high fat diet

Authors: M. LEINEN[1], E. GRANDY[1], A. L. RODRIGUEZ[2,1], L. M. UBEIRA GEBEL[2,1], T. MACHIN[2,1], S. K. SINGH[2,1], M. I. FERNANDEZ[2,1], J. C. DALUGDUG[2,1], E. M. GARCIA-COLON[2], K. LYBESHARI[2], D. R. ALEXANDER[2,1], M. I. MAURA[2,1], M. D. CABRERA GONZALEZ[2,1], C. DE PAULA CUNHA ALMEIDA[2,1], ***M. A. SCHIEFER**[1,3,2];
[1]Malcom Randall VA Med. Ctr., Gainesville, FL; [2]Univ. of Florida, Gainesville, FL; [3]Louis Stokes VA Med. Ctr., Cleveland, OH

Abstract: Obesity (a body mass index ≥30 kg/m^2) is prevalent in the US. In a worsening trend, 31 states have obesity rates ≥30% and none <20%. Studies have found that vagal nerve stimulation (VNS) promotes reduced food intake, weight loss and reduced cravings in animals. A dynamic stimulus with pulsons was found to be more effective than traditional stimuli. In this study, we investigate a novel dynamic VNS waveform to affect weight gain in obesity-prone Sprague Dawley rats. The waveform, which has a time-varying pulse width, was adapted from one that was found to produce a sensation of pressure in the phantom fingers of upper extremity amputees and was chosen because the conveyance of information regarding intragastric pressure by vagal axons may be analogous to the conveyance of pressure on fingertips by upper extremity nerves. We hypothesize that VNS with this novel waveform will result in lower body weight than in naïve or sham populations. Rats were provided with ad libitum access to a high fat (HF) diet and water. Rats were assigned to a naïve (no implant), sham (non-functional implant), or experimental group. Rats in the sham and experimental groups were implanted around 20 weeks of age with a circumferential cuff near the gastroesophageal junction that contained two sets of bipolar electrodes to provide bilateral subdiaphragmatic VNS. Lead wires from the cuff were

routed subcutaneously to a percutaneous exit site on the back. Following recovery, rats in the experimental group received VNS over a period of four weeks. Food consumption, body weight, and activity were recorded throughout the study. At the conclusion of the study, adiposity was quantified using dual energy x-ray absorptiometry (DEXA). Preliminary results suggest that rats in the sham group weighed less than but followed a similar growth curve to those in the naïve group. However, rats that received VNS weighed less and followed a slower growth curve that paralleled that of non-obese rats on a standard diet (Std). Additionally, rats receiving VNS had a lower total body adiposity than sham or naïve rats. The study is ongoing.



Disclosures: **M. Leinen:** None. **E. Grandy:** None. **A.L. Rodriguez:** None. **L.M. Ubeira Gebel:** None. **T. Machin:** None. **S.K. Singh:** None. **M.I. Fernandez:** None. **J.C. Dalugdug:** None. **E.M. Garcia-Colon:** None. **K. Lybeshari:** None. **D.R. Alexander:** None. **M.I. Maura:** None. **M.D. Cabrera Gonzalez:** None. **C. De Paula Cunha Almeida:** None. **M.A. Schiefer:** None.

Poster

142. Neurovisceral Physiology I

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 142.21

Topic: F.06. Autonomic Regulation

Support: NIH Grant U19NS104653
NIH Grant 1R01NS124017
NIH Grant IIS- 1912293
Simons Foundation SCGB 542373
Additional Ventures postdoctoral fellowship from the Life Sciences Research Foundation to Luis Hernandez-Nunez
Harvard Mind Brain and Behavior Initative postdoc fellowship to Luis Hernandez-Nunez

Title: Heart-brain feedback loops: The neural mechanisms underlying cardiac control

Authors: *L. HERNANDEZ-NUNEZ[1], M. C. FISHMAN[2], F. ENGERT[3];
[2]Stem Cell and Regenerative Biol., [3]MCB, [1]Harvard Univ., Cambridge, MA

Abstract: Impairment to the neural control of cardiac function can cause several life-threatening conditions, including arrhythmias and heart failure. Nevertheless, we understand very little about the neural circuits and computations underlying cardiac function. Furthermore, the dynamics of the intracardiac neurons (neurons attached to the heart) that a healthy individual should have remain unknown. This gap in fundamental physiological knowledge occurs because it is technically challenging to make these measurements in vertebrates. To solve this problem, I have developed microscopy techniques that leverage the transparency and size of larval zebrafish to functionally image and manipulate the entire heart and brain with cellular resolution. Using those tools, I am starting to uncover the function of cardiac control circuits that span the intracardiac, autonomic, and central nervous systems. My work contributes to establishing zebrafish as an ideal model organism to study the systems-level neural mechanisms that control cardiac function.

Disclosures: L. Hernandez-Nunez: None. **M.C. Fishman:** None. **F. Engert:** None.

Poster

142. Neurovisceral Physiology I

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 142.22

Topic: F.06. Autonomic Regulation

Support: NIH HEAL/SPARC U01 NS113867-01
NIH R15HL137143-01A1

Title: Chronic intermittent hypoxia induces remodeling of sympathetic innervation in mouse atria

Authors: *A. BIZANTI[1], Y. ZHANG[1], Z. TOLEDO[1], K. T. BENDOWSKI[1], J. CHEN[1], D. B. HOOVER[2], T. L. POWLEY[3], D. GOZAL[4], Z. CHENG[1];
[1]Univ. of Central Florida, Orlando, FL; [2]Dept. of Biomed. Sci., East Tennessee State Univ., Johnson City, TN; [3]Perdue Univ., W Lafayette, IN; [4]The Univ. of Missouri Sch. of Med., Columbia, IL

Abstract: Chronic intermittent hypoxia (CIH) is a commonly used model for sleep apnea, which constitutes a major risk factor for many cardiovascular diseases (CVD) (hypertension, arrhythmias, heart failure, atherosclerosis and ischemic heart and cerebrovascular disease). Autonomic imbalance (sympathetic overactivity and parasympathetic withdrawal) is hypothesized to be a causal contributor of CIH-induced CVD. Previously, we showed that CIH reduced baroreflex control of heart rate and induced vagal cardiac motor neuronal death in the brainstem. CIH activates the central nervous system circuitry, which in turn enhances sympathetic outflow. However, whether CIH induces remodeling of the peripheral cardiac sympathetic innervation remains unknown. Here, C57BL/6J male mice (2 months, n=7/group) were exposed to room air (RA, 21% O_2) or CIH (alternating 21% and 5.7% O_2, every 6 minutes, 10hr/day) for 8-10 weeks. Flat-mounts of their whole left and right atria were prepared and immunohistochemically labeled for tyrosine hydroxylase (TH, a sympathetic postganglionic marker). Using confocal microscopy (or Zeiss M2 Imager) and a Neurolucida Digitization and Tracing system, we scanned the right and left atria and quantitively analyzed the sympathetic axon density in both the RA and CIH experimental groups. Findings included: 1) Several large TH-IR bundles entered the atria and branched out into smaller bundles and eventually ramified into individual axons and their terminals that covered the entire atria. Each bundle projected to a specific area of the left and right atria. However, different bundles could have some overlap of their projection fields. 2) TH-IR neurons were observed in the intrinsic cardiac ganglia (ICG). Most TH-IR axons passed through the ICG and innervated the cardiac muscles, blood vessels and fat cells. 3) CIH significantly remodeled the TH-IR axon innervation of the atria. Specifically, CIH significantly increased the density of TH-IR innervation at the sinoatrial (SA) node, the atrioventricular (AV) node and the auricles ($p < 0.05$, n=7). These results suggest that increased sympathetic innervation may further amplify the effects of enhanced CIH-induced central sympathetic drive to the heart. Along with our previous finding that CIH reduces parasympathetic control of the heart, our work supports the hypothesis that chronic autonomic imbalance underlies CIH-induced CVD. This study was supported by NIH HEAL/SPARC U01 NS113867-01 and NIH R15 R15HL137143-01A1.

Disclosures: A. Bizanti: None. **Y. Zhang:** None. **Z. Toledo:** None. **K.T. Bendowski:** None. **J. Chen:** None. **D.B. Hoover:** None. **T.L. Powley:** None. **D. Gozal:** None. **Z. Cheng:** None.

Poster

142. Neurovisceral Physiology I

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 142.23

Topic: F.06. Autonomic Regulation

Title: Can retrained spinal neurons restore voluntary voiding after complete paralysis?

Authors: *P. GAD[1], H. ZHONG[2], V. EDGERTON[3], E. KREYDIN[4];
[1]SpineX Inc., SpineX Inc., Northridge, CA; [2]UCLA, [3]Rancho Res. Inst., Los Angeles, CA;
[4]Univ. of Southern California, Los Angeles, CA

Abstract: Spinal cord injury (SCI) results in dramatic changes lower urinary tract (LUT) function including the inability to sense bladder fullness, low bladder capacity leading to urinary incontinence (UI) and are the inability to void volitionally. These symptoms correspond to urodynamic (UDS) findings of detrusor overactivity (DO) and detrusor-sphincter-dyssynergia (DSD) and diminished bladder compliance. Our objective was to determine whether noninvasive spinal neuromodulation can retrain voluntary voiding in the acute period after SCI. We hypothesized that non-invasive spinal neuromodulation results in neuroplasticity of the spinal cord and brain during the initial acute period before the chronic physiology of the SCI is established. Two patients, three months after severe injury (P1: T4, AIS B and P2: C6, AIS C) were recruited. Spinal Neuromodulation was delivered using a proprietary SCONE^{TM} device (SpineX, Inc) over the lumbosacral spinal cord for 1 hr/day, 2x/week. LUT function was assessed using UDS, voiding diary and neurogenic bladder symptom score (NBSS) questionnaire at baseline, 6, 12, 18 and 24 weeks. Bowel using the Neurogenic Bowel Dysfunction Score (NBDS) and sexual function, using the International Index for Erectile Function (IIEF) were secondary outcomes. At baseline, both patients reported NBSS scores of P1= 22, P2 = 33. Voiding diary for P1 reported 4.5 IC/day, volume of 375ml/IC, 0.5 UI/day; P2 reported 4.25 IC/day, volume of 379ml/IC, 2 UI/day. During UDS, both participants demonstrated low bladder capacity, DO and DSD leading to low voiding efficiency (VE). After 4-6 sessions, they reported increased bladder sensation and fewer UI episodes. After 10 sessions both reported the ability to void volitionally. The frequency of volitional voiding and volume voided increased over 24 weeks from zero to 2 voids/day and zero ml to 313ml/void for P1 and zero to 4.5 voids/day and zero to 314ml/void for P2. The voiding diary also reported fewer catheterizations needed (4.5 to 3/day for P1 and 4.25 to zero/day for P2). At the end of 24 weeks, NBSS lowered by 11 and 15 points for P1 and P2 and both demonstrated normalization of UDS patterns including reduced DO, increased sensation, increased bladder capacity, diminished DSD and increased VE. Both patients also reported improvements in NBDS scores accompanied by faster bowel programs, reduced usage of suppositories and reduced constipation and improvement in IIEF scores with more frequent and robust erections. In conclusion, noninvasive spinal neuromodulation can restore LUT function in people living with SCI and they are able to go about their lives without needing or worrying about catheterizations or leaks.

Disclosures: **P. Gad:** A. Employment/Salary (full or part-time):; SpineX. **H. Zhong:** None. **V. Edgerton:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); SpineX and Onward. **E. Kreydin:** E.

Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); SpineX.

Poster

142. Neurovisceral Physiology I

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 142.24

Topic: H.11. Language

Support: SNSF PP00P1_157409/1
SNSF PP00P1_183711/1
Vontobel Foundation (Zurich)

Title: Direct subthalamic nucleus stimulation influences speech and voice quality in Parkinson's disease patients

Authors: *S. FRUEHHOLZ[1], N. SULZER[1], G. BRÜNDLER[1], M. STAIB[1], L. L. IMBACH[3], L. STIEGLITZ[4], A. DE VERE-TYNDALL[4], P. KRAUSS[5], C. BAUMANN[4], M. BOBIN[2]; [1]Univ. of Zurich, Zurich, Switzerland; [2]Univ. of Zurich, Univ. of Zurich, Zuerich, Switzerland; [3]Univ. Hosp. Zurich, [4]Univ. Hosp. Zurich, Zurich, Switzerland; [5]Univ. Hosp. Augsburg, Augsburg, Germany

Abstract: Deep brain stimulation (DBS) of the subthalamic nucleus (STN) considerably ameliorates cardinal motor symptoms in Parkinson's disease (PD). Reported STN-DBS effects on secondary dysarthric (speech) and dysphonic symptoms (voice), as originating from vocal tract motor dysfunctions, are however inconsistent with rather deleterious outcomes based on post-surgical assessments. Here, we performed an assessment of instantaneous peri-surgical speech and voice quality changes elicited by direct STN stimulations with variations of central stimulation features (depth, laterality, hemisphere, and intensity). First, perceptual clinical assessments across several raters revealed that certain speech and voice symptoms could be improved with STN-DBS, but this seems largely restricted to right STN-DBS. Second, computer-based acoustic analyses of speech and voice features revealed that both left and right STN-DBS could improve dysarthric speech symptoms, but only right STN-DBS can considerably improve dysphonic symptoms, with left STN-DBS being restricted to only affect voice intensity features. Third, several subareas according to stimulation depth and laterality could be identified in the motoric STN proper and close to the associative STN with optimal (and partly suboptimal) stimulation outcomes. Fourth, low-to-medium stimulation intensities showed the most optimal and balanced effects compared to high intensities. Overall, STN-DBS can considerably improve both speech and voice symptoms in PD based on a carefully arranged stimulation regimen along central stimulation features.

Disclosures: **S. Fruehholz:** None. **N. Sulzer:** None. **G. Bründler:** None. **M. Staib:** None. **L.L. Imbach:** None. **L. Stieglitz:** None. **A. De Vere-Tyndall:** None. **P. Krauss:** None. **C. Baumann:** None. **M. Bobin:** None.

Poster

142. Neurovisceral Physiology I

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 142.25

Topic: F.06. Autonomic Regulation

Support: NIH/NINDS NS099234
NIH/NINDS OD010996

Title: Central pathways involved in the regulation of brown adipose tissue thermogenesis in arctic ground squirrels

Authors: G. CANO[1], S. L. HERNAN[2], P. CHIAVETTA[3], K. L. DREW[4], ***D. TUPONE**[5,3]; [1]Neurosci., [2]Univ. of Pittsburgh, Pittsburgh, PA; [3]Neurolog. Surgery, Oregon Hlth. and Sci. Univ., Portland, OR; [4]Ctr. for Transformative Res. in Metabolism, Univ. of Alaska Fairbanks, Fairbanks, AK; [5]UNIBO, Bologna, Italy

Abstract: Arctic ground squirrels (AGSs) are a unique species of seasonal hibernators that display normal thermoregulation during summer and profound hypothermia during winter, with core temperature reaching subfreezing body temperature of -2.9^{o}C. The central thermoregulatory circuit controlling the switch from normal thermoregulation to hibernation in AGSs is unknown. In rats (non-hibernators) and mice (facultative hibernators), sympathoexcitatory dorsomedial hypothalamus (DMH) neurons projecting to the presympathetic neurons in raphe pallidus (RPa), represent the main excitatory drive for activation of brown adipose tissue (BAT) thermogenic response to skin cooling. Here, we explored if the same pathway exists in AGSs, and if disinhibition of these areas contributes to BAT thermogenesis. Summer-active AGSs (n = 4), with a retrograde tracer (FluoroGold) injected into RPa, were exposed to cold ambient temperature to elicit c-Fos expression. Immunohistochemical analysis of brain sections revealed the existence of a projection from DMH and lateral hypothalamus/perifornical area (LH-PeF) to RPa. However, few neurons in DMH displayed cold-evoked c-Fos expression, although many did in LH-PeF. Cold exposure also elicited remarkable c-Fos expression in the arcuate nucleus (Arc) and the adjacent tuberal region of the lateral hypothalamus (TuLH). To address the role of these areas in driving BAT thermogenesis, a second group of summer-active AGSs (n = 4) was instrumented for recording arterial pressure (AP), heart rate (HR), expiratory CO_2, and temperature of skin, core (T_{CORE}) and BAT (T_{BAT}). Bicuculine ($GABA_A$ antagonist) or vehicle were nanoinjected into the RPa or Arc-TuLH. With T_{CORE} maintained at 38°C (inhibited thermogenesis), disinhibition of RPa or Arc-TuLH increased T_{BAT} and expiratory CO_2 (increased thermogenesis), as well as AP and HR. These results demonstrate that AGSs and commonly used rodent models (rats and mice) share some elements of the thermoregulatory circuit, including the

RPa, Arc, and LH-PeF. Furthermore, these studies identify TuLH as contributing to thermoregulation in this hibernating species. However, the role played by DMH in cold-evoked BAT activation in AGSs remains unclear at the moment. Further studies are needed to characterize the central circuit controlling the switch from normal thermoregulation to hypothermia in AGSs. Understanding this circuit could inform on the development of pharmacological treatments to achieve rapid and controlled hypothermia in humans in clinical settings.

Disclosures: G. Cano: None. **S.L. Hernan:** None. **P. Chiavetta:** None. **K.L. Drew:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Be Cool Pharmaceutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Be Cool Pharmaceutics. **D. Tupone:** None.

Poster

142. Neurovisceral Physiology I

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 142.26

Topic: F.06. Autonomic Regulation

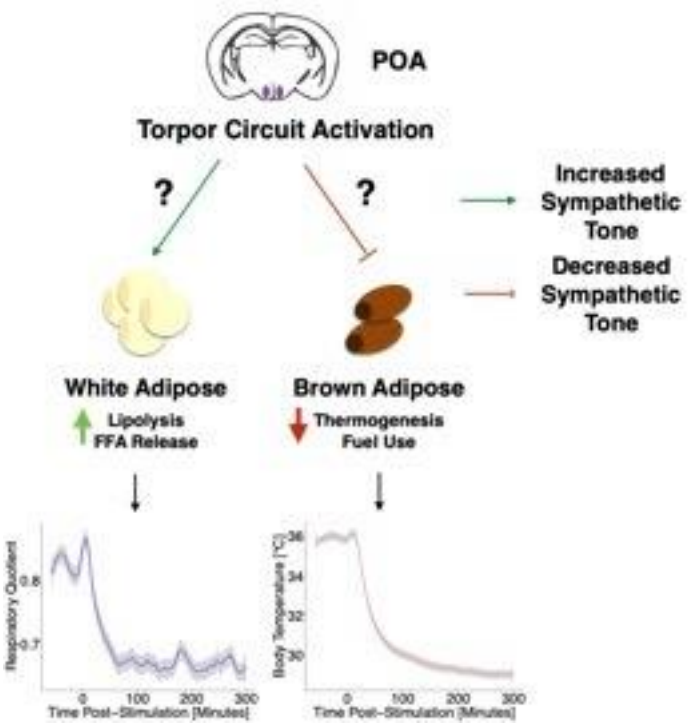
Support: NIH Grant K01DK123197
Warren Alpert Distinguished Scholar Award

Title: Identification of hypothalamic preoptic area neurons that regulate the hypothermic and hypometabolic state of torpor through tissue-specific regulation of the sympathetic nervous system

Authors: J. ROESSLER[1], S. SUN[2], O. WILCOX[5], H. YAO[6], A. LAVIN-PETER[7], M. CICCONET[3], E. ASSAD[3], M. PALMER[3], S. ARONSON[8], A. BANKS[9], E. GRIFFITH[3], M. E. GREENBERG[4], *S. HRVATIN[1];
[1]Whitehead Inst. and MIT, Cambridge, MA; [2]Harvard Med. Sch., Brookline, MA; [4]Dept. of Neurobio., [3]Harvard Med. Sch., Boston, MA; [5]Univ. of California San Diego, San Diego, CA; [6]Stanford Univ., Palo Alto, CA; [7]Whitehead Inst., Cambridge, MA; [8]Oberlin Col., La Jolla, CA; [9]Beth Israel Deaconess Med. Ctr., Boston, MA

Abstract: Torpor and hibernation are fascinating adaptations of warm-blooded animals, endowing them with the ability to survive harsh environments otherwise incompatible with life. How mammals initiate and regulate these hypometabolic and hypothermic states remains largely unknown. Employing a mouse model of fasting-induced torpor, characterized by body temperature as low as 20°C and altered metabolism, this study aims to identify the central and peripheral circuits that initiate this state. Using a FosTRAP approach, we perform a screen across several regions of the hypothalamus, and identify a population of neurons in the preoptic area

(POA) that regulates torpor. Single-nucleus RNA sequencing identified a large subset of these torpor-active cells as glutamatergic Adcyap1+ neurons. Chemogenetic activation of these neurons phenocopies the hypothermic and hypometabolic aspects of torpor, whereas their silencing prevents natural torpor entry, suggesting that these cells serve as core regulators of torpor. In order to enter and maintain torpor, animals need to inhibit thermogenesis, which is primarily driven by the sympathetic nervous system (SNS). We therefore examined whether torpor-regulating neurons inhibit the sympathetic nervous system. Unexpectedly, we observed that stimulation of the torpor circuitry in fed mice rapidly decreases respiratory quotient (RQ = VCO2/VO2, $p < 0.003$) and increases plasma free fatty acids (1.86-fold, $p < 0.003$) without changes in plasma leptin, insulin, and glucagon. These data suggest an increase in lipolysis and switch from glucose to fatty acid catabolism that is mediated by an increase, and not decrease, in sympathetic drive to white adipose tissue. Our data are consistent with a model in which the torpor circuit simultaneously activates and suppresses distinct branches of the SNS to produce the unique physiological effects of torpor. In summary, we identify a population of neurons in the preoptic area that regulates entry into the hypothermic and metabolically suppressed state of torpor through organ-specific modulation of SNS activity.



Disclosures: **J. Roessler:** None. **S. Sun:** None. **O. Wilcox:** None. **H. Yao:** None. **A. Lavin-Peter:** None. **M. Cicconet:** None. **E. Assad:** None. **M. Palmer:** None. **S. Aronson:** None. **A. Banks:** None. **E. Griffith:** None. **M.E. Greenberg:** None. **S. Hrvatin:** None.

Poster

142. Neurovisceral Physiology I

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 142.27

Topic: F.06. Autonomic Regulation

Support: IRP NIH ZIA DK075057
IRP NIH ZIA DK075062
IRP NIH ZIA DK075063

Title: Preoptic area BRS3 neurons increase body temperature predominantly through glutamatergic neurotransmission

Authors: *R. PINOL[1], S. KULKARNI[1], C. HADLEY[1], M. KRASHES[2], M. REITMAN[2]; [1]NIH, NIDDK, Bethesda, MD; [2]NIDDK, NIH, Bethesda, MD

Abstract: The preoptic area (POA) is a key brain region involved in whole-body metabolism and body temperature (Tb), a major contributor to thermogenic, cardiovascular, and behavioral responses that regulate Tb. Ultimately survival depends on proper Tb regulation, making it critical to understand the physiology. The majority of known POA neuronal populations reduce Tb when activated. Using mice, we have identified bombesin-like receptor 3 (BRS3)-expressing POA (POA^{BRS3}) neurons as having this missing functionality. BRS3 is an orphan receptor that regulates energy and cardiovascular homeostasis, but the relevant neural circuits are incompletely understood. We now show that anterior preoptic area BRS3 neurons increase body temperature predominantly through glutamatergic neurotransmission. Optogenetic stimulation of POA^{BRS3} neurons in BRS3-Cre;$Vgat^{fl/fl}$ mice robustly increases Tb, but in Brs3-Cre;$Vglut2^{fl/fl}$ mice only slightly increases Tb. We further used monosynaptic retrograde rabies tracing to map the synaptic input to POA^{BRS3} neurons. More than half the input to POA^{BRS3} neurons is from within the preoptic area. The remaining input comes from a wide variety of regions, including the dorsomedial hypothalamus and arcuate nucleus with each 4% of total input. Notably, input from the parabrachial nucleus was also found. Taken together, our results show that POA^{BRS3} neurons receive input from a wide variety brain regions and rely on glutamatergic neurotransmission to drive robust Tb increases.

Disclosures: R. Pinol: None. **S. Kulkarni:** None. **C. Hadley:** None. **M. Krashes:** None. **M. Reitman:** None.

Poster

143. Fear and Aversive Learning and Memory: Memory Modification

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 143.01

Topic: G.01. Fear and Aversive Learning and Memory

Support: National Institute on Drug Abuse - psilocybin

Title: Low-dose psilocybin enhances novel object recognition but not inhibitory avoidance in adult rats

Authors: *C. E. MILLER, C. R. DEL VALLE, M. M. NAYLOR, H. R. SPARKMAN, C. M. CRUEA, R. E. RICE, B. E. BRAMLAGE, L. P. PUPPEL, M. L. BROWN, A. K. AL-OLIMAT, E. S. DIETZ, P. R. ZOLADZ;
Psychology and Neuroscience, The Sch. of Hlth. and Behavioral Sci., Ohio Northern Univ., Ada, OH

Abstract: Given the recently renewed interest in using psychedelics to aid in the treatment of psychological disorders, we aimed to examine the impact of psilocybin, a 5-HT_{2A} agonist, on learning and memory in rodents. Previous work has demonstrated that psilocybin and other 5-HT_{2A} agonists can enhance fear conditioning, fear extinction, and novel object recognition (NOR). Thus, we predicted that low doses of psilocybin would enhance inhibitory avoidance (IA) and NOR memory. In the first experiment, adult male and female Sprague-Dawley rats underwent step-through IA training (involving 0.45, 0.65, or 1 mA scrambled footshock) and were injected intraperitoneally (i.p.) with vehicle (0.9% saline) or psilocybin (1 mg/kg) immediately afterward. Rats were tested for their IA memory two days later. In the second experiment, adult male and female Sprague-Dawley rats were acclimated to an open field apparatus for 5 minutes on Day 1. The next day, the rats were given i.p. injections of vehicle or psilocybin (0.1 mg/kg) 10 minutes before undergoing NOR training, during which they were exposed to two replicas of an identical object for 3 minutes. On Day 3, one of the objects from NOR training was exchanged for a novel object; rats were exposed to this novel object and a new replica of the object from Day 2 (i.e., familiar object) for 5 minutes. The results showed that psilocybin had no significant impact on IA memory but enhanced novel object recognition memory in both males and females. The differential impact of psilocybin on IA memory and novel object recognition could be explained by the different doses of psilocybin or the different times of drug administration used for each task. Alternatively, they may suggest that psilocybin exerts distinct effects on different types of learning.

Disclosures: C.E. Miller: None. **C.R. Del Valle:** None. **M.M. Naylor:** None. **H.R. Sparkman:** None. **C.M. Cruea:** None. **R.E. Rice:** None. **B.E. Bramlage:** None. **L.P. Puppel:** None. **M.L. Brown:** None. **A.K. Al-Olimat:** None. **E.S. Dietz:** None. **P.R. Zoladz:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); National Institute on Drug Abuse.

Poster

143. Fear and Aversive Learning and Memory: Memory Modification

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 143.02

Topic: G.01. Fear and Aversive Learning and Memory

Support: R56MH126516
R01MH126516

Title: Involvement of the Locus Coeruleus in the Enhancement of Fear Extinction Driven by Vagus Nerve Stimulation

Authors: *D. R. CALDERON[1], R. RODRIGUEZ DE SOUZA[1], C.-T. TSENG[1], C. SANCHEZ[1], J. PLOSKI[2], C. THORN[1], C. MCINTYRE[1];
[1]Neurosci., Univ. of Texas at Dallas, Richardson, TX; [2]Neurosci., Univ. of Pennsylvania, Philadelphia, PA

Abstract: Vagus nerve stimulation (VNS) is FDA approved for use in the treatment of epilepsy, depression, and stroke rehabilitation and is currently being tested as an adjuvant for exposure therapy in the treatment of post-traumatic stress disorder (PTSD) in humans. VNS enhances extinction of conditioned fear and reverses extinction impairments in rat models of PTSD. However, the effects of VNS on neuromodulators involved in emotional learning and memory remain largely undiscovered. Research on the role of norepinephrine (NE) in enhancing emotional learning leads us to the hypothesis that this neurotransmitter may play a role in VNS enhanced extinction. This hypothesis is supported by research showing that VNS increases neuronal activity in the locus coeruleus (LC) and leads to increased levels of NE in limbic system regions involved in storage of fear and extinction memories. These data suggest that VNS-driven LC-NE plays a role in VNS effects on fear extinction. Here, we investigated whether the extinction-enhancing effects of VNS are mediated by LC activity. Male and female tyrosine hydroxylase-Cre+ Long Evans rats received bilateral intra-LC infusions of adeno-associated viral vectors containing the inhibitory opsin ArchT3.0 (AAV8-Ef1a-DIO-ArchT3.0-eYFP) or control virus. Three weeks later, a VNS cuff electrode was implanted around the left cervical vagus nerve and optic fibers were implanted directly above the LC. After a one-week recovery period, rats were subjected to two days of auditory fear conditioning followed, 24 hours later, by a pre-extinction test to quantify fear of the auditory conditioned stimulus (9 kHz tone, 30 sec). On the next day, an extinction session was given where VNS (4 x 2 sec trains, 0.8 mA, 30 Hz) that was overlapped by laser emission (4 x 4 sec pulses, 593 nm) was administered during each of four exposures to the conditioned stimulus. An extinction retention test was given 24 hours later. Fourteen days later, all rats were retested for spontaneous recovery of fear. On all test days, freezing was used as a measure of conditioned fear during four presentations of the conditioned stimulus in the absence of the unconditioned stimulus. Preliminary results indicate that inhibition of the LC during VNS presentations blocks the enhancing effects of VNS on consolidation of extinction learning, 24 hours and 14 days after extinction training paired with VNS. These findings suggest that the extinction-enhancing effects of VNS are mediated by LC activity during extinction. These data support the hypothesis that VNS enhances extinction memory by recruiting a neuromodulatory system that is involved in the enhancement of long-term storage of fear memories.

Disclosures: D.R. Calderon: None. **R. Rodriguez de Souza:** None. **C. Tseng:** None. **C. Sanchez:** None. **J. Ploski:** None. **C. Thorn:** None. **C. McIntyre:** None.

Poster

143. Fear and Aversive Learning and Memory: Memory Modification

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 143.03

Topic: G.01. Fear and Aversive Learning and Memory

Support: 31922089 National Natural Science Foundation of China

Title: Can emotion regulation facilitate subsequent control of unwanted memories?

Authors: *H. XIE, X. LIN, X. HU;
Psychology, The Univ. of Hong Kong, Hong Kong, China

Abstract: Unwanted memories are often emotionally charged. Difficulties in forgetting unwanted memories could deteriorate mental health. We investigated whether cognitive reappraisal, via weaking emotional tones of unwanted memories, can facilitate subsequent memory control processes.
Participants (N = 44, 12 males; 23.2 ± 3.3 years old) learned 48 object-scene pairings, followed by an emotion regulation (ER) task during which they were instructed to either naturally watch or reappraise the scenes. Subsequently, a Think/No-Think (TNT) task was performed, with continuous EEGs recorded. During this task, objects from the pairings were presented as cues, and participants were asked to either think of the associated scenes as detailed as possible (T condition) or suppress the associated scenes from entering awareness (NT condition). At the end of each trial, participants indicated on how often the associated scenes had involuntarily intruded into their mind during the presentation of the objects. Afterwards, participants completed a recall and emotion rating task to examine their memories on the object-scene pairings and their subjective feelings about the described scenes.
Behavioral results showed that compared with naturally watch, reappraisal: 1) reduced the negativity of emotional scenes during the ER task ($p < 0.001$); 2) marginally increased intrusion proportions for NT trials during the last block of the TNT task ($p = 0.067$); 3) improved memory performance for NT pairings ($p = 0.043$) but reduced the negativity of suppressed emotional memories during subsequent recall ($p = 0.017$). The event-related potential (ERP) results showed that larger centro-parietal P3 was elicited when suppressing the retrieval of the reappraised vs. watched scenes ($p = 0.027$). Furthermore, multivariate pattern analysis (MVPA) with cortical EEG patterns revealed that during retrieval, the emotional valence of reappraised scenes cannot be decoded based on the whole-brain EEG patterns, possibly because the reappraisal weakened negative feelings toward negative emotional memories.
These results demonstrated a dissociative effect of cognitive reappraisal on emotion and memory. While cognitive reappraisal did not facilitate (and even hindered) the subsequent control and forgetting of unwanted memories, it weakened the negative tone of unwanted memories, making them less troubling when being recalled later. Our study provides the first evidence for the impact of emotion regulation on subsequent memory control.

Disclosures: H. Xie: None. **X. Lin:** None. **X. Hu:** None.

Poster

143. Fear and Aversive Learning and Memory: Memory Modification

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 143.04

Topic: G.01. Fear and Aversive Learning and Memory

Support: Janeway Grant
NSERC 206686

Title: Exploration of Backward Conditioning for Reactivation-Dependent Amnesia of Contextual Fear Memories in Female Mice

Authors: *J. TRASK, P. MACCALLUM, Y. MARTIN, A. SWIFT-GALLANT, J. BLUNDELL;
Psychology, Mem. Univ. of Newfoundland, St. John's, NL, Canada

Abstract: The manner in which we acquire and encode fear memories affects recall. In forward fear conditioning (FC, Classical Pavlovian Conditioning), animals associate a cue such as a tone (Conditioned Stimulus; CS) with the preceding shock (Unconditioned Stimulus; US). In backward conditioning (BC), however, this is reversed with the cue presented after the shock delivery. Consequently, the cue does not predict the shock; rather, subsequent presentation of the cue indirectly reactivates the context's memory and therefore, the context-shock association. While the mechanisms underlying FC are relatively well-known, less is known about those underlying BC. Moreover, there is a lack of knowledge of these processes in female mice. Hence, our first goal was to assess the effects of contextual extinction on cued-memory recall in FC and BC female mice. Sixty female C57/BL6 mice underwent either BC (context A, footshock+tone) or FC (context A, tone+footshock) in context A. Two days later, half of the mice were exposed to conditioning context A (extinction trials) and half were exposed to a novel context C (no extinction trials). Both BC and FC mice show increased freezing to context A compared to FC and BC conditioned mice who were exposed to the novel context (context C). Following the extinction trials, however, all four groups showed equal amounts of freezing (in context A or context C). These data suggest that extinction of the context occurred in both FC and BC mice. One day later, freezing behavior was measured to the tone (in novel context B) for all mice. BC mice that had been extinguished to the context showed reduced freezing to the tone compared to all other groups. These data suggest that fear to the backward CS is mediated by the retrieval of a contextual fear memory in female mice. Our second goal was to begin to identify the underlying mechanism. The mechanistic target of rapamycin (mTOR) kinase, a critical regulatory factor in protein synthesis, is known to be involved in long-lasting forms of activity-dependent behavioral and synaptic plasticity. We show that reconsolidation of a FC contextual fear memory is blocked with systemic rapamycin (mTOR inhibitor) in female mice. Currently, we are assessing the effects of rapamycin on reconsolidation of a BC fear memory, as well as the influence of estrus cycle. Future studies will examine upstream and downstream molecular targets of the mTOR pathway. Ultimately, identifying the mechanism underlying fear memories may contribute to advancing the treatment for fear- and stress-related disorders such as phobias or post-traumatic stress disorder.

Disclosures: **J. Trask:** None. **P. MacCallum:** None. **Y. Martin:** None. **A. Swift-Gallant:** None. **J. Blundell:** None.

Poster

143. Fear and Aversive Learning and Memory: Memory Modification

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 143.05

Topic: G.01. Fear and Aversive Learning and Memory

Support: NIH R21AG068423

Title: Utilization of a novel intrabody to enhance fear memory through postsynaptic enrichment of calcium/calmodulin-dependent protein kinase II alpha

Authors: *A. CHIFOR[1], J. CHOI[1], J. PARK[2];
[1]Dept. of Pharmacol., [2]Dept. of Pharmacology, Dept. of Neurol., Wayne State Univ. Sch. of Med., Detroit, MI

Abstract: Long-term potentiation (LTP), the selective strengthening of synaptic connections following recent activation, has widely been accepted as the underlying biological mechanism responsible for learning and memory. During LTP, N-methyl-D-aspartate receptors (NMDARs) are activated resulting in a surge of postsynaptic calcium levels. It further leads to the postsynaptic activation of calcium/calmodulin-dependent kinase II alpha (CaMKIIα), which subsequently initiates a cascade of cellular events that ultimately result in the strengthening of synaptic connections. Thus, given CaMKIIα's critical role in LTP, we hypothesize that an increase in CaMKIIα levels at postsynaptic, NMDAR-proximal regions would improve memory formation. Here, we developed a novel intrabody against the GluN1 subunit of the NMDAR by screening a library of intrabody candidates using phage display selection, yeast two-hybrid screening, and eliminating redundant clones. One clone showed the robust colocalization with and binding to GluN1 in a heterologous cell system, which we termed VHH-Anti-GluN1 (VHHAN1). Using immunostaining and quantitative analysis, VHHAN1's ability to target endogenous GluN1 and recruit CaMKIIα was then validated within adeno-associated virus (AAV)-infected hippocampal neurons expressing the VHHAN1-CaMKIIα fusion protein (2.2-fold increase compared with CaMKIIα expression alone, $P < 0.0001$). Finally, injected mice were then exposed to fear conditioning experiments which demonstrated that VHHAN1-mediated recruitment of CaMKIIα results in significantly improved contextual fear memory in comparison to non-injected, CaMKIIα-expressing, and kinase-inactive CaMKIIα-VHHAN1-expressing control mice (n = 10-12 mice per group with equal sex distribution) (2.4-fold memory improvement, $P < 0.05$). This intrabody and its application provide a novel molecular tool to further investigate synapse and memory biology and could potentially be applied to improve memory in dementia and related memory disorders.

Disclosures: **A. Chifor:** None. **J. Choi:** None. **J. Park:** None.

Poster

143. Fear and Aversive Learning and Memory: Memory Modification

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 143.06

Topic: G.01. Fear and Aversive Learning and Memory

Support: NIMH MHR01107435
NIH grant T32 MH064913.

Title: Role of 2-AG signaling in dorsal hippocampus during extinction of contextual fear conditioning

Authors: *L. RAMOS-MEDINA[1], S. PATEL[2], L. E. ROSAS-VIDAL[2];
[1]Vanderbilt Univ., Nashville, TN; [2]Psychiatry and Behavioral Sci., Northwestern Univ., Chicago, IL

Abstract: Anxiety Disorders, along with Trauma- and Stressor-related Disorders, are among the most diagnosed mental health problems in the United States. A cardinal characteristic of these disorders is a failure in the process of extinction, or learning that context stimuli and cues previously associated to a trauma event are now safe. Previous data from our lab and others have shown that endogenous cannabinoids such as 2-arachynoylglycerol (2-AG) are needed for the extinction of auditory fear conditioning and modulation of the fear response (Shonesy et al., 2014; Jenniches et al., 2016; Cavener et al., 2018; Marcus et al., 2020). Nevertheless, the role of 2-AG in rodents exposed to contextual fear paradigms is less understood. Thus, we tested whether acquisition of conditioned fear to a context was regulated by DAGL activity via administration of DO34 (an inhibitor of 2-AG synthesis) or vehicle 2 h prior to the fear conditioning sessions. We observed no significant differences in freezing behavior in DO34-treated C57bl/6j male mice (aged 6-10 weeks old) compared to vehicle-treated controls during any of the conditioning days [P=0.4651, F(1,23) = 0.5519]. On the other hand, pharmacological inhibition during extinction training revealed that male mice treated with DO-34 are unable to extinguish the fear associated to the context [P=0.0002; F (1, 18) = 22.68], with preliminary data supporting this also female counterparts. However, there is no significant effect increase in anxiety-like behavior, as measured by the Open Field and Elevated Plus Maze tests. Altogether, we suggest the observed phenotype might reflect a deficit specific to the extinction learning process, but not in its retrieval once consolidated (P>0.05) nor in the acquisition of the original fear memory. Our next step is to characterize neural activity in the dorsal hippocampus (dHIPP) in normal and 2-AG deficient mice. Our overarching hypothesis is that during a traumatic exposure, 2-AG modulation in dHIPP is required for proper extinction learning. An alteration of 2-AG signaling would result in neurons with a heightened activity that sustains the freezing behavior, even after a prolonged time after extinction. This could constitute a mechanism of why contextual information and cues associated with a traumatic exposure are resistant to extinction. Both pharmacological inhibition of 2-AG synthesis in wild type mice and region-specific

deletion of the DAGL gene in the dorsal hippocampus via a Cre-driven system will be employed to render a 2-AG deficient phenotype.

Disclosures: L. Ramos-Medina: None. **S. Patel:** None. **L.E. Rosas-Vidal:** None.

Poster

143. Fear and Aversive Learning and Memory: Memory Modification

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 143.07

Topic: G.01. Fear and Aversive Learning and Memory

Support: NIH R01 GM118801

Title: Conditional knockout of α5-$GABA_A$Rs from CCK-expressing neurons alters long-term memory and its modulation by etomidate, but not short-term memory

Authors: *D. BATTISTINI, A. ABDULZAHIR, M. G. PERKINS, R. A. PEARCE; Anesthesiol., Univ. of Wisconsin, Madison, WI

Abstract: The general anesthetic etomidate suppresses long-term memory through its action on α5-$GABA_A$Rs. We reported previously that selectively eliminating these receptors from all interneurons (Gad2-cre x floxed Gabra5 mice) prevented etomidate from suppressing long-term memory. Here, we explored the effects of eliminating α5-$GABA_A$Rs from subsets of Cck- and Gad2-expressing neurons. Conditional α5-KO mice were made by crossing Cck-Cre, Gad2-Cre, or both (Gad2-Cre and Cck-Cre) mice with floxed Gabra5 mice. Long-term memory was assessed by the context preexposure facilitation effect (CPFE) contextual fear conditioning paradigm, using freezing to context as a surrogate for memory. Short-term memory was assessed by Y-maze spontaneous alteration. α5-KO mice and their pseudo-WT (pWt) littermates were compared following IP administration of saline (ctrl) or etomidate 7 mg/kg IP (ETOM) 30 minutes before day 1 (preexposure) of CPFE. Data are presented as mean ± SEM. Statistical comparisons were performed using unpaired Welch's t-tests (Graphpad Prism). In CPFE experiments, ETOM reduced freezing in pWT mice (ctrl 41±2.2%, n=30; ETOM 21±1.4%, n=27; $p<0.0001$). Unexpectedly, CCK-α5-KO mice exhibited deficient long-term memory compared to pWT even under in the absence of drug (ctrl 22±2.6%, n=14; $p<0.0001$ vs pWT ctrl). Even more surprisingly, and in contrast to Gad2-α5-KO mice in which ETOM did not alter freezing (ctrl 41±3.8%, n=12; ETOM 41±4.5%, n=13; $p=0.95$), ETOM greatly increased freezing in CCK-α5-KO mice (ctrl 22±2.6%, n=14; ETOM 58±6.0%, n=18; $p=<0.0001$). To test whether these effects derived from α5-KO in interneurons vs. pyramidal neurons, we compared effects in Gad2-α5-KO to Gad2+Cck-α5-KO mice. Memory remained impaired in the Gad2+Cck-α5-KO (ctrl 28±4.9%, n=14; $p=0.049$ vs. Gad2-α5-KO ctrl), indicating that baseline memory impairment resulted from α5-KO from Cck-expressing pyramidal neurons. However, ETOM had no effect on freezing in Gad2+Cck-α5-KO mice (ctrl 28±4.9%, n=14; ETOM 19±5.2%, n=12; $p=0.21$), suggesting that etomidate-induced memory impairment or

enhancement derives from actions on interneurons. In Y-maze SA experiments, Cck-α5-KO mice and p-WT mice exhibited similar rates of alternation (pWT 36±4.1%, n =8; Cck-α5-KO 39±1.9%, n=8; p=0.50), indicating that short-term memory remains intact in these mice. We conclude that α5-$GABA_A$Rs on both Cck-expressing pyramidal neurons and interneurons contribute to long-term memory and its modulation by etomidate.

Disclosures: D. Battistini: None. **A. Abdulzahir:** None. **M.G. Perkins:** None. **R.A. Pearce:** None.

Poster

143. Fear and Aversive Learning and Memory: Memory Modification

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 143.08

Topic: G.01. Fear and Aversive Learning and Memory

Support: Discovery Grant form Natural Sciences and Engineering Research Council of Canada

Title: Role of dopamine D3 receptor in unconditioned and conditioned memory modulation

Authors: *T. D. LAPOINTE[1], F. LERI[2];
[1]Univ. of Guelph, Univ. of Guelph, Guelph, ON, Canada; [2]Univ. Guelph, Univ. Guelph, Guelph, ON, Canada

Abstract: Our group recently demonstrated that post-training exposure to unconditioned stimuli (US; cocaine, heroin, nicotine) or their conditioned stimuli (CS; contextual) enhance memory consolidation by activating dopaminergic receptors. In an attempt to uncover the extent of overlap between neural mechanisms of unconditioned and conditioned memory modulation, the dopamine (DA) D3 receptor (D3R) became of particular interest because of its expression within neurocircuits involved in motivation, learning and memory, and because D3R antagonists appear to have selective inhibitory effects on responses to CSs. Therefore, it is possible that the D3R is predominantly involved in memory modulation facilitated by exposure to CSs and may not be involved in memory enhancement promoted by unconditioned stimuli. To test this hypothesis, we employed a signaled active avoidance procedure (30 trials/session; 0.8 mA) and tested the effects of foot-shock, as well as of the avoidance CS in the absence of foot-shock, after eight sessions of training, on the consolidation of object recognition memory (sample and choice phases separated by 72 hrs), in male Sprague-Dawley rats. It was found that immediate post-sample exposure to foot-shock, or to the avoidance CS, both facilitated object memory. Importantly, post-sample administration of the D3R antagonist NGB-2904 (5 mg/kg) selectively blocked conditioned memory modulation. Taken together, these results indicate the D3R is recruited during the consolidation of memory that occurs following exposure to a CS but not a US, and consequently suggests that the neurochemical pathways of unconditioned and conditioned memory consolidation can be dissociated.

Disclosures: **T.D. Lapointe:** None. **F. Leri:** None.

Poster

143. Fear and Aversive Learning and Memory: Memory Modification

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 143.09

Topic: G.01. Fear and Aversive Learning and Memory

Support: Z01ES090089
R01NS022061
U01MH109104

Title: Cholinergic signaling in the ventral Subiculum participates in cue-associated threat learning

Authors: *S. WANG[1], D. A. TALMAGE[2], J. YAKEL[1], L. W. ROLE[3];
[1]NIH, Ion Channel Lab, NIEHS, Research Triangle Park, NC; [2]NIMH, [3]NIH, NINDS, Bethesda, MD

Abstract: The ventral subiculum (vSub) mediates the information exchange between the ventral hippocampus (vHipp) and multiple brain regions related to threat learning, including the basal lateral amygdala (BLA). The vSub function is also regulated by cholinergic inputs from the basal forebrain. It has been shown that pharmacological manipulations on acetylcholine (ACh) receptors in general, the vHipp can alter the performance of threat learning. However, the specific role of cholinergic signaling in the vSub during the acquisition and retrieval of threat memory remains unclear. Our previous ex vivo data confirmed that ACh can modulate the neuronal activity of vSub pyramidal neurons. In this study we use in vivo assays to assess how cholinergic signaling in the vSub modulates the neural activity in a cue-associated threat learning paradigm.To investigate the dynamic change of cholinergic signaling in vSub, we expressed a genetically encoded ACh sensor ($GRAB_{Ach3.0}$) in vSub neurons and used a spectrometer-based fiber photometry system to monitor the ACh level. We found that the acetylcholine level was not responsive to naïve tone (conditioned stimulus) during training but showed significant increase after foot shock (unconditioned stimulus). During retrieval, the ACh level increased significantly when the animal is given the tone alone in a novel context. Interestingly, a similar trend was found when we used in vivo calcium imaging to measure vSub neural activity in the same behavior task. We found ~80% of neurons that we monitored showed no change to naïve tone during training but had a brief increase after foot shock. After the tone shock pairing, these neurons divergently showed either a significant increase or decrease in activity in response to the tone cue during retrieval. To further test the relationship between ACh level and vSub neural activity, we used chemogenetics to inhibit ACh release specifically in the vSub during the memory retrieval. We found that inhibiting ACh signaling attenuated the expression of threat memory and induced a decrease in the number of active neurons. These results support the idea

that ACh in vSub participates in regulating threat memory by modulating the local neural circuits.

Disclosures: S. Wang: None. **D.A. Talmage:** None. **J. Yakel:** None. **L.W. Role:** None.

Poster

143. Fear and Aversive Learning and Memory: Memory Modification

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 143.10

Topic: G.01. Fear and Aversive Learning and Memory

Title: Repeated exposure to contextual novelty enhances fear extinction memories

Authors: E. K. LOCK, Y. FUKUNAGA, E. K. SCHULMAN, S. E. GONZALEZ, *V. A. CAZARES;
Psychology and Neurosci. Program, Williams Col., Williamstown, MA

Abstract: Novelty enhances several types of learning and memory and promotes hippocampal reactivation and plasticity. Paradoxically, novelty can also hinder some types of memory, such as recall of fear extinction. Fear extinction is context-specific; thus if a (extinguished) conditioned stimulus (CS), such as a tone, is experienced in any context except for the one in which it was extinguished, it will re-elicit the fear response, a phenomenon termed fear renewal. We have previously showed that fear extinction training in a series of novel contexts overcomes fear renewal and leads to enhanced fear extinction learning as well as improved fear extinction recall 7 days later. We now extend these findings to show this paradigm also improves fear extinction recall 30 days later. Furthermore, we show that this novel-context enhancement of fear extinction requires the hippocampus by using chemogenetic activation or inhibition to impair fear extinction in animals trained in serial novel contexts but not those trained repeatedly in a single context. Finally, we use TRAP2 mice (which indelibly label Fos-expressing neurons, as a marker of neural activity) to demonstrate differential activation on day 2 and day 3 of fear extinction training in the hippocampus and medial prefrontal cortex between mice trained with novel contexts or a single context.

Disclosures: E.K. Lock: None. **Y. Fukunaga:** None. **E.K. Schulman:** None. **S.E. Gonzalez:** None. **V.A. Cazares:** None.

Poster

143. Fear and Aversive Learning and Memory: Memory Modification

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 143.11

Topic: G.01. Fear and Aversive Learning and Memory

Support: Norwegian Research Council NRC 230413
NIH Grant MH100349

Title: Reduced innate fear expression after chemogenetic inactivation of the ventral hippocampus

Authors: *L. RAGAZZI[1], S. V. JORDBRÆK[1], M. SABARIEGO[2], I. ZUTSHI[3], J. K. LEUTGEB[4,5], S. LEUTGEB[4,5], V. H. BRUN[1,6], K. B. KJELSTRUP[1,6];
[1]Inst. for Clin. Med., UiT The Arctic Univ. of Norway, Tromso, Norway; [2]Program in Neurosci. and Behavior, Mount Holyoke Col., South Hadley, MA; [3]New York Univ. SOM, New York Univ. Sch. of Med., New York, NY; [4]Neurobio. Department, Sch. of Biol. Sci., UCSD, La Jolla, CA; [5]Kavli Inst. for Brain and Mind, Univ. of California, San Diego UCSD, La Jolla, CA; [6]Univ. Hosp. of North Norway (UNN), Tromso, Norway

Abstract: Expression of defense behavior in appropriate situations is essential for survival, and the ventral hippocampus (VH) has been identified as necessary for context-dependent fear responses. However, the specific contribution of VH to fear behavior is still uncertain. We developed a new task that could generate satisfactory and long-lasting fear responses in Long-Evans rats. In this task, the smell of natural predator (coyote urine) and a remote-controlled snake-like toy were either individually presented or paired to evoke fear responses. When paired, we observed a more pronounced and lasting avoidance behavior over time. To evaluate whether the VH contributes to the expression of innate fear itself or to remembering where innate fear was experienced, we either silenced or lesioned the VH and measured place avoidance at different time points. In particular, place avoidance to the odor/snake exposure was tested during and after exposure at 24, 48, and 72 h. Fear related behaviors such as freezing, head out, and avoidance of the conditioned chamber were assessed at each time point in four experimental groups: 1) pAAV-hSyn-hM4D(Gi)-mCherry virus targeted bilaterally to the VH with CNO inactivation only on the day of exposure to the odor/snake, 2) pAVV-hSyn-eGFP CNO - control, 3) bilateral VH ibotenic acid lesions, and 4) VH sham lesions. Both, the sham lesion and the pAVV-hSyn-eGFP CNO, control groups showed a marked place avoidance to the stimuli both during exposure and during retrieval after 24 h, 48 h, 72 h, indicating the existence of innate fear as well as of contextual fear memory. In contrast, the lesioned and pAAV-hSyn-hM4D(Gi)-mCherry - CNO inactivated animals did not show any clear defensive behaviors at any time point. Compared to their respective controls, VH lesions and chemogenetic inactivation prevented or significantly reduced the development of place preference and suppressed defensive responses.Our data suggest that activity of neurons in the VH is necessary for the manifestation of innate fear and, as a consequence, for the acquisition of a contextual fear memory.

Disclosures: L. Ragazzi: None. **S.V. Jordbræk:** None. **M. Sabariego:** None. **I. Zutshi:** None. **J.K. Leutgeb:** None. **S. Leutgeb:** None. **V.H. Brun:** None. **K.B. Kjelstrup:** None.

Poster

143. Fear and Aversive Learning and Memory: Memory Modification

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 143.12

Topic: G.01. Fear and Aversive Learning and Memory

Title: Simulated owl predation during foraging differentially alters choice behavior between sex in rats

Authors: M. M. OLSEN, H. D. NGUYEN, N. C. WARD, A. M. AMAYA, H. K. ABOUEICH, *P. M. BAKER;
Psychology, Seattle Pacific Univ., Seattle, WA

Abstract: Existing research on the predator cue circuit has indicated that there are observed differences between sexes of animals either directly or indirectly exposed to a predator stimulus. Following exposure to a predator stimulus, animals display increases in predator directed attention, and alterations to motivational states (such as reproductive behavior, pain, and hunger). Little research has explored whether exposure to predation is associated with differential responses to decision-making across a variety of tasks. Therefore, understanding the neural circuits involved in the prioritization of motivational states when a predator stressor is present can aid in understanding sex differences in these processes in both adaptative (e.g. escaping from imminent threat) and maladaptive (prolonged stress) conditions. To determine how repeated exposure to a predator stressor differentially affects effort-based decision-making and fear-based behavior, an ethologically relevant visual predator stressor in the form of a 3D realistic owl was utilized in both male and female Long Evans rats. Predation exposure was accomplished by plunging a decoy owl into an open foraging area which rodents were allowed to explore for a maximum of three minutes. Subjects were given up to three exposures to the owl stimulus a day, until a total of 9 exposures had been achieved. Twenty-four hours following the final owl exposure, measures of effort-based decision making and anxiety-like behavior were administered between exposed and unexposed rats. Subjects were randomly assigned to complete an effort-related choice T-maze, the elevated plus maze, marble burying, and the defensive withdrawal tests. This series of tests was repeated on subjects 48 hours following final predator exposure. Preliminary results indicated that prior to testing procedures the average preference for a high reward in the effort-related choice T-maze was 67 ± 14% for female rats and 82.5 ± 4.3%. for male rats. Following testing procedures, the average preference for the high reward was 67.7 ± 3.9% for female rats, and 67.1 ± 6.2% for male rats. Indicating that male and female rodents are differentially affected on an effort-related choice task. Preliminary results also indicate that the average preference for the high reward was 72.9 ± 4.3% for control rats, and 63 ± 4% for owl exposed rats suggesting that rodents exposed to a predator stimulus are differentially affected compared to control rats. Ongoing experiments will also examine whether activation of the predator cue circuit differentially affects the observed behavior between sex on these tasks.

Disclosures: M.M. Olsen: None. **H.D. Nguyen:** None. **N.C. Ward:** None. **A.M. Amaya:** None. **H.K. AbouEich:** None. **P.M. Baker:** None.

Poster

143. Fear and Aversive Learning and Memory: Memory Modification

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 143.13

Topic: G.01. Fear and Aversive Learning and Memory

Support: Hungarian Academy of Sciences Momentum II program
National Research, Development and Innovation Office, Hungary grants EFOP-3.6.1-16-2016-00008, EFOP 3.6.6-VEKOP-16-2017-00009
National Research, Development and Innovation Office, Hungary grant KKP133871/KKP20
Ministry of Innovation and Technology of Hungary grant TKP2021-EGA-28 (AB)
Ministry of Human Capacities, Hungary grant 20391-3/2018/FEKUSTRAT
EU Horizon 2020 Research and Innovation Program No. 739593 – HCEMM
Hungarian Scientific Research Fund grants NN125601 and FK123831

Title: Closed-loop modulation of sleep spindles: a potential therapeutic approach in PTSD-like rat model

Authors: *L. BARCSAI[1,4,5], R. SIERRA[2], L. PEDRAZA[2], G. KOZAK[2], P. RAFI[2,4], M. LORINCZ[2,3,6], A. BERENYI[2,4,7,5];
[1]Dept. of Physiol., [2]Dept. of Phsysiology, [3]Dept. of Physiology, Anat. and Neurosci., Univ. of Szeged, Szeged, Hungary; [4]Neunos ZRt, Szeged, Hungary; [5]HCEMM-SZTE Magnetotherapeutics Res. Group, Szeged, Hungary; [6]Neurosci. Div., Cardiff Univ., Cardiff, United Kingdom; [7]Neurosci. Institute, New York Univ., New York, NY

Abstract: Post-traumatic stress disorder (PTSD) is a serious psychiatric condition affecting ~6% of the world's population at least once in their lifetime. Any kind of traumatic event can trigger the onset of the disease. Chronic stress can trigger panic attacks, elevated anxiety, night terrors and fear generalization. The symptoms are associated with the reconstruction of traumatic memories suggesting a strong mnemonic component. Since the memory systems are strongly involved in the disorder, our aim was to manipulate the oscillations linked to memory consolidation. Fear extinction has already been established as an exposition-based approach for fear reduction in animals and humans. Previously our group showed that extinction combined with closed loop hippocampal sharp-wave ripple triggered stimulation of the median forebrain bundle (MFB) can reduce fear in rats. To promote translational applicability, in this study we investigated if cortical oscillations linked to memory consolidation (e.g., sleep spindles), which can be easily detected with non- or semi-invasive techniques, may serve as triggers in this approach. Young male wistar rats were exposed to a high intensity cued fear conditioning training, followed by 3 days of extinction. After each extinction session the animals received 3 hours of closed-loop MFB electrical stimulation, by detecting sleep spindles from the medial prefrontal cortex. Fear responses were repeatedly tested each day for one month. Our results show that animals who received closed loop stimulation significantly reduced their fear expression compared to the non-stimulated and open loop stimulation groups on the long-term, but not on the short term. Our results open new venues for the identification of cortical

oscillatory landmarks as stimulation triggers, suitable for future non-invasive clinical application. Altogether, our results show for the first time, a potential on-demand, closed loop stimulation to treat pathological fear memories based exclusively in cortical oscillations.

Disclosures: **L. Barcsai:** None. **R. Sierra:** None. **L. Pedraza:** None. **G. Kozak:** None. **P. Rafi:** None. **M. Lorincz:** None. **A. Berenyi:** None.

Poster

143. Fear and Aversive Learning and Memory: Memory Modification

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 143.14

Topic: G.01. Fear and Aversive Learning and Memory

Support: •Hungarian Academy of Sciences Momentum II program
•National Research, Development and Innovation Office, Hungary grants EFOP-3.6.1-16-2016-00008, EFOP 3.6.6-VEKOP-16-2017-00009
•National Research, Development and Innovation Office, Hungary grant KKP133871/KKP20
•Ministry of Innovation and Technology of Hungary grant TKP2021-EGA-28
•Ministry of Human Capacities, Hungary grant 20391-3/2018/FEKUSTRAT
•EU Horizon 2020 Research and Innovation Program No. 739593 – HCEMM
•Hungarian Scientific Research Fund grants NN125601 and FK123831

Title: Closed-loop stimulation of infralimbic cortex reduces anxiety and prevents fear generalization during memory consolidation and reconsolidation

Authors: *L. K. PEDRAZA CORREA[1], R. SIERRA[2], A. PEJIN[2,5], L. BARCSAI[3,5,6], Q. LI[4], L. GELLERT[2], M. LőRINCZ[2,7,8], A. BERENYI[4,5,6,9];
[1]Univ. of Szeged, Univ. of Szeged, Dept. of Physiol., Szeged, Hungary; [2]Univ. of Szeged, Szeged, Hungary; [3]Univ. of Szeged, Szeged, Iceland; [4]Univ. of Szeged, Univ. of Szeged, Szeged, Hungary; [5]Neunos Ltd, Szeged, 6725, Hungary, Szeged, Hungary; [6]HCEMM-SZTE Magnetotherapeutics Res. Group, Univ. of Szeged; Szeged, 6720, Hungary, Szeged, Hungary; [7]Dept. of Physiology, Anat. and Neuroscience, Fac. of Sci. Univ. of Szeged; Szeged, 6726, Hungary, Szeged, Hungary; [8]Neurosci. Division, Cardiff University, Museum Avenue, Cardiff CF10 3AX, UK, Cardiff, United Kingdom; [9]Neurosci. Institute, New York University; New York, NY 10016, USA, Nyc, NY

Abstract: Fear memory generalization is a central hallmark in the broad range of anxiety and trauma-related disorders. Recent results from our laboratory suggest that fear memories can be attenuated using closed-loop (CL) neurostimulation guided by the real-time detection of dorsal hippocampal sharp-wave ripples (dSWRs) during extinction. In this study, dSWRs were used to trigger the infralimbic cortex (IL) stimulation, a well-known cortical structure implicated in the inhibitory control of basolateral amygdala (BLA). Using Wistar rats, we applied high intensity

cue fear conditioning training to induce fear generalization. Immediately after learning or a short memory reactivation, animals received 3h intervention using a real time dSWRs detection inducing the IL electrical stimulation (10 pulses, 0.2-ms width at 100 μA, 50 Hz). 24h later, rats underwent test to the conditioned stimuli (CS+) or a neutral one (CS-). In order to evaluate the effect of our intervention during fear extinction, animals were exposed to 20 non-reinforced CS+ and 24h later to a renewal test. We found that animals with CL stimulation immediately after training expressed fear to the CS+ but not CS- suggesting discrimination while open-loop (OL) and non-stimulated groups expressed fear generalization. CL stimulation lost efficacy if applied 48h after training, however, the effect can be recovered using a short memory reactivation before the CL intervention. This short reactivation promotes protein-synthesis-dependent reconsolidation since fear expression could be disrupted by intra-BLA infusion of anisomycin. The fear discrimination induced by CL intervention also contributes to fear reduction during extinction, since we found a strong correlation between discrimination and low fear expression during renewal. CL but not OL stimulation increases gamma power and incidence in the BLA after the stimulation period. In particular, there is a significant positive correlation between gamma incidence and fear discrimination. Both closed and open loop IL stimulation reduced anxiety-like behavior in the elevated plus maze. Our results suggest that dSWRs are implicated in the discrimination of cued fear memories. Cl-IL stimulation increase BLA gamma activity contributing to discrimination and the enhancement of fear extinction. These findings can be extended to memory reconsolidation-based approaches opening new avenues for electrical neuromodulation techniques aimed to attenuate aversive memory traces after retrieval.

Disclosures: **L.K. Pedraza Correa:** None. **R. Sierra:** None. **A. Pejin:** None. **L. Barcsai:** None. **Q. Li:** None. **L. Gellert:** None. **M. Lőrincz:** None. **A. Berenyi:** None.

Poster

143. Fear and Aversive Learning and Memory: Memory Modification

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 143.15

Topic: G.01. Fear and Aversive Learning and Memory

Support:
•Hungarian Academy of Sciences Momentum II program
•National Research, Development and Innovation Office, Hungary grants EFOP-3.6.1-16-2016-00008, EFOP 3.6.6-VEKOP-16-2017-00009
•National Research, Development and Innovation Office, Hungary grant KKP133871/KKP20
•Ministry of Innovation and Technology of Hungary grant TKP2021-EGA-28
•Ministry of Human Capacities, Hungary grant 20391-3/2018/FEKUSTRAT
•EU Horizon 2020 Research and Innovation Program No. 739593 – HCEMM
•Japan Society for the Promotion of Science grant 18KK0236

Title: Controlling pathologic fear expression through closed-loop brain stimulation

Authors: *R. O. SIERRA[1], L. K. PEDRAZA[2], L. BARCSAI[2,5,6], A. PEJIN[2,7], G. KOZAK[3], Y. TAKEUCHI[8], M. LőRINCZ[4,9,10], O. DEVINSKY[11], A. BERENYI[3,5,6,12];
[1]Univiersity of Szeged, Univ. of Szeged, Dept. of Physiol., Szeged, Hungary; [3]Univ. of Szeged, [2]Univ. of Szeged, Szeged, Hungary; [4]Univ. of Szeged, Szeged, Iceland; [5]HCEMM-SZTE Magnetotherapeutics Res. Group, Univ. of Szeged; Szeged, 6720, Hungary, Szeged, Hungary; [6]Neunos Ltd, Szeged, 6725, Hungary, Szeged, Hungary; [7]3Neunos Ltd, Szeged, 6725, Hungary, Szeged, Hungary; [8]Dept Biopharmaceutical Sci. Pharmacy, Facult Pharmaceut. Sci, Hokkaido Univ, Sapporo, Japan, Sapporo, Japan; [9]Dept. of Physiology, Anat. and Neuroscience, Fac. of Sci. Univ. of Szeged; Szeged, 6726, Hungary, Szeged, Hungary; [10]Neurosci. Division, Cardiff University, Museum Avenue, Cardiff CF10 3AX, UK, Cardiff University, United Kingdom; [11]Dept. of Neurology, NYU Langone Comprehensive Epilepsy Ctr., NYU, NY; [12]Neurosci. Institute, New York University; New York, NY 10016, USA, Nyc, NY

Abstract: Traumatic experiences can trigger neuropsychiatric diseases such as posttraumatic stress disorder (PTSD). Mnemonic features like fear generalization and resistance to the extinction, prevents the effectiveness of psychotherapy and pharmacological treatments. Sharp-wave ripples (SWRs) are well known to play a critical role in spatial memory consolidation. However, how SWRs mediates the consolidation of emotional memories is poorly understood. In this study, we evaluated the relationship between SWRs and memory consolidation after extinction sessions, a highly context-dependent process. Using Long Evans rats, we applied high intensity cue fear conditioning training to induce fear generalization and a phenotype resistant to extinction. 24h later, rats underwent extinction sessions once per day until achieving remission (i.e. 85% reduction in freezing). Immediately after extinction, animals received 1 hour closed loop (CL) intervention by the electrical stimulation of the medial forebrain bundle (MFB; train lasting 100 ms, 14 pulses 1-ms long, 100μA square-wave pulses at 140 Hz) triggered by SWRs detection. Since the MFB stimulation could condition place preference, we hypothesize that pairing SWRs occurrences with MFB stimulation could change the emotional valence in a fear memory trace. After remission, animals were submitted to renewal test in a hybrid context 24h and 25 days later. We found that CL-SWRs stimulation, compared with open-loop and non-stimulated groups, significantly decreases the number of days to achieve a successful extinction. The low fear expression is maintained in the renewal test. This effect was prevented by the inhibition of Rac1 in the basolateral amygdala (BLA), a key-protein of dendritic spine remodeling and also by the antagonism of amygdalar D2 dopamine receptors. Disruption of SWRs by ventral hippocampal commissural stimulation (single-pulse of 0.5 ms, 5-15 V) results in slow extinction learning and fear persistence in different environments beyond the extinction context. These results suggest SWRs help to consolidate fear extinction memories and closed loop neuromodulation-based MFB stimulation timed to SWRs can alleviate pathologic fear reactions in a rodent model of PSTD. No adverse effects were seen, suggesting this is a potential therapy for PTSD and anxiety disorders as non-pharmaceutical alternative.

Disclosures: R.O. Sierra: None. **L.K. Pedraza:** None. **L. Barcsai:** None. **A. Pejin:** None. **G. Kozak:** None. **Y. Takeuchi:** None. **M. Lőrincz:** None. **O. Devinsky:** None. **A. Berenyi:** None.

Poster

144. Neurobiology of Fear

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 144.01

Topic: G.01. Fear and Aversive Learning and Memory

Support: NWO VICI 453-15-009

Title: Striatal dopamine release upon hearing others' pain vocalizations

Authors: *F. NELISSEN[1], E. Z. POH[1], J. GOEDHOOP[1], E. SOYMAN[2], V. GAZZOLA[1], I. WILLUHN[1], C. KEYSERS[1];
[1]Netherlands Inst. For Neurosci., Amsterdam, Netherlands; [2]Kadir Has Univ., Istanbul, Turkey

Abstract: Generally considered to be a foundational component of empathy, emotional contagion refers to the process by which the emotional state of one individual spreads to another. In a much used rodent model of emotional contagion, an “observer” rat will freeze after witnessing a “demonstrator” receiving footshocks, thereby showing evidence that the distress of the demonstrator was contagious. This effect is increased in observers that have prior experience of footshocks. One information channel, through which the demonstrators can affect the emotional state of the observers, is the audible pain vocalizations called squeaks. We have recently shown the importance of the auditory modality in this contagion by replacing the demonstrators with the playback of previously recorded squeaks, and found this to trigger substantial freezing. As prior studies showed that striatal dopamine release is implicated in prosocial behavior, e.g., increased release upon hearing 50 kHz sounds, in the present study we aimed to investigate striatal dopamine release of pre-exposed and naïve rats in response to the playback of pain squeaks and other control sounds. Electrodes were implanted in adult Long-Evans rats for fast-scan cyclic voltammetry measurements and were randomly divided into the pre-exposure and naïve groups. Only animals in the pre-exposure group were administered four unsignaled footshocks (0.8 mA, 1 sec, 240-360 sec intertrain interval). After habituation to a different context, all animals were presented with recordings of pain squeaks from unknown conspecifics, the phase-scrambled control versions of the original squeaks, and 50 kHz rat ultrasonic vocalizations as positive control stimuli. Here, we report that hearing 50 kHz vocalizations induces striatal dopamine release, as reported by us previously. However, such dopamine release in response to 50 kHz vocalizations was decreased in pre-exposed as compared to naïve animals. We also report that squeak playbacks triggered a transient dopamine-signal decrease in pre-exposed animals but not naïve animals; and that this difference was not observed in response to the playback of the phase-scrambled control sounds. These findings indicate that striatal dopamine is influenced by signals of conspecifics suggesting positive (50kHz) and aversive (pain squeaks) states in the same direction as similar states would in the self; and these effects are influenced by the listeners past aversive experiences. These findings could provide insights into the neural mechanisms through which the experiences of others can act as reinforcers or punishment in instrumental learning.

Disclosures: F. Nelissen: None. **E.Z. Poh:** None. **J. Goedhoop:** None. **E. Soyman:** None. **V. Gazzola:** None. **I. Willuhn:** None. **C. Keysers:** None.

Poster

144. Neurobiology of Fear

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 144.02

Topic: G.01. Fear and Aversive Learning and Memory

Support: KAKENHI 19H05234

Title: Bidirectional prefrontal control of fear extinction learning through projections to the brainstem noradrenaline system

Authors: *M. WATANABE[1,2], A. UEMATSU[1,3,4], J. P. JOHANSEN[1,2];
[1]Ctr. for Brain Sci., RIKEN, Wako-shi, Japan; [2]Grad. Sch. of Arts and Sci., [3]Grad. Sch. of Sci., [4]Intl. Res. Ctr. for Neurointelligence, The Univ. of Tokyo, Tokyo, Japan

Abstract: The brainstem locus coeruleus (LC), the major source of noradrenaline to the forebrain, plays important roles in emotional regulation. Compared to its efferent projections to distinct target regions, it is poorly understood how different afferent inputs regulate the LC-noradrenaline system to control emotional responses. One particularly significant question is whether and how prefrontal cortical regions, important in cognitive processing, influence the brainstem noradrenergic system.
Here we used anatomical tracing and viral optogenetic approaches in rats to elucidate the detailed prefrontal-to-LC anatomical connectivity and test whether prefrontal innervation of the LC modulates fear extinction learning. Using anterograde and retrograde tracing approaches, we found that the LC/pericoeruleus (peri-LC) area receives projections from the prelimbic (PL) and infralimbic (IL) cortices, which have been associated with fear expression and extinction, respectively. Notably, we found that the peri-LC, a region that contains LC-noradrenergic dendrites and GABAergic neurons that adjust LC-noradrenaline outflow, receives distinct, topographically organized innervation from PL and IL.
Next we examined whether the PL and IL synaptic inputs to the LC participate in extinction of auditory fear memories. Using optogenetic terminal inhibition, we found that inactivation of IL-to-LC input during extinction training impaired formation of long-term extinction memories. By contrast, inactivation of PL-to-LC input strengthened long-term extinction memories. These results show that PL and IL opposingly regulate formation of long-term fear extinction memories through innervation of the LC-noradrenergic system.
To determine what information is transmitted through the PL-to-LC and IL-to-LC pathways during fear extinction, we are currently working on fiber photometry recording experiments from LC-projecting neurons in either PL or IL. Results of these experiments will be also discussed in the presentation.

Disclosures: M. Watanabe: None. **A. Uematsu:** None. **J.P. Johansen:** None.

Poster

144. Neurobiology of Fear

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 144.03

Topic: G.01. Fear and Aversive Learning and Memory

Support: MOST 107-2410-H-006-054
MOST 108-2410-H-006-043
MOST 109-2410-H-006-038

Title: Effect of amygdala lesion on conditioned taste aversion under dexmedetomidine-induced anesthesia in rats

Authors: *C.-H. CHENG, H.-Y. HSIAO, D.-Y. CHEN;
Dept Psychology, Natl. Cheng Kung Univ., Tainan, Taiwan

Abstract: Taste aversion may be acquired without conscious awareness. For example, patients receiving chemotherapy usually develop aversions to food, but they may be unaware of the association between taste and nausea during therapy. It has been suggested that similar processes may be involved in other eating disorders such as anorexia nervosa. It is possible that such kind of learning may be preserved even without full consciousness. In the present study, we explored whether conditioned tasted aversion (CTA) can be acquired under dexmedetomidine-induced anesthesia. In addition, we also examined the role of the amygdala in this kind of implicit learning and memory. Male Sprague-Dawley rats were placed on a 23.5-hr water deprivation schedule. The animals were allowed daily 30 min access to water. On the conditioning day, they were anesthetized by dexmedetomidine (0.06 mg/kg, s.c.). Thirty minutes later, 0.1 % saccharin solution was pumped to their tongues for 10 minutes at a rate of 0.3 ml/min. Their tongues were rinsed by water to remove the taste of saccharin afterwards. In the CTA group, rats received one dosages of nicotine (0.05, 0.5, 1.0 mg/kg, s.c.) to induce illness. The control group received saline instead. After 20 minutes, they received atipamezole (0.6 mg/kg, s.c.) to reverse the effect of anesthesia. In the following day, their aversion to saccharin solution were assessed by two-bottle tests while they were awake. The results showed rats injected with nicotine have significantly lower saccharin intake than those injected with saline. In the next experiment, the lesion group was injected with ibotenic acid (5.0 microgram / 0.5 microliter) into the bilateral amygdala, and the sham group was injected with phosphate buffered saline. After one week of recovery period, all rats received saccharin paired with 1.0 mg/kg nicotine under anesthesia, as described in the previous experiment. The results showed that the amygdala lesion group drank more saccharin solution than that of sham group. It seemed that lesion of the amygdala impaired CTA learning under anesthesia. In summary, CTA can be acquired under anesthesia and this memory could be performed under awake state. The amygdala also plays a critical role in this kind of learning, which is consistent to our previous finding using modified inhibitory avoidance learning under anesthesia. Taken together, our studies demonstrated that certain types of implicit learning can occur under anesthesia, and the underlying neural mechanisms may be similar to learning while awake.

Disclosures: C. Cheng: None. **H. Hsiao:** None. **D. Chen:** None.

Poster

144. Neurobiology of Fear

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 144.04

Topic: G.01. Fear and Aversive Learning and Memory

Support: NIH Grant MH115947
Beckman Scholars Program for Undergraduate Research

Title: Adult male rats exhibit time-of-day differences in the recall of trace conditioned fear and extinction

Authors: *M. J. HARTSOCK, A. B. FAUSNAUGHT, A. W. CHOI, S. M. DOBBY, R. L. SPENCER;
Dept. of Psychology and Neurosci., Univ. of Colorado Boulder, Boulder, CO

Abstract: The circadian system profoundly influences most learning and memory processes, generating time-of-day differences in the speed of learning and the strength of memory recall. Past work in rats and humans has demonstrated circadian modulation of delayed conditioned fear extinction, a prefrontal-cortex-dependent learning and memory process important for the treatment of fear-based mental disorders. In delayed conditioned fear extinction, a cue (often a tone) co-terminates with an aversive stimulus (often a shock). We have shown previously that circadian rhythms in delayed conditioned fear extinction recall require intact circadian function in the prefrontal cortex (Woodruff et al, *eNeuro*, 2018), suggesting that circadian function in the prefrontal cortex gives rise to circadian rhythms in prefrontal-cortex-dependent processes. Here, using adult male Sprague-Dawley rats, we characterize time-of-day differences in another prefrontal-cortex-dependent emotional learning and memory paradigm: trace conditioned fear and extinction. Trace conditioned fear and extinction differ from delayed conditioned fear and extinction in that trace conditioned fear and extinction include a time interval, or trace, between the termination of the cue and delivery of the aversive stimulus. In the trace paradigm, the prefrontal cortex appears to be engaged during both fear and extinction. Accordingly, in the trace paradigm, we find stronger fear recall during the inactive phase and stronger extinction recall during the active phase. These findings align with our results from the delayed conditioned fear paradigm, indicating greater fear suppression during the active phase. In addition, the behavioral differences we observe in the trace paradigm are reflected in *c-Fos* gene expression in the prefrontal cortex. Our findings are consistent with the circadian regulation of trace conditioned fear and extinction, providing evidence of rhythms in another prefrontal-cortex-dependent emotional learning and memory paradigm.

Disclosures: M.J. Hartsock: None. **A.B. Fausnaught:** None. **A.W. Choi:** None. **S.M. Dobby:** None. **R.L. Spencer:** None.

Poster

144. Neurobiology of Fear

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 144.05

Topic: G.01. Fear and Aversive Learning and Memory

Support: ARC DECRA

Title: Distinct Prefrontal Cortex Activity in Fear Memory Consolidation

Authors: *R. MAREK;
The Univ. of Queensland, Queensland Brain Inst., Brisbane, Australia

Abstract: It is well established that the prefrontal cortex (PFC) is a vital contributor in the regulation of emotional memories. In rodents, the prelimbic (PL) and infralimbic (IL) cortex of the medial PFC (mPFC) are implicated in regulating different stages of fear and extinction. However, recent findings have started to question the distinct role of the PL and IL in selectively modulating fear learning and extinction, respectively. Thus, we here investigated interactions within the mPFC during fear learning, and the retrieval of consolidated memories.
By labelling learning-specific neural populations (engram cell) using inducible activity-dependent labelling (AAV-pRAM-d2TTA-TRE-ChR2-WPRE and AAV-cfos-ERT2-Cre-ERT2-PEST) in mice, we here show that the consolidation of fear memories using cued fear conditioning involves a significant shift from wide-spread mPFC activity during fear learning towards layer 2/3 activity, which is not restricted to specific mPFC-regions. Furthermore, examination of the local circuitry in the mPFC using patch-clamp recording *ex vivo* suggests a high level of inhibitory neurons being allocated into the fear engram, hinting at a distinct characteristic of the mPFC circuitry in fear processes. However, the tagging of the retrieval engram in context-conditioning revealed a significant shift of neural activity into deep layers of the mPFC. This suggest that specific learning paradigms differentially recruit the mPFC based on defined synaptic integration. Finally, *in vivo* optogenetic activation of fear retrieval engram neurons in the mPFC during extinction learning prevents extinction, resulting in the persistence of fear-related behaviours.
Taken together, these findings reveal a dynamic role of mPFC sub-layers, rather than mPFC sub-regions, in regulating appropriate fear responses.

Disclosures: R. Marek: None.

Poster

144. Neurobiology of Fear

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 144.06

Title: WITHDRAWN

Poster

144. Neurobiology of Fear

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 144.07

Topic: G.01. Fear and Aversive Learning and Memory

Support: NIH Grant R01MH110594
NIH Grant R01MH116937
NIH Grant P50MH106435-06A1
McKnight Foundation Award

Title: Using dermal skin laser as a precise nociceptive stimulus for the study of pain and value-guided decision-making in rodents and non-human primates

Authors: *J. PAI[1], T. OGASAWARA[1], E. S. BROMBERG-MARTIN[1], K. OGASAWARA[1], R. W. GEREAU, IV[2], I. E. MONOSOV[1];
[1]Neurosci., [2]Anesthesiol., Washington Univ. in St Louis, Saint Louis, MO

Abstract: Pain affects decision-making, memory, perception, and numerous other facets of behavior and subjective experience. However, it is not yet well understood how pain affects the neural computations underlying many of these processes. The study of these questions has been limited by a lack of a nociceptive stimulus that is temporally precise, dynamically adjustable, and usable over many trials in a single experimental session. We show that dermal laser stimulation (infrared neodymium:yttirum-aluminum perovskite (Nd:YAP), 1.34 μm wavelength) already used in human studies of aversion, can be used for this purpose in monkeys and mice. We trained head-fixed mice (n = 8) to associate distinct auditory tones with different magnitudes of water reward and laser punishments to the back. Mice slowed their running and licked in advance of rewards, and they ran faster in advance of laser punishments. These anticipatory behaviors scaled with the predicted magnitude of reward amount and laser power. Our data shows that dermal laser is a highly useful tool for the study of valence-related behaviors in rodents. Next, we tested if the laser could be used in non-human primates to test how negative value affects decision related computations. We trained monkeys (n = 2) on a value-guided decision-making task where subjects could choose between offers indicating varying magnitudes of juice reward and laser power. Monkeys considered both juice amount and laser power when making their choices. Laser stimulation had a negative value that scaled with laser power - that is, monkeys were willing to give up more reward to avoid stronger laser stimulation. We then investigated how single neurons in the orbitofrontal cortex - a region known to be involved in reward guided decisions - signal the value of rewards and punishments during decision making. To this end, we recorded from single neurons in OFC while monkeys did our task and identified that the OFC contained subsets of neurons that reflected the monkeys' preferences of both rewards and punishments. Also, neurons that significantly signaled reward value, as a group, tended to vary

their activity in response to reward and punishment magnitudes in opposite directions, consistent with encoding of subjective value. Using the dermal laser, we obtained results that show that the OFC plays a role in multi-attribute decisions in which monkeys must weigh rewarding and aversive outcomes. Across this work, we present evidence that dermal laser stimulation can be used to deliver temporally precise, aversive stimuli with a good dynamic range to quantitatively study aversion-related processing and cognitive computations in several key model organisms.

Disclosures: **J. Pai:** None. **T. Ogasawara:** None. **E.S. Bromberg-Martin:** None. **K. Ogasawara:** None. **R.W. Gereau:** None. **I.E. Monosov:** None.

Poster

144. Neurobiology of Fear

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 144.08

Title: WITHDRAWN

Poster

144. Neurobiology of Fear

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 144.09

Topic: G.01. Fear and Aversive Learning and Memory

Support: K99NS119783 (CEV)
R35NS116854 (IMR)

Title: Contribution of the medial cerebellar nucleus to innate freezing behaviors

Authors: *C. E. VAAGA, I. M. RAMAN;
Neurobio., Northwestern Univ., Evanston, IL

Abstract: Survival requires animals to rapidly recognize and appropriately respond to acute threats within the environment. Such defensive behaviors rely on innate neural circuits dedicated to threat detection, integration of sensorimotor inputs, and execution of appropriate behavioral responses. Our recent work indicates that the medial cerebellar nucleus exerts modulatory control over freezing-related neurons in the ventrolateral periaqueductal gray, a region known to be involved in defensive freezing behavior. Here, we examine the cerebellar contribution to innate freezing in mice. Looming visual stimuli, mimicking aerial predators, evoked freezing periods of equivalent durations in both male and female mice (males: 31.4 ± 4.0 s; females: 38.5 ± 3.6 s, unpaired t-test $p = 0.2$). Such freezing, however, rapidly habituated (stimulus 1: 36.4 ±

4.2 s; stimulus 3: 20.1 ± 3.6 s, paired t-test $p < 0.001$) on the timescale of minutes. To test whether cerebellar output modulates the efficacy with which looming visual stimuli engage freezing, we optogenetically manipulated Purkinje cell activity during innate freezing paradigms, with the goal of clamping cerebellar output. Optogenetic stimulation of vermal Purkinje cells, which is predicted to suppress cerebellar output, greatly reduced normal freezing durations in response to looming visual stimuli (WT mice: 35.0 ± 2.7 s; L7::ChR2 mice: 9.9 ± 2.8 s, unpaired t-test $p < 0.001$), and reversed the pattern of habituation across trials. To investigate neuronal activity during these manipulations, we recorded from medial cerebellar nuclear cells in awake, head-fixed mice. In vivo, loose-cell attached recordings revealed sex differences in the basal firing rate of neurons in the medial cerebellar nucleus (males: 68.2 ± 6.2 sp/s; females: 126.5 ± 14.6 sp/s, unpaired t-test $p < 0.001$). These firing rates were fell sharply when vermal Purkinje cells were stimulated with the optogenetic protocols that influenced behavior. Together, these results suggest that cerebellar output from the medial nuclei may permit and/or facilitate the ability of mice to engage in innate defensive behaviors.

Disclosures: C.E. Vaaga: None. **I.M. Raman:** None.

Poster

144. Neurobiology of Fear

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 144.10

Topic: G.01. Fear and Aversive Learning and Memory

Support: NINDS

Title: Caution influences avoidance and approach behaviors differently

Authors: J. ZHOU, S. HORMIGO, S. MUHAMMAD, ***M. A. CASTRO-ALAMANCOS**; Univ. of Connecticut Sch. of Med., Univ. of Connecticut Sch. of Med., Farmington, CT

Abstract: While conflict between incompatible goals has well-known effects on actions, in many situations the same action may produce harmful or beneficial consequences during different periods in a non-conflicting manner -e.g., crossing the street during a red or green light. To avoid harm, subjects must be cautious to inhibit the action specifically when it is punished -as in passive avoidance, but act when it is beneficial -as in active avoidance or active approach. In mice of both sexes performing a signaled action to avoid harm or obtain reward, we found that addition of a new rule that punishes the action when it occurs unsignaled delays the timing of the signaled action in an apparent sign of increased caution. Caution depended on task signaling, contingency, and reinforcement type. Interestingly, caution became persistent when the signaled action was avoidance motivated by danger but was only transient when it was approach motivated by reward. Although caution is represented by the activity of neurons in the midbrain, it developed independent of frontal cortex or basal ganglia output circuits. These results indicate

that caution disrupts actions in different ways depending on the motivational state and may develop from unforeseen brain circuits.

Disclosures: J. Zhou: None. **S. Hormigo:** None. **S. Muhammad:** None. **M.A. Castro-Alamancos:** None.

Poster

144. Neurobiology of Fear

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 144.11

Topic: G.01. Fear and Aversive Learning and Memory

Support: R01-MH097243
R01-MH119670

Title: Mechanical allodynia following Repeated Social Defeat induced sensitization

Authors: *S. SWANSON[1], E. GOODMAN[1], J. P. GODBOUT[2], J. F. SHERIDAN[3];
[1]The Ohio State Univ. Neurosci. Grad. Program, Columbus, OH; [2]Neurosci., Ohio State Univ. Dept. of Neurosci., Columbus, OH; [3]Inst. for Behavioral Med. Res., Ohio State Univ., Columbus, OH

Abstract: Psychological stress may play a key role in the development of chronic pain-related conditions. Repeated social defeat (RSD) in mice causes a convergence of neuronal, central inflammatory (microglia), and peripheral immune (monocytes) pathways leading to prolonged anxiety, social withdrawal and enhanced sensitivity to pain. This increased pain sensitivity 14 hours after RSD was microglia dependent and reversed by microglia elimination. RSD also promotes “stress-sensitization,” that results in amplified responses from exposure to an acute stress with exaggerated inflammation, monocyte accumulation, and neurobehavioral deficits. Therefore, the objectives of this study were to determine the extent to which RSD caused long-term pain sensitization and assess the role of microglia in this process. To address these objectives two studies were completed. In the first study, mice were exposed to RSD and mechanical allodynia was assessed after acute defeat exposure (1 cycle of social defeat) at 28 and 45 days (d) after RSD. Acute defeat 28d after RSD led to an increased inflammatory mRNA profile (Il1b,Tnf) in the spinal cord and mechanical allodynia. This sensitivity to pain after RSD, however, was resolved by 45d after RSD. Thus, RSD caused a transient increase in pain sensitivity. In the second study, mice were stress sensitized by RSD and then subjected to a colony stimulating factor receptor (CSF1R) antagonist protocol to induce the turnover of microglia. This protocol was comprised of microglia depletion for 7 days after RSD (7 day elimination) and repopulation for 21 days after RSD. Microglia elimination at 7d and repopulation of microglia at 28d was confirmed by Iba-1-lalbeling. Next, pain sensitivity to acute defeat was determined 28 days after RSD with or without the forced turnover of microglia. As expected, acute stress 28d after RSD caused mechanical allodynia. Nonetheless, the forced

turnover of microglia had no effect on this pain sensitivity at 28 days after RSD. Thus, these data indicate that forced turnover of microglia after “stress sensitization” did not reverse the increase in pain sensitivity to acute defeat at 28d. In conclusion, there was transient effect on pain after RSD that was independent of sensitized microglia.

Disclosures: S. Swanson: None. **E. Goodman:** None. **J.P. Godbout:** None. **J.F. Sheridan:** None.

Poster

144. Neurobiology of Fear

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 144.12

Topic: G.01. Fear and Aversive Learning and Memory

Support: The hospital for Sick Children's Reastracomp fellowships
Strata foundation
CIHR; MOP-74650

Title: Extinction engram silences an original fear engram in the lateral amygdala.

Authors: *S. PARK[1], J. JUNG[2], P. W. FRANKLAND[2], S. A. JOSSELYN[2];
[1]The hospital for sick children, [2]The Hosp. For Sick Children, The Hosp. For Sick Children, Toronto, ON, Canada

Abstract: Memories for events are thought to be represented in sparse, distributed neuronal ensembles (or engrams). During an event, neurons that are more excitable or active are recruited or allocated to an engram. Our previous works have presented that fear memory engram is strongly correlated with the neuronal excitability of the randomly selected neurons in the lateral amygdala (S. Park et al., 2016; Rashid et al., 2016). Recent studies suggested that extinction training can recruit neuronal populations unlike fear neurons (Lacagnina et al., 2019). However, relatively little is known about how extinction engram is related to fear engram. Here we examined how extinctoin engram works in the lateral amygdala (LA). To manipulate the excitability of neurons, we used a strategy that allowed us to either activate (via ChR2) or inhibit (via NpHR3) the same neurons at different points in our experiment. First, we showed that after behavioral extinction (16 CS tones, no foot-shock), optogenetic activation of the original fear engram induces memory recall without any change in fear extinction memory. We allocated fear memory to randomly selected neurons, stimulating ChR2 (1mW, 20Hz, 473nm, 30s). Optogenetic stimulation on the neurons allocating fear memory induced fear responses in the extinction training context. This finding is consistent with previous results showing that behavioral extinction requires “new learning” rather than a modification of the original memory trace (Zhang et al., 2020). Second, we applied DREADD (hM4Di, an inhibitory receptor) to specifically silence extinction engram neurons and fiber photometry to observe the change of Ca^{2+} signals from fear engram neurons. To silence hM4Di-expressing neurons allocating

extinction memory, the mice were systemically administered CNO or vehicle 1 hr before testing. Besides optogenetic memory allocation, we used a robust activity marking system (RAM) to label active neuronal ensembles (Sorensen, 2016). This approach enables fear and extinction engram to be tagged in the same animals. We found that the inhibition of extinction engram causes the mice to show increased freezing behavior, raising Ca^{2+} signals from fear engram neurons. Lastly, we tested if extinction engram is changeable to fear engram. For this experiment, we used the viruses having 'Cre-off' system. After extinction, we tried to allocate new fear memory to extinction engram neurons, optogenetically stimulating them. We found that extinction engram could be overwritten by another fear training, and the extinction engram becomes fear engram. Together, these findings begin to help us understand the fate of an engram (fear & extinction) once formed.

Disclosures: S. Park: None. **J. Jung:** None. **P.W. Frankland:** None. **S.A. Josselyn:** None.

Poster

144. Neurobiology of Fear

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 144.13

Topic: G.01. Fear and Aversive Learning and Memory

Support: China's national key R & D plan 2018YFA0701400
National Natural Science Foundation of China U20A20221
Key R & D plan of Zhejiang Province 2020C03004

Title: Revealing brain-wide connections of nucleus CE in primate amgdala using 7T fMRI and infrared neural stimulation

Authors: *L. LI[1,2], A. PING[3], A. WANG ROE[1,4,2];
[1]Dept. of Neurosurg. of the Second Affiliated Hospital, Interdisciplinary Inst. of Neurosci. and Technology, Zhejiang Univ., HangZhou, China; [2]Key Lab. for Biomed. Engin. of Ministry of Education, Zhejiang Univ., HangZhou, China; [3]Dept. of Neurosurgery, The Second Affiliated Hosp. of Zhejiang Univ. Sch. of Med., HangZhou, China; [4]MOE Frontier Sci. Ctr. for Brain Sci. and Brain-machine Integration, Sch. of Brain Sci. and Brain Medicine, Zhejiang Univ., HangZhou, China

Abstract: Objective The amygdala is a core nucleus of the limbic system and is one of the most highly connected structures in the brain. It is comprised of multiple subnuclei, including the basal, lateral, and central (CE) nuclei. Here, we focus on CE, a nucleus believed to be heavily related to physiological aspects of limbic function. Although multiple anatomical studies and resting state MRI studies have revealed connections of CE, the underlying functional circuits of different loci within CE are not well understood. We address this question using a novel mapping method called INS-fMRI, in which infrared neural stimulation of submillimeter loci in the brain elicits focal responses at connected sites, thereby revealing functional mesoscale networks at

brainwide scale. **Methods** In two anesthetized macaque monkeys, 200µm optical fibers were precisely targeted to CE and compared with results from stimulation of other subnuclei of the amygdala (Shi et al 2021Neuroimage). During delivery of pulsed 1875nm laser stimulation, high-resolution functional MRI images of the brains were acquired on a 7T MRI. Identification of functionally connected sites was determined by correlation with GLM model. **Results** Based on 87 stimulation sites, 15 of which were in CE, and 329 stimulation runs, we found activated sites in the brain were highly specific, focal, and sparse in number, a finding consistent with our previous findings from other cortical and subcortical sites. Stimulation of each site in CE activated a brainwide set of specific loci, which included sensory and cognitive cortical areas, but were more heavily linked with lociin brainstem and hypothalamus reflecting physiological limbic response. The specificity of activation nodes suggested single sites in CE are related to circuits involved in behaviors such as food acquisition, social behavior, and navigation. **Conclusion** Using 7T-fMRI and INS, our results suggest that CE comprises distinct mesoscale nodes which are access points to highly integrative (linking sensory, motor, cognitive, limbic nodes) networks. Our data offers unique functional understanding of how brainwide networks achieve behavioral specificity.

Disclosures: L. Li: None. **A. Ping:** None. **A. Wang Roe:** None.

Poster

144. Neurobiology of Fear

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 144.14

Topic: G.01. Fear and Aversive Learning and Memory

Support: ERC
SNSF
Novartis
Marie Curie
EMBO

Title: Learning-induced immediate-early gene expression in the amygdala

Authors: *K. M. HAGIHARA, N. KARALIS, A. LÜTHI;
Friedrich Miescher Inst., Basel, Switzerland

Abstract: Experience-dependent neuronal plasticity underlies learning and memory. The expression of activity-dependent immediate-early genes (IEGs) is believed to be a consequence of neuronal activity during learning, connecting the gap between the experience and the molecular machinery of the neurons underlying the formation of a stable memory (Yap and Greenberg, 2018). A recent line of research, using c-fos promoter-driven expression of optogenetic effectors, suggests that neuronal subpopulations activated during learning contribute to subsequent memory recall (Liu et al., 2012; Garner et al., 2012), thus supporting the concept

of stable memory engrams (Semon, 1921; Hebb, 1949; Josselyn and Tonegawa, 2020). However, to what extent IEG-expression induced by learning reflects neuronal activity during learning is not known. Indeed, direct electrophysiological recordings from Fos-positive and Fos-negative neurons in the hippocampal CA1 revealed that although Fos-positive neurons were more bursty, the relationship between mean neuronal firing rates and subsequent Fos expression was weak (Tanaka et al., 2018). Furthermore, other IEGs than Fos are also thought to play distinct roles in neuronal plasticity (Minatohara et al.,2015; Yap and Greenberg, 2018; Tyssowski and Gray, 2019; Sun et al., 2020). However, whether distinct IEGs are differentially expressed in response to learning-associated neuronal activity patterns in vivo is not known.
In the current study, we established a novel opto-physiological method that enabled us to assess neuronal activity in freely behaving mice engaging in classical auditory fear conditioning and to correlate activity during learning and retrieval with learning-induced immediate-early gene expression in basolateral amygdala neurons. Whereas Fos and Arc were expressed in subpopulations exhibiting distinct activity patterns during learning, the vast majority of Fos and Arc-expressing neurons were not preferentially activated during memory retrieval, raising questions regarding the interpretation of previous engram reactivation studies. To understand the mechanism underlying artificially induced memory retrieval, we performed electrophysiological recording of neuronal ensembles, while stimulating the IEG-expressing neurons. Based on these observations, we propose a novel perspective on the role of learning-induced immediate-early gene expression.

Disclosures: **K.M. Hagihara:** None. **N. Karalis:** None. **A. Lüthi:** None.

Poster

144. Neurobiology of Fear

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 144.15

Title: WITHDRAWN

Poster

144. Neurobiology of Fear

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 144.16

Topic: G.01. Fear and Aversive Learning and Memory

Support: NIH R00MH123673

Title: Accumbens Acetylcholine Release is Required for Cue-Dependent Aversive Learning

Authors: A. BELILOS[1], C. SANDERS[1], A. SENGUPTA[1], G. SCHOENBAUM[1], ***T. FRANCIS**[2];
[1]Natl. Inst. on Drug Abuse, Baltimore, MD; [2]Drug Discovery and Biomed. Sci., Univ. of South Carolina, Columbia, SC

Abstract: The Nucleus Accumbens (NAc) functions as a brain hub for processing motivational information that dictate response to both rewarding and aversive stimuli. How this region converts salient environmental information to learned, motivated response is not well known. Highly salient, aversive stimuli promote release of neuromodulators, such as acetylcholine, which may contribute to this learning. To test the requirement of NAc acetylcholine in associative learning and response, we subjected mice to a Pavlovian fear conditioning paradigm to promote the association of a white noise cue to an aversive foot shock. Using the *in vivo* optical acetylcholine sensor GRAB-Ach3.0, we found acetylcholine release scaled with foot shock intensity in the absence of cues, suggesting cholinergic interneurons (ChI) are important for associating strength of salient aversive events with outcomes. The neuropeptide substance P is released from NAc dopamine 1 (D1) receptor medium spiny neurons (MSNs) following salient stimuli. We found D1-MSNs were activated by aversive foot shock, released substance P, and caused a phase-dependent increase in *in vivo* extracellular acetylcholine from ChIs. Additionally, activation of substance P receptors on ChIs during conditioning was required for enhanced acetylcholine release and cue-dependent recall. It was also found acetylcholine release was predictive of the shock during repeated conditioning trials as well as the to the cue or absence of shock during recall. These results suggest acetylcholine release by substance P is required for scaling aversive learning. Substance P promotes excitatory, long-term potentiation selectively on dopamine 2 (D2) receptor MSNs via muscarinic signaling. Signatures of substance P long-term potentiation were observed on NAc D2-MSNs following aversive learning which required substance P receptor and muscarinic receptor signaling. Additionally, we found cell-type specific MSN activity in response to conditioned cues which optogenetic inhibition was able to suppress or abolish. Overall, we found associative aversive learning requires NAc release of substance P on cholinergic neurons, release of acetylcholine from ChIs, and plasticity and signaling on D2-MSNs which convey the associative stimulus. This work unveils a role for the NAc acetylcholine in encoding fundamental aversive learning mechanisms and has broad implications for aberrant salience processing observed in anxiety and mood disorders such as post-traumatic stress disorder and behavioral depression.

Disclosures: A. Belilos: None. **C. Sanders:** None. **A. Sengupta:** None. **G. Schoenbaum:** None. **T. Francis:** None.

Poster

144. Neurobiology of Fear

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 144.17

Topic: G.01. Fear and Aversive Learning and Memory

Support: National Science Centre, PRELUDIUM 2019/33/N/NZ4/03011

Title: How do midbrain dopaminergic neurons code aversion? It depends··· on the brain state

Authors: *G. IZOWIT[1], M. MARZEC[1], M. WALCZAK[1], G. DRWIęGA[1], W. SOLECKI[2], T. BŁASIAK[1];
[1]Dept. of Neurophysiol. and Chronobiology, [2]Dept. of Neurobio. and Neuropsychology, Jagiellonian Univ. in Krakow, Krakow, Poland

Abstract: Dopaminergic neurons (DA) of the ventral tegmental area (VTA) and substantia nigra pars compacta (SNc) constitute the base of the reward and motivation system in the mammalian brain. Among many functions, they are involved in generation of motivational drive elicited by incentive salience of perceived internal and external stimuli. Currently, DA neurons in VTA&SNc are divided into two populations based on their responses to aversive stimuli (AS): value and salience coding. Value-coding DA neurons are thought to mark a negative value of AS by decreasing their level of activity in response to it, while salience-coding DA neurons increase their activity during AS application, coding in this manner the importance of an event. Given that both the level and pattern of VTA&SNc DA neurons activity depend on alternating brain states under urethane anesthesia, we wanted to check whether their responses to AS are also brain state dependent. In the course of this study, the second question was raised: How do lateral habenula neurons (LHb), which are one of the most important VTA&SNc inputs related to aversion coding, respond to AS during different brain states under urethane anesthesia. Firstly, we carried out *in vivo* extracellular recordings of single midbrain DA neurons combined with optotagging and recorded their responses to electrical footshocks from urethane-anaesthetized rats. Secondly, we recorded activity and responses to AS of LHb neurons using Multi-Electrode Arrays. Consistently with the literature, we observed two neuronal subpopulations of both VTA&SNc and LHb that responded to AS by decreasing or increasing their activity. However, we also recorded previously undescribed populations of VTA&SNc and LHb neurons that are characterized by dynamic changes in the type of response to AS between low theta frequency and slow wave brain states under urethane anesthesia. The majority of both VTA&SNc and LHb neurons that responded to AS in a brain state-dependent manner were inhibited by the stimulus during cortical activation (low-theta frequencies) but changed their response into excitatory with the appearance of slow wave activity. This study sheds new light on the interplay of LHb-VTA&SNc in AS-coding as well as influence that the general state of the brain may exert on the processing of aversion. The existence of neuronal populations' ability to switch between different types of response to environmental stimuli depending on behavioral states may open a new chapter of a scientific discussion about how information received and sent by certain neurons may be coded, processed, and modulated.

Disclosures: G. Izowit: None. **M. Marzec:** None. **M. Walczak:** None. **G. Drwięga:** None. **W. Solecki:** None. **T. Błasiak:** None.

Poster

144. Neurobiology of Fear

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 144.18

Topic: G.01. Fear and Aversive Learning and Memory

Support: NIMH IRP 1ZIAMH002950

Title: A thalamo-striatal circuit promotes the learning of active avoidance

Authors: J. MA[1], ***E. E. MACDONALD**[2], M. A. PENZO[3];
[1]Natl. Inst. Of Mental Health, Natl. Inst., Natl. Inst. Of Mental Health, Natl. Inst., Bethesda, MD;
[3]Natl. Inst. of Mental Hlth., [2]Natl. Inst. of Mental Hlth., Bethesda, MD

Abstract: Defensive behaviors vary as a function of the spatiotemporal distance of threats. For example, in rodents, imminent threats can trigger defensive reactions like freezing and flight, whereas more distal threats engage other defensive strategies including active avoidance behavior. Surprisingly, while the neural mechanisms that underlie defensive reactions like freezing are widely described thanks to decades of research employing Pavlovian conditioning paradigms, the mechanisms that mediate the learning and expression of active avoidance remain largely unknown. We recently reported that the posterior paraventricular thalamus (pPVT) drives the expression of active avoidance via projections to the nucleus accumbens (NAc) (pPVT-NAc). Here, we expand on these observations by demonstrating that the pPVT guides avoidance learning by modulating safety-related dopamine release in the NAc shell (NAcSh). First, using fiber photometry we found that the activity of pPVT-NAc projections is increased during the safety period after both successful avoidance responses and escape from active threats. Importantly, optogenetic silencing of these thalamo-striatal projections during the safety period attenuated active avoidance learning. Next, using a combination of fiber photometry of the genetically encoded dopamine sensor dLight with optogenetic manipulations of thalamic afferents, we found that activation of pPVT-NAc projections is required for safety-related dopamine release in the NAcSh. Notably, optogenetic activation of the pPVT-NAc pathway promoted dopamine release in the NAcSh of trained subjects. Overall, our results highlight that the pPVT-NAc pathway is critical for the learning of active avoidance likely by promoting the reinforcing actions of dopamine release during the safety period.

Disclosures: J. Ma: None. **E.E. Macdonald:** None. **M.A. Penzo:** None.

Poster

144. Neurobiology of Fear

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 144.19

Topic: G.01. Fear and Aversive Learning and Memory

Support: NIH MH122023
NSF OAC-1730655

Title: Computational tutorials to illustrate fear learning in the amygdala

Authors: *G. GLICKERT[1], S. NAIR[2], S. JOHNSON[3], J. VELASQUEZ[4], I. BANKS[1], S. S. NAIR[1];
[1]Electrical & Computer Engin., Univ. of Missouri, Columbia, MO; [2]Med. student, AUC Sch. of Med., St. Maartens, Sint Maartin; [3]Mathematics, Arizona State Univ., Tempe, AZ; [4]Biol., High Point Univ., High Point, NC

Abstract: Computational tutorials to illustrate fear learning in the amygdala
Greg Glickert[1], Sachin Nair[2], Sarah Johnson[3], Julia Velasquez[4], Isabel Banks[1], Satish S. Nair[11]Department of Electrical & Computer Engineering, University of Missouri, Columbia[2]Medical student, Psychiatry, AUC School of Medicine, St. Maartens[3]Department of Mathematics, Arizona State University, Tempe[4]Department of Biology, High Point University, North Carolina
Computational neuroscience is increasingly being used as a tool to help reverse engineer brain circuits. To illustrate reverse engineering concepts, our prior work had developed six generic computational hands-on tutorials using the Google Colab environment as freely available notebook tutorials that can be run on any browser without the need for install. The series of six tutorials explain neuroscience fundamentals in the functioning of both single neurons, and small networks with interactive controls that allow students to work with the simulations with no prior programming experience.
We extend this development by considering a specific region of the brain, the amygdala, and illustrate the role of such tutorials in reverse engineering the mammalian fear circuit at the cellular/circuit level using an example of fear learning in rodents. This follow-up series begins with a simple activity of "sketching one's own fear circuit" to illustrate the neurons, brain regions, and pathways involved in fear learning. The tone and shock pathway are then explained, with simple models permitting the user, for instance, to increase or decrease the firing rate of cochlear neurons to see its effect on other neurons in the tone pathway. The other concepts explained sequentially include disinhibition, and Hebbian plasticity using the calcium learning rule. The tutorial series culminates in a 12-cell model of the amygdala that forms a 'test-bed' to illustrate rodent auditory fear conditioning using the Pavlovian tone-shock protocol. The user can adjust the parameters online and almost immediately see its effect on the outputs, providing an appreciation of the neuronal correlates of such conditioning. The tutorial set we present is suitable for instruction to undergraduates and graduate students in several disciplines including biology, neuroscience, biomedical engineering, electrical engineering, and the medical school. Furthermore, we believe such tutorials could also be integrated into the high school curriculum.
This research was supported in part by grants NIH MH122023 and NSF OAC-1730655 to SSN – to be included separately.
1

Disclosures: G. Glickert: None. **S. Nair:** None. **S. Johnson:** None. **J. Velasquez:** None. **I. Banks:** None. **S.S. Nair:** None.

Poster

144. Neurobiology of Fear

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 144.20

Topic: G.01. Fear and Aversive Learning and Memory

Support: NIH (M.J.S.)
NSF NeuroNex(M.J.S.)

Title: *In Vivo* Voltage Imaging Reveals Dopaminergic Signaling That Integrates Innate and Learned Valences to Regulate Memory Dynamics in Drosophila Melanogaster

Authors: *C. HUANG[1], J. LUO[2], S. WOO[3], L. ROITMAN[3], J. LI[4], V. A. PIERIBONE[6], M. KANNAN[7], G. VASAN[7], M. J. SCHNITZER[5];
[1]James Clark Center; Dept. of Biol., [2]James Clark Center; Howard Hughes Med. Inst., [3]James Clark Ctr., [4]Howard Hughes Med. Institute; CNC Program, [5]Dept. of Biology; Dept. of Applied Physics; Howard Hughes Med. Inst., Stanford Univ., Stanford, CA; [6]Yale Univ., [7]Dept. of Cell. and Mol. Physiol., Yale Univ., New Haven, CT

Abstract: When making decisions, animals need to use both innate and learned valence information to account for sensory cues that have been reliable across evolution while also retaining the flexibility to adapt to new environments. In the brains of multiple species, innate and learned sensory valence signals are initially encoded by distinct neural populations but then reconverge in downstream brain structures that guide behavioral choices. However, it remains unknown whether and how innate sensory valence cues shape the acquisition of learned valence information. To study the interactions between innate and learned processes, we focused on dopamine-dependent learning in the mushroom body region of *Drosophila*, a parallel recurrent architecture with multiple learning units working in parallel but also sharing interconnections. Using time-lapse, *in vivo* optical voltage imaging to record neural spiking with millisecond-resolution across days, we show that direct interactions between innate and learned sensory valence signals jointly regulate memory formation and expression via modulation of dopamine teaching signals. Specifically, we found that valence information about innate sensory cues (e.g., punishment, reward, and odor cues) directly shapes the spiking of PPL1-dopamine neurons (PPL1-DANs) in a bidirectional manner. Associative conditioning modulates these neural representations in a way that combines innate and learned valence information and allows the PPL1-DANs to regulate learning efficiency in their downstream targets, mushroom body output neurons (MBONs). Two specific dopamine neurons and their corresponding mushroom body learning units control short-term memory formation, whereas spiking changes in other two PPL1-DANs that occur after repeated conditioning promote long-lasting memories. A computational model constrained by the mushroom body connectome and our spiking data with over 1 million spikes from over 500 flies explains how dopaminergic signaling integrates innate and learned valence data to regulate memory storage and extinction dynamically. The model yields non-intuitive predictions regarding the effects of different training protocols, which our experiments confirm. Overall, the mushroom body achieves flexible learning through dopamine-mediated integration of innate and learned valences within parallel sets of DAN/MBON learning units that share feedback interconnections. This hybrid mechanism may be a general means by which ecologically relevant information regulates learning and memory in other species and brain structures relying on dopaminergic signaling, including the vertebrate basal ganglia.

Disclosures: **C. Huang:** None. **J. Luo:** None. **S. Woo:** None. **L. Roitman:** None. **J. Li:** None. **V.A. Pieribone:** None. **M. Kannan:** None. **G. Vasan:** None. **M.J. Schnitzer:** None.

Poster

144. Neurobiology of Fear

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 144.21

Topic: G.01. Fear and Aversive Learning and Memory

Support: NIH 5R01MH106617
NARSAD /BBRF

Title: Prefrontal network neurodynamics controls fear modulation

Authors: *J. PASTORE[1], J. MAYER[1], J. STEINHAUSER[1], K. SHULER[1], J. SPEIGEL, III[1], T. BAILEY[1], V. PAPALEXAKIS[2], M. CHROBAK[2], E. KORZUS[1];
[1]Psychology, [2]Computer Sci. & Engin., Univ. of California Riverside, Riverside, CA

Abstract: The goal of the proposed studies is to identify brain dynamics that underlie safety learning. Fear behavior is regulated by the medial prefrontal cortex (mPFC) via fear excitation and inhibition, which may be due to complex connectivity within the hippocampus-amygdala-prefrontal circuit. Real-time recordings from a large neuronal population acquired from the prefrontal cortex using head-mounted miniature microscopes during learning on a fear discrimination task revealed distinct prefrontal neuronal assemblies, which show safety learning-triggered quantitative changes. Probabilistic models are used to determine the conditional dependence of assemblies' activation patterns that reflect rapid prefrontal network dynamics underlying emotional states. To evaluate large-scale circuit dynamics associated with fear discrimination learning, the calcium-sensitive fluorescent protein GCaMP6f is expressed in the prelimbic subdivision (PL) of the mPFC followed by an assessment of real-time prefrontal network changes in response to dangerous and safe context stimuli across the behavioral testing. An unsupervised tensor decomposition analysis detected distinctive neuronal populations involved in network learning across the temporal component of the behavioral sessions and across multiple days of stimuli (context) presentation. To better understand the overall network dynamics, population coding, and predictive properties of neural interactions, we constructed a novel graph-theory-based computational model using the spike data of the calcium traces. Sorting of behavioral states based on network dynamics' basic properties and attributes isolated parameters critical for describing PL circuit state shifts that reflect emotional states and develop a mechanistic model of the temporal structure of multiple assemblies' state shifts associated with safety learning. The graph-theory computational model revealed discrete alteration of global parameters of the large-scale network underlying safety learning and local neuronal parameters that explain how the network relays the neural information-theoretic measure of predictive behavior. Understanding neural mechanisms underlying fear modulation during fear

discrimination learning is clinically relevant as fear memory overgeneralization is a hallmark of phobias, PTSD, and generalized anxiety disorder.

Disclosures: **J. Pastore:** None. **J. Mayer:** None. **J. Steinhauser:** None. **K. Shuler:** None. **J. Speigel:** None. **T. Bailey:** None. **V. Papalexakis:** None. **M. Chrobak:** None. **E. Korzus:** None.

Poster

144. Neurobiology of Fear

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 144.22

Topic: G.01. Fear and Aversive Learning and Memory

Title: Decoding trauma-induced neural alterations in frontostriatal fear processing

Authors: *L. ISLAMI[1], M. EGGL[2], T. TCHUMATCHENKO[2], B. LUTZ[1];
[1]Leibniz Inst. for Resilience Res., Mainz, Germany; [2]Univ. Med. Ctr. of the Johannes Gutenberg-University Mainz, Mainz, Germany

Abstract: After exposure to a traumatic event, susceptible individuals can develop post-traumatic stress disorder (PTSD), a mental disorder characterized by intrusive re-experiencing of the fearful event. In the process, patients exhibit severe long-term impairments in cortical and subcortical brain regions involved in memory, emotion regulation and self-related information processing leading to impaired fear regulation and safety learning as well as altered cognition, tasks mainly coded by the frontostriatal network. However, trauma-induced long-term alterations in the neural computation of susceptible individuals in the prelimbic part of the ventromedial prefrontal cortex (PL) and nucleus accumbens (NAc) are poorly understood. We used a single-trauma model in male mice to induce long-term behavioural changes. Based on the freezing behaviour during trauma reminders we classified individuals into subgroups with resilient and susceptible phenotypes. Then, mice underwent a cued fear conditioning paradigm with two acoustic conditioned stimuli to observe discriminative safety learning and alterations in cognition. Along with the longitudinal behavioural analysis, we performed in-vivo calcium imaging in over 60 freely moving male mice, aiming at understanding the impact of trauma exposure on neural computation in NAc and PL during the emergence of trauma-susceptible and trauma-resilient phenotype. Trauma-induced phenotype classification showed that the susceptible mice have impaired safety learning and negative alterations in cognition during the discriminative conditioning paradigm compared to resilient mice. Our in-vivo calcium imaging data show that individuals with a PTSD-like phenotype have substantial differences in neural coding in PL and NAc neurons exclusively initiated by a combination of trauma exposure with trauma reminders and one month incubation period. Furthermore, we examined the population dynamics during fear consolidation, extinction, and renewal and identified variance in neuronal subpopulations driving different behaviour clusters in both phenotypes. Together, using a clinical translatable rodent model of PTSD, our work demonstrates the importance of frontostriatal brain regions during PTSD development, impaired threat regulation and safety learning.

Disclosures: **L. Islami:** None. **M. Eggl:** None. **T. Tchumatchenko:** None. **B. Lutz:** None.

Poster

144. Neurobiology of Fear

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 144.23

Topic: G.01. Fear and Aversive Learning and Memory

Title: Temporal dynamics of neuronal excitability in the lateral amygdala mediates allocation to an engram supporting conditioned fear memory

Authors: *A. HOORN[1,2], S. LESUIS[1], A. RASHID[1], P. FRANKLAND[1,2,3,4], S. JOSSELYN[1,2,3,4];
[1]Neurosciences & Mental Hlth., The Hosp. for Sick Children (SickKids), Toronto, ON, Canada; [2]Physiol., [3]Psychology, [4]Inst. of Med. Sci., Univ. of Toronto, Toronto, ON, Canada

Abstract: Memories are encoded by ensembles of neurons (engrams) that are active during learning. Neurons important in an engram (engram cells) are sparsely distributed across the brain. Within a given brain region, eligible neurons compete for allocation to an engram and neurons with increased excitability at the time of training are biased to be allocated to an engram. Previous findings show that neurons with increased excitability during training also have increased excitability for ~6 h. Because of this, two separate but similar training episodes within a 6 h time period tend to be co-allocated to a similar population of neurons and remembered together. Here, we examined the temporal dynamics of neuronal excitability important for allocation to an engram. We focused on the lateral amygdala (LA) and cued fear memory. We expressed both an excitatory and inhibitory opsin in the same sparse, random subset of LA neurons. At different times before fear conditioning, we optically activated this sparse subset of neurons to allocate them to the engram. To examine whether these neurons were indeed critical components of the engram, we tested mice both in the absence of light and with optical stimulation to inhibit this same population of neurons. We find that optogenetic stimulation of neurons up to 6 h, but not 12 h or 24 h, before training biases their allocation to the engram. These findings indicate that excitability in the LA is temporally defined and plays a critical role in neuronal selection to a fear engram.

Disclosures: **A. Hoorn:** None. **S. Lesuis:** None. **A. Rashid:** None. **P. Frankland:** None. **S. Josselyn:** None.

Poster

144. Neurobiology of Fear

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 144.24

Topic: G.01. Fear and Aversive Learning and Memory

Support: Flag-era Project HA-ction
Fondazione CR Firenze
EU Horizon Europe grant 945539

Title: A resource to decipher brain circuits underlying aversive memory

Authors: *A. FRANCESCHINI[1], C. CHECCUCCI[2], I. COSTANTINI[3], G. MAZZAMUTO[4], F. S. PAVONE[5], L. SILVESTRI[6];
[1]Univ. of Florence, Univ. of Florence, Sesto Fiorentino, Italy; [2]Dept. of Engin., [3]Dept. of Biol., Univ. of Florence, Florence, Italy; [4]INO - CNR, LENS, INO - CNR, LENS, Sesto Fiorentino, Italy; [5]Univ. Florence, Univ. Florence, Sesto Fiorentino (FI), Italy; [6]European Lab. For Non-Linear Spectroscopy, European Lab. For Non-Linear Spectroscopy, Sesto Fiorentino, Italy

Abstract: The neuronal and molecular mechanisms underlying behavioural responses triggered by fear have received wide interest now, especially with the surge of fear-related disorders associated with the recent Covid-19 pandemic. Fear responses are functionally adaptive behaviours that are strengthened as memories. Indeed, knowing fear circuitry could be the turning point for the comprehension of this emotion and its pathological states, even addressing potential treatments. Therefore, how to tackle the problem of memory? Understanding memory dynamics presents fundamental technological challenges and calls for the development of new tools and methods able to analyze the entire brain with single-neuron resolution and cell-type specificity. In this context, we developed a pipeline for mapping neuronal activation at micron resolution, combining transgenic approach, clearing protocol, high-resolution light-sheet microscopy, and automated 3D image analysis. This method allowed to visually capture the engram of aversive memory, visualizing all activated neurons of a specific phase of memory, in a sort of quantitative snapshot photo. The combination of high-resolution imaging and 3D analysis for processing sub-cellular information became the key point of this pipeline, enabling robust quantitative analysis of the whole brain.This pipeline was validated using a classical behavioural paradigm, step-through passive inhibitory avoidance, to analyse neuronal activation patterns across the entire brain of male and female mice, at selected time points. This approach highlighted a strong sexual dimorphism, during fear learning and recall, which was not evident from the behavioural task. Further, it identified brain regions whose degree of activity correlated to specific behavioural features. *The combination of behavioural, transgenic, optical, and computational methods presented here represents an important tool to disentangle the neuronal pathways involved in fear memories, paving the way to the development of more precise therapeutic strategies.*

Disclosures: A. Franceschini: None. **C. Checcucci:** None. **I. Costantini:** None. **G. Mazzamuto:** None. **F.S. Pavone:** None. **L. Silvestri:** None.

Poster

144. Neurobiology of Fear

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 144.25

Topic: G.01. Fear and Aversive Learning and Memory

Support: Center on Compulsive Behaviors Fellowship

Title: Paradoxical response of medial septal GAD2 GABAergic neurons to rewarding and aversive stimuli

Authors: *C. B. CALVA, J. COUDRIET, S. IKEMOTO;
Natl. Inst. on Drug Abuse, Baltimore, MD

Abstract: It is fundamental for humans and animals to seek rewards and safety from threats. To begin understanding neural mechanisms for such processes, we employed intracranial self-stimulation (ICSS), a model procedure for reward-seeking behavior, using optogenetic manipulations. In particular, we examined the roles of medial septal GABAergic (MS GABA) neurons using vGAT-Cre and GAD2-Cre mice. Mice quickly learned to stimulate MS GAD2 neurons (n=6), but not vGAT neurons (n=6). Next, we examined how these neuronal populations respond during appetitive and aversive contexts. AAV9-syn-FLEX-jGCaMP7f-WPRE was injected into the MS, and a probe was implanted in vGAT- and GAD2-Cre mice for fiber photometry. We then performed Pavlovian conditioning procedures with three different tones paired with a 100%, 50%, or 0% chance of a water reward or foot shock. MS vGAT neurons displayed heterogenous responses between mice (n= 6): vGAT neurons did not consistently respond to water rewards or cues predicting water rewards. By contrast, both certain and uncertain cues and water rewards decreased the activity of MS GAD2 neurons (n=4). During the shock procedure, MS vGAT neurons increased activity in response to foot shock, but not shock-paired tones, while MS GAD2 neurons displayed ramping activity during shock-paired tones and increased activity in response to shock. In sum, the results suggest that while vGAT is expressed in functionally heterogenous populations of MS GABA neurons, GAD2 is expressed in relatively homogenous MS GABA neurons. Concerning MS GAD2 neurons, we obtained paradoxical results: First, we found that MS GAD2 neurons are involved in reward-seeking behavior as indicated by ICSS. Second, MS GAD2 neurons display decreased activity to rewards and cues predicting rewards. Third, MS GAD2 neurons increased activity in response to punishment and cues predicting punishment. We are currently examining our hypothesis that MS GAD2 neurons play a role in seeking for safety from threats, but not seeking for classical rewards.

Disclosures: **C.B. Calva:** None. **J. Coudriet:** None. **S. Ikemoto:** None.

Poster

144. Neurobiology of Fear

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 144.26

Topic: G.01. Fear and Aversive Learning and Memory

Support: Korea (NRF) 2018R1A3B1052079

Title: Dopaminergic transmission and neuronal activity of the posterior basolateral amygdala are necessary for active avoidance learning

Authors: *J. PYO, S. LEE, S. CHOI, J. KIM;
POSTECH, Pohang-si, Korea, Republic of

Abstract: Over the decades, research has shown that the basolateral amygdala is necessary for threat memory and defensive behavior. Most studies focused on passive freezing behavior in an inescapable situation. However, in reality, animals also can actively avoid when they predict near harmfulness. To reveal neuronal circuits that switch two different defensive behavior, freezing and avoidance, we adopt the auditory two-way active avoidance paradigm with pharmacological treatment, fiber photometry, viral tracing and chemogenetics. Here we show the dopamine transient in the posterior basolateral amygdala (pBLA) and the activity of the $pBLA^{Ppp1r1b+}$ neuron are necessary for avoidance learning.

Disclosures: J. Pyo: None. **S. Lee:** None. **S. Choi:** None. **J. Kim:** None.

Poster

144. Neurobiology of Fear

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 144.27

Topic: G.01. Fear and Aversive Learning and Memory

Title: Hippocampal norepinephrine and dopamine dynamics during a test of context-dependent memory after partial and complete disruption of norepinephrine signaling

Authors: *L. R. WILSON[1], N. W. PLUMMER[1], I. Y. EVSYUKOVA[1], C. L. BAIRD[1], D. PATINO[1], K. G. SMITH[1], N. R. SCIOLINO[2], J. D. CUSHMAN[1], P. JENSEN[1];
[1]Neurobio. Lab., Natl. Inst. of Envrn. Hlth. Sci., Research Triangle Park, NC; [2]Dept. of Physiol. and Neurobio., Univ. of Connecticut, Storrs, CT

Abstract: Norepinephrine (NE) plays an important, though poorly understood role in hippocampus-dependent contextual fear. In order to more fully investigate the role of NE, we used in-vivo fiber photometry and $GRAB^{NE}$ and $GRAB^{DA}$ sensors to examine NE and dopamine (DA) dynamics in hippocampal CA1 during contextual fear conditioning in two novel mouse models of disrupted NE signaling compared to wildtype littermate control. The first mouse model contains a dopamine beta hydroxylase hypomorphic allele resulting in approximately 50% reduction in hippocampal NE content (Dbh^{hypo}) and the second model results in the complete loss of NE content in the hippocampus ($Dbh^{LC\text{-}null}$). We found that $Dbh^{LC\text{-}null}$ mice showed impaired contextual fear retrieval at both recent (24 hours) and remote (2 weeks) time points after the

context-shock pairing. The *Dbh*^{hypo} mice showed reduced freezing compared to controls at 24 hours, but no difference at two weeks. This pattern argues that LC-NE synthesis is necessary for both recent and remote contextual fear, but partial reduction of NE synthesis specifically impacts the recent time point. In response to the shock GRABNE photometry showed a large release of NE that was completely absent in the Dbh$^{LC\text{-}null}$. Analysis of precise temporal dynamics during the recent context test showed a reduction in NE release during freezing that was not present in Dbh$^{LC\text{-}null}$. This reduction was absent at the remote test, indicating reduced hippocampal NE modulation at the remote test. GRABDA photometry showed a similar increase in DA release in response to the shock, however, DA release was elevated in Dbh^{hypo} and Dbh$^{LC\text{-}null}$ mice. We also found that DA release was decreased during freezing at both the recent and remote tests. Overall, these findings argue that intact NE release in hippocampal CA1 is critical for both recent and remote contextual fear and provide novel insights into the precise temporal dynamics of both NE and DA during freezing.

Disclosures: L.R. Wilson: None. **N.W. Plummer:** None. **I.Y. Evsyukova:** None. **C.L. Baird:** None. **D. Patino:** None. **K.G. Smith:** None. **N.R. Sciolino:** None. **J.D. Cushman:** None. **P. Jensen:** None.

Poster

144. Neurobiology of Fear

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 144.28

Topic: G.01. Fear and Aversive Learning and Memory

Support: National Institute of Mental Health (R21MH117483
University of Cincinnati College of Medicine Research Innovation/Pilot Grant
NIH T32 NS007453-18

Title: Airway inflammation and fear: the role of IL17A and subfornical organ (SFO)-prefrontal cortex (PFC) engagement

Authors: *E. ALLGIRE[1], R. AHLBRAND[3], L. MAILE[2], S. DAVIDSON[2], I. LEWKOWICH[4], R. E. MCCULLUMSMITH[5], R. SAH[1];
[1]Pharmacol. and Systems Physiol., [2]Dept. of Anesthesia, Univ. of Cincinnati, Cincinnati, OH; [3]VA, Cincinnati, OH; [4]Cincinnati Children's Hosp. Med. Ctr., Cincinnati, OH; [5]Neurosciences, Univ. of Toledo, Toledo, OH

Abstract: There is considerable interest in identifying predisposition factors that promote vulnerability to posttraumatic stress disorder (PTSD), a prevalent psychiatric condition with maladaptive fear responses that persist beyond typical trauma response. Recent studies suggest an association between PTSD and asthma. Recently we reported impaired fear extinction in mice with allergen house dust mite (HDM) induced severe (T helper 2/Th17-driven) airway inflammation (AI) but not mild/moderate (Th2-driven) asthma suggesting a role of Th17/IL17A

in fear extinction deficits. Reduced recruitment of the infralimbic cortex (IL), an extinction regulatory area, was seen in Th2/Th17 mice. Further, the subfornical organ (SFO), a region of peripheral-to-central communication, exhibited neuroimmune changes after severe AI. Coupled with our recent observations of direct SFO to IL projections, we hypothesized integration of Th17/IL17A signals with the SFO and PFC in mice with Th2/Th17 expansion. Our objective is to delve into the SFO as the interface for integration of immune signals and relay to forebrain sites regulating fear. Further, we aim to explore the direct role of IL17A on SFO as a potential mediator of these outcomes.
To achieve this, we characterized the transcriptomic and immune profiles of Th2 v Th2/Th17-driven AI and explored direct IL-17a to the SFO. We gave 3 weekly treatments of intratracheal HDM to adult male BALB/c mice with control antibody (IgG) v αC5R. We collected 1) mPFC and SFO for bulk RNAseq and Enrichr pathway analysis 2) lung, serum, SFO and mPFC for multiplex ELISA of Th1, Th2, Th17, and CC/CXC mediators. Finally, for preliminary IL-17a analysis we 3) IL17A-evoked activation of SFO neurons in FosCreERT2:Ai14 mice and 4) patch clamp electrophysiology.
Transcriptomic analysis found that, in severe AI, pathways relevant to T cells and cytokines are upregulated in the SFO. In the PFC, immune changes more specifically suggest Th17/IL17A-relevant pathways. SFO infusion of rIl17A revealed increased $cFos^{+ve}$-$tdtomato^{+ve}$ cells and preliminary studies show enhanced excitability versus baseline with action potential peak amplitude reaching significance. Collectively, these data suggest that severe airway inflammation-linked immune mediators engage the SFO to modulate PFC and fear extinction. Overall, our work provides novel mechanistic information about a "body-to-brain" pathway by which AI regulates fear-relevant pathologies (i.e., PTSD). Our work has implications beyond allergic asthma, as IL17A is elevated in other pulmonary pathologies (e.g. ARDS, COVID-19) highlighting a risk for cortical dysfunction and fear pathologies.

Disclosures: E. Allgire: None. **R. Ahlbrand:** None. **L. Maile:** None. **S. Davidson:** None. **I. Lewkowich:** None. **R.E. McCullumsmith:** None. **R. Sah:** None.

Poster

144. Neurobiology of Fear

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 144.29

Topic: G.01. Fear and Aversive Learning and Memory

Support: DFG SFB1193 Grant INST247/852-1
DFG Research Grant DU1433/4-1

Title: Dopaminergic circuits mediating fear extinction learning

Authors: X. I. SALINAS-HERNÁNDEZ, D. ZAFIRI, *S. DUVARCI;
Inst. of Neurophysiol., Goethe Univ. Frankfurt, Frankfurt, Germany

Abstract: Fear extinction is a learning process during which the repeated presentations of a stimulus that no longer predicts an aversive outcome lead to a gradual decrease in conditioned fear responses. Deficits in this form of safety learning are a hallmark of anxiety disorders and thus understanding the neural basis of fear extinction has clinical significance. To initiate extinction learning, the absence of the expected aversive outcome (unconditioned stimulus, US) must be detected and signaled to the brain regions mediating fear extinction. However, the neuronal circuits underlying such a prediction error (PE) signal that initiates extinction learning have remained largely elusive. We recently showed that a subset of dopamine (DA) neurons in the ventral tegmental area (VTA) is activated by omission of the aversive US during fear extinction, specifically during the beginning of extinction when the US omission is unexpected. Furthermore, temporally-specific optogenetic inhibition or excitation of DA neurons at the time of the US omission revealed that this signal is both necessary for, and sufficient to accelerate, normal fear extinction learning. Together, these findings demonstrated that a subset of VTA DA neurons encode a PE-like signal to drive fear extinction learning. However, the neural circuits through which this DA signal initiates extinction learning is largely unknown. The first step in addressing this question is to identify the projection target of DA neurons that encode omission of the US during fear extinction. To this end, we are currently investigating the contribution of major VTA DA projections to extinction learning. Our results show that different DA projections exhibit diverse activity patterns during fear extinction. These results provide initial insights into DA circuits underlying extinction learning.

Disclosures: X.I. Salinas-Hernández: None. **D. Zafiri:** None. **S. Duvarci:** None.

Poster

145. Neural Circuits and Encoding of Emotional Behaviors

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 145.01

Topic: G.04. Emotion

Support: NIMH Grant 1R01MH116203
SFARI Grant #388708

Title: The pontomesencephalic PACAPergic pathway mediates panic-like behavioral and somatic symptoms in mice

Authors: *S. J. KANG[1], J. KIM[2], D.-I. KIM[1], B. Z. ROBERTS[1,3], S. HAN[1];
[1]Salk Inst. for Biol. Studies, Salk Inst. for Biol. Studies, La Jolla, CA; [2]Ctr. For Cognition and Sociality/Ibs, Ctr. For Cognition and Sociality/Ibs, Daejeon, Korea, Republic of; [3]UCSD, La Jolla, CA

Abstract: Panic disorder (PD) is characterized by uncontrollable fear accompanied by somatic symptoms that distinguishes it from other anxiety disorders. Neural mechanisms underlying these unique symptoms are not completely understood. Here we report that the pituitary

adenylate cyclase-activating polypeptide (PACAP)-expressing neurons in the lateral parabrachial nucleus projecting to the dorsal raphe (DR) are critical for panic-like behavioral and physiological alterations. These neurons are activated by panicogenic stimuli, but inhibited in conditioned fear and anxiogenic conditions. Activating these neurons elicits strong defensive behaviors and rapid cardiorespiratory increase without creating aversive memory, whereas inhibiting them attenuates panic-associated symptoms. Chemogenetic or pharmacological inhibition of downstream DR PACAP receptor-expressing neurons completely abolishes panic-like symptoms, demonstrating that the pontomesencephalic PACAPergic pathway mediates panicogenesis, and provides promising therapeutic target for treating PD.

Disclosures: **S.J. Kang:** None. **J. Kim:** None. **D. Kim:** None. **B.Z. Roberts:** None. **S. Han:** None.

Poster

145. Neural Circuits and Encoding of Emotional Behaviors

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 145.02

Topic: G.04. Emotion

Support: NIH/NINDS DP1 NS116783
NIH/NIA R01 AG064051
NIH/NIBIB R01 EB030884
NIH/NIMH RF1 MH114227
IBS-R001-D1-2020-a00

Title: Hemispherically lateralized rhythmic oscillations in the cingultate-amygdala circuit drive affective empathy in the mouse

Authors: S.-W. KIM[1], ***M. KIM**[1,2], J. BAEK[1], C.-F. LATCHOUMANE[1], G. GANGADHARAN[6], Y. YOON[1], D.-S. KIM[7], Y.-S. KIM[8], J. LEE[2,3,4,5], H.-S. SHIN[1]; [1]Ctr. for Cognition and Sociality, Inst. for Basic Sci., Daejeon, Korea, Republic of; [2]Dept. of Neurol. and Neurolog. Sci., [3]Dept. of Bioengineering, [4]Dept. of Neurosurg., [5]Dept. of Electrical Engin., Stanford Univ., Stanford, CA; [6]Manipal Acad. of Higher Educ., Manipal, India; [7]Col. of Medicine, Soonchunhyang Univ., Chungcheongnam-Do, Korea, Republic of; [8]Chungnam Natl. Univ., Daejeon, Korea, Republic of

Abstract: Humans and animals can acquire fear through observing distress of others under aversive events. The behavioral assay for observational fear has established in rodents as a behavioral model for study underlying emotional contagion, a basic form of affective empathy. However, the neural process engaged at the specific moment when empathic response is triggered by socially acquired information has not yet been clearly identified. Here, we report that synchronized and lateralized 5-7 Hz neural oscillations in the right anterior cingulate cortex (rACC) and right basolateral amygdala (rBLA) are specifically and causally linked with the

emergence of observational fear responses in mice. Optogenetic inhibition experiments revealed that reciprocal projections between the rACC and rBLA are essential for observational fear, but not for fear induced by a direct foot-shock experience. Notably, 5-7 Hz oscillations in the rACC and rBLA were selectively increased at the onset of freezing in observational fear responses but not at the freezing induced by recall of a preexisting emotional association. A closed-loop disruption demonstrated that the synchronized 5-7 Hz oscillations in the rACC and rBLA are essential for observational fear responses. The increase/decrease in theta power induced by optogenetic manipulation of the hippocampal theta rhythm selectively and bi-directionally modulated observational fear. Together, these results indicate that hippocampal dependent 5-7 Hz theta oscillations in the cingulo-amygdala circuit in the right hemisphere are the selective and essential neural process that drives empathic fear, but not for freezing in general.

Disclosures: S. Kim: None. **M. Kim:** None. **J. Baek:** None. **C. Latchoumane:** None. **G. Gangadharan:** None. **Y. Yoon:** None. **D. Kim:** None. **Y. Kim:** None. **J. Lee:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); LVIS. F. Consulting Fees (e.g., advisory boards); LVIS. **H. Shin:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); SL Bigen. F. Consulting Fees (e.g., advisory boards); SL Bigen.

Poster

145. Neural Circuits and Encoding of Emotional Behaviors

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 145.03

Topic: G.04. Emotion

Support: NSERC Discovery Grant 506730

Title: Characterization of the neural machinery for escape behaviours

Authors: *Y. HONG[1], J. BANG[1], A. K. BRINK[2], J. S. DIN[3], H. CHANG[3], J. KIM[2,1];
[1]Cell and Systems Biol., [2]Psychology, [3]Univ. of Toronto, Toronto, ON, Canada

Abstract: Animals rely on fear responses to survive in natural habitats. In particular, prey species are required to respond to predatory threat through a series of innate defensive behaviours such as freezing and escaping. The anterior hypothalamic nucleus (AHN) is a brain region within the medial hypothalamic defense system which has been identified as a flight-inducing structure. However, the cell-type-specific roles of AHN neurons remain unclear. Here, we demonstrate that neurons positive for the α subunit of calcium/calmodulin-dependent protein kinase II (CaMKIIα) in the AHN mediate escape behaviours. Using fiber photometry, we found that CaMKIIα^{+} AHN neurons dynamically respond to predators. Moreover, optogenetic stimulation of these neurons induced robust defensive behaviours. Lastly, anatomical tracing experiments revealed that both GABAergic and CaMKIIα^{+} AHN neurons project to the same

topographic areas of the periaqueductal grey (PAG). Together, these results provide strong preliminary evidence that CaMKIIα^+ AHN neurons regulate escape behaviours through projections to the PAG.

Disclosures: **Y. Hong:** None. **J. Bang:** None. **A.K. Brink:** None. **J.S. Din:** None. **H. Chang:** None. **J. Kim:** None.

Poster

145. Neural Circuits and Encoding of Emotional Behaviors

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 145.04

Topic: G.04. Emotion

Support: National Health Research Institute (NHRI-EX110-10912NI)
Ministry of Science and Technology (108-2331-B-006-025-MY2)
Ministry of Science and Technology (109-2331-B-039-MY3)

Title: Vagal afferent signaling to the basolateral amygdala regulates colitis induced anxiety-like behaviors

Authors: *C.-H. CHEN[1], T.-C. TSAI[1], Y.-J. WU[4,2], K.-S. HSU[1,3];
[1]Inst. of Basic Med. Sciences, Col. of Med., [2]Inst. of Clin. Medicine, Col. of Med., [3]Dept. of Pharmacology, Col. of Med., Natl. Cheng Kung Univ., Tainan, Taiwan; [4]Dept. of Neurol., Natl. Cheng Kung Univ. Hosp., Tainan, Taiwan

Abstract: Inflammatory bowel disease (IBD) is a relapsing-remitting disorder characterized by chronic inflammation of the gastrointestinal (GI) tract. Up to 30 % of IBD patients present with comorbidity of psychiatry disorders. However, the mechanistic link between gut-to-brain communication is still elusive and thus hinders clinical treatment of comorbid psychiatry disorders. Vagus nerve is the major neural pathway for gut-to-brain communication and has been reported to regulate innate anxiety, yet the influence of vagal signals beyond the first relay of nucleus of the solitary tract is also unclear. In this study, we aimed to characterize gut-to-brain signaling and neural circuits of colitis gut via vagus nerve for the induction of anxiety-like behaviors. Dextran sodium sulfate were applied to establish colitis model in mice and anxiety-like behaviors assayed by open field, elevated plus maze and light/dark boxes. To study colitis gut vagal signaling from the gut to the brain, gastric vagotomy and saporin based lesioning of vagal afferent neurons were utilized. According to c-Fos expression and neural tracing analysis, Nucleus of solitary tract (NTS) to locus coeruleus (LC) norepinephrinergic (NE^+) projection to basal lateral amygdala (BLA) were focused as targeted brain circuit for chemogenetic manipulation. We find that interfering with vagal afferent transmission to the brain reduces colitis induced anxiety-like behaviors and by suppressing LC (NE^+ neurons) to BLA neural activity decreased the anxiety level of colitis mice. In conclusion, our results demonstrate that acute colitis leads to activation of vagal afferent signaling from the GI tract to regulate the LC-

NE system in the BLA via the NTS, which then promotes the development of anxiety. Results from this study uncover an unidentified and important neural circuit mechanism underlying the comorbid anxiety during acute DSS-induced colitis and reveal that targeting LC-NE projections to the BLA may represent a new therapeutic avenue for treating comorbid anxiety associated with IBD.

Disclosures: C. Chen: None. **T. Tsai:** None. **Y. Wu:** None. **K. Hsu:** None.

Poster

145. Neural Circuits and Encoding of Emotional Behaviors

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 145.05

Topic: G.04. Emotion

Title: Investigating the impact of acute stress on cross-frequency coupling and its relationship to endocrinological outcomes

Authors: *G. BERRETZ[1], J. PACKHEISER[2];
[1]Biopsychology, Ruhr Univ. Bochum, Bochum, Germany; [2]Social Brain Lab., Netherlands Inst. for Neurosci., Amsterdam, Netherlands

Abstract: Acute stress constitutes a strong impact on the brain and on cognitive and affective processing. On the neural level, acute stress modifies attention, memory, and executive functions; moreover, it is related to an increase in stress hormones and negative affect. Electroencephalography (EEG) is a suitable tool to investigate the influence of acute stress on brain activity non-invasively as it measures fluctuations in the excitability of neural populations as oscillations in the EEG signal. Cross-frequency coupling (CFC) between activity in the delta (1-4 Hz) and beta (14-30 Hz) frequency bands has been implicated as a potential neural correlate of stress regulation processes: frontal delta-beta CFC could reflect communication between subcortical structures involved in the generation of negative affect and frontal cortical structures associated with the regulation of said affect. To investigate the influence of acute stress on delta-beta CFC and its role in stress regulation, 50 participants underwent acute stress induction via social evaluative threat as well as a control procedure on separate days. EEG data were recorded during stress induction and control procedure. We calculated amplitude-to-amplitude (AAC) correlations and phase-to-amplitude coupling (PAC) between the delta and beta band activity at frontal (F3, F4, Fz) and parietal (P3, P4, Pz) electrodes. Non-parametric Wilcoxon signed-rank tests between mean frontal and parietal AAC during stress and control procedure revealed higher AAC during stress at parietal electrodes (p <.001). Non-parametric Wilcoxon signed-rank tests between mean frontal and parietal PAC during stress and control procedure revealed higher PAC during stress at frontal (p<.01) and parietal electrodes (p<.01) compared to the control condition. Spearman correlations between mean AAC, mean PAC, and markers of the physiological stress response (salivary cortisol and alpha-amylase) were not significant. Our results indicate that acute stress has a strong influence on cross-frequency coupling between the delta and beta bands.

However, these changes were not associated with changes in physiological stress markers, calling the validity of delta-beta CFC as a marker for stress regulation into question; rather, changes in delta-beta CFC seem to be a marker of acute stress itself.

Disclosures: G. Berretz: None. **J. Packheiser:** None.

Poster

145. Neural Circuits and Encoding of Emotional Behaviors

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 145.06

Topic: G.04. Emotion

Support: DA041482
DA047678

Title: Dynamic modulation of interpeduncular nucleus GABAergic neurons by stress controls stress-induced anxiety

Authors: *P. M. KLENOWSKI[1], R. ZHAO-SHEA[2], S. MOLAS[4], T. G. FREELS[1], A. R. TAPPER[3];
[2]Brudnick Neuropsychiatric Res. Inst., [3]Neurobio., [1]Univ. of Massachusetts Chan Med. Sch., Worcester, MA; [4]Dept. of Neurobiology, Brudnick Neuropsychiatric Res. Inst., Univ. of Massachusetts Med. Sch., Worcester, MA

Abstract: Recent work has identified a role for the medial habenulo-interpeduncular nucleus (MHb-IPN) circuit in the pathophysiology of drugs of abuse, particularly nicotine. This circuit also mediates the acute aversive effects of high nicotine doses and is a critical node for anxiety during nicotine withdrawal, a known stressor in mice. However, it is not known if the IPN is dynamically regulated by stress in vivo and if/how the IPN contributes to stress-induced behavior. To investigate the response of IPN neurons to acute stress, we expressed GCaMP into GABAergic IPN neurons and used in-vivo fiber photometry to record changes in GCaMP fluorescence during and following restraint stress, a powerful acute stressor in mice. During periods of restraint, we detected significant increases in GCaMP fluorescence from GABAergic IPN neurons, which persisted post-stress and was concomitant with heightened measures of anxiety-like behavior in the elevated plus maze and open field test. We also measured GCaMP activity from GABAergic IPN neurons during stress-induced self-grooming behavior. We observed significant reductions in IPN GABAergic during self-grooming bouts, possibly in an attempt to limit stress-activation of the IPN and minimize stress-induced anxiety. To test this hypothesis, we used optogenetics to silence IPN GABAergic neurons in restrained mice and measured stress-induced anxiety and grooming behavior. Photoinhibition of IPN GABAergic neurons significantly reduced measures of anxiety-like behavior and post-stress grooming. Taken together, our results highlight the IPN as a stress-responsive brain area that exhibits heightened activity during and following acute stress exposure, which leads to increased anxiety-like

behavior that in turn, mediates anxiolytic behavioral responses to reduce IPN GABAergic activity as a novel stress-reduction mechanism.

Disclosures: P.M. Klenowski: None. **R. Zhao-Shea:** None. **S. Molas:** None. **T.G. Freels:** None. **A.R. Tapper:** None.

Poster

145. Neural Circuits and Encoding of Emotional Behaviors

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 145.07

Topic: G.04. Emotion

Support: Clayton Foundation
NIMH R37 MH102441
NCCIH Pioneer Award DP1-AT009925
Howard Hughes Medical Institute
Salk Institute for Biological Studies
NIMH R01-MH115920
Kavli Foundation

Title: Neurotensin orchestrates valence assignment in the amygdala

Authors: *H. LI[1], P. NAMBURI[3], J. M. OLSON[4,3], M. BORIO[1], M. E. LEMIEUX[2], A. BEYELER[5,3], G. CALHOON[6,3], N. HITORA-IMAMURA[7,3], A. A. COLEY[1], A. LIBSTER[1], A. BAL[8,1], X. JIN[9,10], H. WANG[11], C. JIA[12,1], A. FELIX-ORTIZ[3], V. DE LA FUENTE[13,3], V. BARTH[3], H. KING[3], J. REVANNA[1], K. BATRA[1,12], L. KEYES[1,14], N. PADILLA COREANO[15,1], C. SICILIANO[16,3], K. M. MCCULLOUGH[17], R. WICHMANN[3,1,14], K. J. RESSLER[17], I. R. FIETE[3], F. ZHANG[10], Y. LI[11], K. M. TYE[1,14];
[2]Neurobio., [1]Salk Inst. for Biol. Studies, La Jolla, CA; [3]MIT, Cambridge, MA; [4]Psychology Dept and Neurosci. Program, Brandeis Univ., Waltham, MA; [5]Neurocentre Magendie, INSERM 1215, BORDEAUX, France; [6]Bates Col., Lewiston, ME; [7]Kumamoto Univ., Kumamoto, Japan; [8]Psychology, Johns Hopkins Univ., Baltimore, MD; [9]Scripps Inst., La Jolla, CA; [10]Broad Inst. of MIT and Harvard, Cambridge, MA; [11]Peking Univ., Beijing, China; [12]Univ. of California San Diego, La Jolla, CA; [13]Univ. de Buenos Aires, Buenos Aires, Argentina; [14]Howard Hughes Med. Inst., La Jolla, CA; [15]SNL, Univ. of Florida, GAINVESVILLE, FL; [16]Pharmacol., Vanderbilt Univ., NASHVILLE, TN; [17]Harvard Med. Sch., Belmont, MA

Abstract: The ability to associate temporally segregated information and assign positive or negative valence to environmental cues is paramount for survival. Studies have shown that different basolateral amygdala (BLA) projections are potentiated following reward or punishment learning. However, we do not yet understand how valence-specific information is routed to the BLA neurons with the appropriate downstream projections. Nor do we understand how to reconcile the subsecond timescales of synaptic plasticity with the longer timescales

separating predictive cues from their outcomes. Here, we demonstrate that neurotensin (NT) neurons in the paraventricular nucleus of the thalamus (PVT) projecting to the BLA (PVT-BLA:NT) mediate valence assignment by exerting concentration-dependent modulation in BLA during associative learning. Mice were first trained to associate distinct auditory tones with either sucrose reward or footshock punishment, and then underwent a discrimination task in which reward and punishment trials were randomly selected. We found that optogenetic activation of the PVT-BLA:NT projection promotes reward learning (*P=0.018), while PVT-BLA projection-specific *Nt* gene knockout augments punishment learning (*P=0.0396). Using genetically encoded calcium and NT sensors, we further revealed that both calcium dynamics within the PVT-BLA:NT projection and NT concentrations in the BLA are enhanced after reward learning (calcium: *P=0.0125; NT: *P=0.001) and reduced after punishment learning (calcium: *P=0.0145; NT: *P=0.0162). Finally, we showed that CRISPR-mediated knockout of the *Nt* gene in the PVT-BLA pathway blunts BLA neural dynamics and attenuates the preference to active behavioral strategies to reward and punishment predictive cues (n=683). Taken together, we have identified NT as a neuropeptide that signals valence in the BLA, and showed that NT is a critical neuromodulator that orchestrates positive and negative valence assignment in amygdala neurons by extending valence-specific plasticity to behaviorally-relevant timescales.

Disclosures: **H. Li:** None. **P. Namburi:** None. **J.M. Olson:** None. **M. Borio:** None. **M.E. Lemieux:** None. **A. Beyeler:** None. **G. Calhoon:** None. **N. Hitora-Imamura:** None. **A.A. Coley:** None. **A. Libster:** None. **A. Bal:** None. **X. Jin:** None. **H. Wang:** None. **C. Jia:** None. **A. Felix-Ortiz:** None. **V. de la Fuente:** None. **V. Barth:** None. **H. King:** None. **J. Revanna:** None. **K. Batra:** None. **L. Keyes:** None. **N. Padilla Coreano:** None. **C. Siciliano:** None. **K.M. McCullough:** None. **R. Wichmann:** None. **K.J. Ressler:** None. **I.R. Fiete:** None. **F. Zhang:** None. **Y. Li:** None. **K.M. Tye:** None.

Poster

145. Neural Circuits and Encoding of Emotional Behaviors

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 145.08

Topic: G.04. Emotion

Support: Howard Hughes Medical Institute
Salk Institute for Biological Studies
Clayton Foundation
Kavli Foundation
Dolby Family Fund
NIMH R01-MH115920
NIMH R37-MH102441

Title: Amygdalostriatal transition zone neurons encode sustained valence to direct conditioned behaviors

Authors: *F. MILLS[1], C. R. LEE[1,2], J. R. HOWE[2], H. LI[1], S. SHAO[3], M. N. KEISLER[1,4], M. E. LEMIEUX[1], R. WICHMANN[1], H. S. CHEN[5], R. R. PATEL[1], A. L. GROSS[6], F. H. TASCHBACH[1,2], K. BATRA[1,2], L. R. KEYES[1,4], M. K. BENNA[2], C. M. ROOT[2], K. M. TYE[1,2,4];
[1]Salk Inst. for Biol. Studies, La Jolla, CA; [2]Univ. of California San Diego, La Jolla, CA; [3]Beijing Univ., Beijing, China; [4]Howard Hughes Med. Inst., La Jolla, CA; [5]MIT, Cambridge, MA; [6]Wellesley Col., Wellesley, MA

Abstract: The ability to respond appropriately to stimuli that predict rewards or punishments lies at the core of evolutionary fitness, and is disrupted in a number of neuropsychiatric disease states. The amygdalostriatal transition zone (ASt) is anatomically poised to provide a shortcut between corticolimbic and basal ganglia circuitry, and mediate behavioral responses to stimuli in parallel with the amygdala. Like the amygdala, the ASt receives converging sensory input from the thalamic and cortical pathways. However, the projections of the ASt are distinct from canonical outputs of the amygdala complex, and are integrated with striatal circuits involved in action selection. Despite this intriguing circuit connectivity, the function of the ASt is almost completely unknown. Here, we characterized the transcriptomic profile of the ASt in comparison to neighboring amygdalar or striatal nuclei, and collect cellular resolution recordings of genetically-defined neurons during a valence discrimination task to interrogate the functional role of ASt circuitry. We first used single-nucleus RNA sequencing (snRNASeq) to generate a comprehensive profile of gene expression in ASt neurons, and find that the ASt is a genetically distinct from adjacent GABAergic brain regions (n=18-25 mice, >15000 cells per brain region, >50k unique molecular identifiers per cell). RNAscope labelling also showed a greater proportion of neurons expressing dopamine receptor 2 (D2+) than dopamine receptor 1 (D1+) in the ASt compared to other regions of the striatum (n=8 mice, >8 sections per group, Chi-square test, p=0.0032). Using in vivo electrophysiology we found that ASt neuron responses to a shock-predicting cue were significantly greater following fear conditioning in ‘paired group’ mice compared with ‘unpaired group’ controls (n=8 mice, 30 neurons Paired, n=5 mice, 27 neurons Unpaired, p=0.028, RM ANOVA). We also identify distinct groups of ASt neurons that encode opposing responses to cues predicting reward and punishment, including sustained responses to negative valence cues (n=9 mice, n=41 neurons). Calcium imaging data also indicates that D2+ ASt neurons specifically show increased conditioned cue responses following fear conditioning (n=3 mice, 73 neurons Paired, n=4 mice, 46 neurons Unpaired, p=0.046). Finally, optogenetic inhibition of D2+ ASt neurons causes a striking reduction in conditioned fear responses to a shock-predicting cue (43% decreased freezing, p=0.0145, paired t-test, n=8 mice NpHR, n=9 mice eYFP). Consequently, our findings show that the ASt is an overlooked and critical structure for encoding learned associations to direct motivated behaviors.

Disclosures: F. Mills: None. **C.R. Lee:** None. **J.R. Howe:** None. **H. Li:** None. **S. Shao:** None. **M.N. Keisler:** None. **M.E. Lemieux:** None. **R. Wichmann:** None. **H.S. Chen:** None. **R.R. Patel:** None. **A.L. Gross:** None. **F.H. Taschbach:** None. **K. Batra:** None. **L.R. Keyes:** None. **M.K. Benna:** None. **C.M. Root:** None. **K.M. Tye:** None.

Poster

145. Neural Circuits and Encoding of Emotional Behaviors

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 145.09

Topic: G.04. Emotion

Support: Howard Hughes Medical Institute
Salk Institute for Biological Studies
Clayton Foundation
Kavli Foundation
Dolby Family Fund
NIMH R01-MH115920
NIMH R37-MH102441

Title: Downstream targets of DRN dopamine neurons represent distinct facets of the experience of social isolation

Authors: G. A. MATTHEWS[1,2], **C. R. LEE**[1,3], M. E. LEMIEUX[1,2], E. M. BREWER[2], M. BORIO[1], R. MIRANDA[1,2,3], L. KEYES[1], E. PERONI[2], G. S. PEREIRA[2], A. LOPEZ MORAGA[2], A. PALLÉ[2], E. Y. KIMCHI[2], G. P. SCHNEIDER[1,4], F. H. TASCHBACH[1,3], M. G. CHAN[1,4], N. PADILLA-COREANO[1,2], R. WICHMANN[1,2], M. K. BENNA[3], *K. M. TYE[1,2,3,4]; [1]Salk Inst. for Biol. Studies, La Jolla, CA; [2]MIT, Cambridge, MA; [3]Univ. of California San Diego, La Jolla, CA; [4]Howard Hughes Med. Inst., La Jolla, CA

Abstract: Social isolation and perceived loneliness can lead to negative health consequences including mood disorders, shortened lifespan, cancer, and heart disease. The psychological definition of loneliness includes the three features of (1) driving a prosocial state, (2) inducing aversion and (3) being distinct from generalized anxiety. We previously demonstrated that dorsal raphe nucleus (DRN) dopamine neurons using dopamine transporter (DAT)-Cre transgenic male mice (DRNDAT) give rise to the constellation of features that comprise loneliness (Matthews et al., 2016). However, we wanted to determine whether the behavioral features were governed by the same or distinct circuits - thereby informing whether a loneliness-like state is mediated by multiple parallel circuits or a single, integrated circuit. Here, we focused on the downstream projections of DRNDAT neurons, allowing us to target this subpopulation of cells. We investigated three prominent DRNDAT downstream targets—the bed nucleus of the stria terminalis (BNST), central amygdala (CeA), and posterior basolateral amygdala (BLP)—to probe how DRNDAT photostimulation promotes different facets of ethological behaviors through these separable circuit components. Photoactivation of the DRNDAT-CeA projection promoted social behavior (n=21 mice; p=0.027) and photostimulation of the DRNDAT-BNST projection promoted exploratory behavior (n=22 mice; p=0.0298), while the DRNDAT -BLP projection supported place avoidance (n=12 mice; p=0.0455). Given that DRNDAT-CeA projections promoted social behavior, we performed calcium imaging using GCaMP7f and miniature microendoscopes during social interaction. To explore how dynamic signals from DRNDAT neurons influenced the population dynamics of the downstream CeA, we simultaneously imaged CeA neurons while intermittently activating DRNDAT input in freely-moving mice during the resident intruder assay and the 3-chamber social preference assay. We identified distinct populations of neurons that responded to social stimuli in the presence or absence of DRN DAT photostimulation (n=11 mice, n=273 CeA neurons; forming 9 clusters).

Our findings support a role for DRNDAT projections in promoting distinct features of the response to novel social stimuli-orchestrating a coordinated, flexible response through recruitment of specific downstream circuits. Uncovering the neural circuit mechanisms which govern sociability and revealing the neural representation of a loneliness-like-state are keys to understanding the fundamental need for social connection.

Disclosures: **G.A. Matthews:** None. **C.R. Lee:** None. **M.E. Lemieux:** None. **E.M. Brewer:** None. **M. Borio:** None. **R. Miranda:** None. **L. Keyes:** None. **E. Peroni:** None. **G.S. Pereira:** None. **A. Lopez Moraga:** None. **A. Pallé:** None. **E.Y. Kimchi:** None. **G.P. Schneider:** None. **F.H. Taschbach:** None. **M.G. Chan:** None. **N. Padilla-Coreano:** None. **R. Wichmann:** None. **M.K. Benna:** None. **K.M. Tye:** None.

Poster

145. Neural Circuits and Encoding of Emotional Behaviors

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 145.10

Topic: G.04. Emotion

Support: Howard Hughes Medical Institute
Salk Institute for Biological Studies
Clayton Foundation
Kavli Foundation
Dolby Family Fund
NIMH R01-MH115920
NIMH R37-MH102441

Title: Medial prefrontal cortex dynamics contribute to social homeostasis by representing social isolation

Authors: *C. R. LEE[1,2], G. P. SCHNEIDER[1,3], D. TSIN[1,2], K. BATRA[1,2], A. BAKHTI-SUROOSH[1,2], M. G. CHAN[1,3], R. WICHMANN[1], T. PEREIRA[1], K. M. TYE[1,2,3];
[1]Salk Inst. for Biol. Studies, La Jolla, CA; [2]Univ. of California San Diego, La Jolla, CA; [3]Howard Hughes Med. Inst., La Jolla, CA

Abstract: Intriguingly, divergent social behaviors emerge from different durations of social isolation, with acute isolation typically increasing prosocial behaviors and chronic isolation typically increasing antisocial behaviors (Lee et al., 2021). Previously, we found that dorsal raphe dopamine neurons mediate a loneliness-like state and innervate the medial prefrontal cortex (mPFC) (Matthews et al., 2016). We also found that the mPFC represents social rank, and that social rank predicts causal manipulations to recapitulate loneliness-like features (Matthews et al., 2016; Padilla-Coreano et al., 2022). Here, to explore how the (mPFC) encodes social information and undergoes a state change following isolation, we used *in vivo* cellular resolution calcium imaging, ultrasonic vocalization (USV) recordings, computer vision, and machine

learning tools. We designed a resident intruder task wherein adult male mice are sequentially presented with a novel juvenile male, adult male, and adult female mouse in group-housed and isolated conditions. Using neural activity from the mPFC during interaction with the juvenile, we observed robust decoding of housing status (grouped or isolated) from the neural activity of mPFC during social behavior ($p = 0.0035$, effect size 31.68% of mean, 0.618 decoding accuracy). This is in contrast to our ability to weakly decode if animals were group-housed or isolated based on central amygdala (CeA) activity ($p = 0.0054$, effect size = 12.32% of mean, 0.549 decoding accuracy). We then performed pose estimation and behavioral feature extraction using a custom pipeline based on SLEAP (Pereira et al., 2022) and unsupervised clustering for behavioral motif discovery. However, following UMAP-based dimensionality reduction, we did not find any significant differences in behavioral motifs between group-housed and isolated mice. Although we did not detect significant differences in behavioral pose tracking from computer vision, we found that 24-hrs social isolation resulted in fewer short duration and more long duration vocalizations, increasing the average call duration ($p<0.0001$, n=6 mice). Additionally, we found that 24-hrs social isolation changes the frequency distribution of USV calls, resulting in an increase of low- and mid-range frequency calls and a reduction in high frequency calls ($p<0.0001$, n=6 mice). We find that social isolation changes the motivation to seek social contact as reflected by changes in the profile of USVs, and that mPFC represents social housing conditions more robustly than the CeA. Taken together, this suggests a role for the mPFC in storing information about social homeostasis and detected social input.

Disclosures: **C.R. Lee:** None. **G.P. Schneider:** None. **D. Tsin:** None. **K. Batra:** None. **A. Bakhti-Suroosh:** None. **M.G. Chan:** None. **R. Wichmann:** None. **T. Pereira:** None. **K.M. Tye:** None.

Poster

145. Neural Circuits and Encoding of Emotional Behaviors

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 145.11

Topic: G.04. Emotion

Support: Howard Hughes Medical Institute
Salk Institute for Biological Studies
Clayton Foundation
Kavli Foundation
Dolby Family Fund
NIMH R01-MH115920
NIHM R37-MH102441

Title: Amygdala-cortical circuit determinants of social isolation-induced alcohol consumption

Authors: *R. PATEL[1], M. PATARINO[2], A. VAN HOEK[1], K. KIM[1], F. TASCHBACH[1], H. LI[3], C. LEE[5], R. MIRANDA[1], K. BATRA[4], L. KEYES[1], A. M. LIBSTER[6], R. WICHMANN[1],

M. K. BENNA[1], K. M. TYE[7];
[1]Salk Inst. for Biol. Studies, La Jolla, CA; [2]Univ. of Washington, Seattle, WA; [3]Neurosci., Salk Inst., San Diego, CA; [4]Electrical & Computer Engin., Salk Inst., La Jolla, CA; [5]Neurosci., UCSD, La Jolla, CA; [6]Neurobio., Hebrew Univ. of Jerusalem, Jerusalem, Israel; [7]Systems Neurosci. Lab., Salk Inst. for Biol. Sci., La Jolla, CA

Abstract: Although there are correlations between stress and increased alcohol consumption, as further supported by the surge in alcohol sales and use during the COVID-19 pandemic, little is known about the neurobiological mechanisms underlying these phenomena. What brain changes are induced by stressors that trigger alcohol drinking? We found that social rank predicts alcohol drinking (r^2 = 0.25; **p = 0.01; n = 26), where subordinates drink more than dominants (**p < 0.01; n = 3/group), and that social isolation further increases alcohol drinking in all mice (***p < 0.001; n = 14), while decreasing sucrose drinking (*p < 0.05; n = 6). We then found that social isolation increases neural excitability in the basolateral amygdala (BLA) (*p < 0.05; n = 13-14 cells), and stimulating BLA terminals in the medial prefrontal cortex (mPFC) is sufficient to increase consumption of alcohol (***p < 0.001; n = 6/group). To reveal how social isolation modifies BLA representations of alcohol, we used longitudinal cellular resolution calcium imaging and machine learning. We found that alcohol responsive amygdala functional clusters turnover following social isolation (n = 309 neurons/ 6 mice). To determine the impact of amygdala functional turnover on representation of alcohol, we used a generalized linear model (GLM) and found population-level amygdala dynamics was sufficient to decode alcohol verses water consumption, and social isolation increases GLM decoding performance. In contrast, social isolation decreases GLM decoding performance of sucrose verses water consumption, consistent with the diametrically opposing effects of social isolation on alcohol and sucrose consumption. To then determine how amygdala inputs can modify mPFC representations of alcohol, we combined optogenetics and imaging and found that amygdala-cortical terminal activation abolishes positive valence responses to sucrose without altering negative valence responses to shock (n = 708 neurons/ 6 mice), suggesting that the amygdala-cortical circuit induces a negative affective or loneliness-like state by inhibiting positive encoding cortical neurons which may motivate alcohol use. Together, we identified a cellular substrate of social isolation and resolved a role for the amygdala-cortical circuit in stress-induced escalated alcohol drinking.

Disclosures: R. Patel: None. **M. Patarino:** None. **A. Van Hoek:** None. **K. Kim:** None. **F. Taschbach:** None. **H. Li:** None. **C. Lee:** None. **R. Miranda:** None. **K. Batra:** None. **L. Keyes:** None. **A.M. Libster:** None. **R. Wichmann:** None. **M.K. Benna:** None. **K.M. Tye:** None.

Poster

145. Neural Circuits and Encoding of Emotional Behaviors

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 145.12

Topic: G.04. Emotion

Support: Salk Institute for Biological Studies
Howard Hughes Medical Institute
Clayton Foundation
Kavli Foundation
Dolby Family Fund
NIMH R01-MH115920
NIMH R37-MH102441

Title: Elucidating overlapping neural ensembles that encode social pain and physical pain

Authors: *C. JIA[1,2], F. ALOBOUDI[1,2], A. TRAN[1,2], K. BATRA[1,2], C. R. LEE[1,2], A. BAL[3,2], M. CHAN[2,4], R. R. PATEL[2], J. DELAHANTY[2,4], R. WICHMANN[2], L. R. KEYES[2,4], Y. LI[5], T. D. PEREIRA[2], H. LI[2], K. M. TYE[2,4,1];
[1]Univ. of California San Diego, La Jolla, CA; [2]Salk Inst. for Biol. Studies, La Jolla, CA; [3]Johns Hopkins Univ., Baltimore, MD; [4]Howard Hughes Med. Inst., La Jolla, CA; [5]Peking Univ. Sch. of Life Sci., Beijing, China

Abstract: Social pain, the emotional pain caused by aversive experiences with one's social group, can have deleterious effects on both mental and physical health. The "pain overlap theory" proposes that the experience of social pain overlaps with and modulates the physical pain experience. However, we do not know the neural substrates where social and physical pain overlap in circuitry. To address this gap, we have designed a novel Social Exclusion paradigm, in which mice are separated from their cagemates by a switchable glass divider that becomes transparent during each trial and observe their cagemates collectively consume a reward for 60 trials. Two paradigm controls include: 1) Tone Only: Mice are excluded with no mice on the other side. 2) One Mouse: Mice are excluded with one mouse on the other side. Each of the 60 trials for Social Exclusion, Tone Only, and One Mouse are separated into two categories (FOMO vs Fine) using a new supervised machine learning algorithm, AlphaClass, and k-means clustering. Fear Of Missing Out (FOMO) behavior, is operationally defined by mice engaging in climbing, rearing near, or staring through the divider towards the social group during each trial. Trials during which mice did not orient towards the social group during reward collection are termed "Fine" trials. We found that FOMO behavior is significantly elevated in trials of Social Exclusion, compared to Tone Only controls (*P = 0.0108). After experiencing Social Exclusion, mice have significantly increased affective pain behavior after hot plate relative to included controls (**P= 0.0012). To study the neural substrates that might mediate social exclusion-induced emotional hyperalgesia, we are looking into the anterior insular cortex (aIC). Using cellular resolution calcium imaging, we have discovered the aIC contains neural ensembles responsive to social exclusion. Population based analyses demonstrates that the subspaces of neural trajectories for Social Exclusion lie orthogonal to that of controls, suggesting that the encoding of social exclusion is distinct. Furthermore, to explore the role of neuromodulators in mediating either social exclusion or pain behaviors, we applied a fluorescent endocannabinoid sensor during social exclusion and pain behavior. We found that during Social Exclusion only, there is a significant increase in fluorescent activity (*P = 0.0134) during Fine trials, but not during FOMO trials, or any control condition trials. Together these findings suggest that the experience of social exclusion can be represented distinctly within mice and can be used as a paradigm to study the overlap between social and physical pain.

Disclosures: **C. Jia:** None. **F. Aloboudi:** None. **A. Tran:** None. **K. Batra:** None. **C.R. Lee:** None. **A. Bal:** None. **M. Chan:** None. **R.R. Patel:** None. **J. Delahanty:** None. **R. Wichmann:** None. **L.R. Keyes:** None. **Y. Li:** None. **T.D. Pereira:** None. **H. Li:** None. **K.M. Tye:** None.

Poster

145. Neural Circuits and Encoding of Emotional Behaviors

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 145.13

Topic: G.04. Emotion

Support: Howard Hughes Medical Institute
Salk Institute for Biological Studies
Clayton Foundation
Kavli Foundation
Dolby Family Fund
NIMH R01-MH115920
NIMH R37-MH102441

Title: Visualizing the Longitudinal Development of Stress-Induced Anhedonia From Representations of Valence in the PFC

Authors: *A. A. COLEY[1], J. M. DELAHANTY[2,3], A. RAMOT[4], R. PAMINTUAN[2,5], L. LINDERHOF[2,5], V. LIU[2,5], C. JIA[2,5], H. ADVIKOLUNA[2,5], S. SHATHAYA[2,5], K. BATRA[2,5], D. LEDUKE[2,5], F. TASCHBACH[2,5], R. WICHMANN[2], H. LI[2], K. B. FISCHER[2], M. K. BENNA[5], T. KOMIYAMA[5], K. M. TYE[6,5,3];
[1]Salk Inst. for Biol. Studies, La Jolla, CA; [2]The Salk Inst. for Biol. Studies, La Jolla, CA; [3]Howard Hughes Med. Inst., La Jolla, CA; [4]Neurosci., Univ. of California San Diego, San Diego, CA; [5]Univ. of California San Diego, La Jolla, CA; [6]Systems Neurosci. Lab., Salk Inst. for Biol. Sci., La Jolla, CA

Abstract: A critical issue within the mental health field is the lack of granularity in diagnostic practices. For example, a patient that is sleeping and eating too much may be prescribed the same antidepressant as a patient who is sleeping and eating too little. This may explain the low rates of efficacy for first line antidepressants and begs further dissection. Anhedonia, described as the inability to experience pleasure, is a core feature expressed in both major depressive disorder and schizophrenia. Anhedonia is linked to a dysregulation within the brain reward pathways that includes the medial prefrontal cortex (mPFC), which is highly involved in emotional and valence processing, critical for encoding hedonic values. Dopamine (DA) tightly regulates mPFC cortical activity and associated behavior and is implicated in anhedonia. However, it remains unknown how DA modulates mPFC valence-specific neuronal population activity during anhedonia. *We hypothesize that mPFC valence-encoding processes are disrupted during stress-induced anhedonia.* To test this, we implemented learned helplessness (LH) and chronic mild stress (CMS) protocols to induce anhedonia in mice. Our preliminary findings showed a significant

reduction in reward consumption and sociability in LH mice (Pearson Correlation, r=-0.69, p=0.03), but not CMS mice (r=-0.16, p=0.58), suggesting a difference in behavioral phenotypes depending on the stress. Next, we performed longitudinal *in vivo* 2-photon calcium imaging with optogenetics techniques to photostimulate DA inputs in the mPFC while measuring mPFC population activity and dynamics in mice exposed to LH and CMS. Following acute exposure to CMS, we observed a significant decrease in mPFC activity during aversive trials in susceptible mice compared to resilient and control groups (ANOVA, ($F(2,398)=13.66$, $p<0.001$; Tukey-Kramer, Sus/Res, p=0.004, Sus/Con, $p<0.001$, Res/Con, p=0.18). Interestingly, susceptible mice revealed a significant increase in activity during reward trials compared to resilient groups (ANOVA, ($F(2,398)=7.26$, p=0.0008; Sus/Res, p=0.002, Sus/Con, p=0.999, Res/Con, p=0.003), but no change in control mice. These results indicate that anhedonic states influence mPFC valence encoding properties, and that acute, severe stressors can lead to distinct etiologies from chronic, mild stress. Altogether, these experiments point to the need for increased granularity in the measurement of both behavior and neural activity, as these factors can decode the induction conditions of stress-induced anhedonia, as well as the underlying biological pathology, propelling us towards a future of individualized medicine.

Disclosures: **A.A. Coley:** None. **J.M. Delahanty:** None. **A. Ramot:** None. **R. Pamintuan:** None. **L. Linderhof:** None. **V. Liu:** None. **C. Jia:** None. **H. Advikoluna:** None. **S. Shathaya:** None. **K. Batra:** None. **D. LeDuke:** None. **F. Taschbach:** None. **R. Wichmann:** None. **H. Li:** None. **K.B. Fischer:** None. **M.K. Benna:** None. **T. Komiyama:** None. **K.M. Tye:** None.

Poster

145. Neural Circuits and Encoding of Emotional Behaviors

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 145.14

Topic: G.04. Emotion

Support: 2P50MH100023-06

Title: Gaze following in third-party observers of simulated social conflict shows few reflexive and many mentalizing features

Authors: *T. CHAMP, S. LEE, A. B. MARTIN, C. M. BOLLES, S. KIM, K. M. GOTHARD; Physiol., Univ. of Arizona, Tucson, AZ

Abstract: Humans and non-human primates can point with their eyes, redirecting the visual attention of their social partner toward areas of high interest in their visual field. By following the gaze of interacting individuals, the observer obtains information about the emotions, mental states, and intentions of others. We presented three adult monkeys (*Macaca mulatta*) with videos of simulated social interactions and quantified their eye movements to determine which observed behaviors were conducive to joint-attention and gaze-following (JAGF) saccades. Social conflict was simulated by juxtaposing two videos depicting a threatening and an appeasing (or affiliative)

individual facing each other, with the timing of the facial and bodily displays adjusted to mimic an exchange of facial signals. Histograms of JAGF saccade counts per frame were generated for each observer and individual movie monkey. Each histogram showed the clustering (or not) of JAGF saccades generated by an observer monkey in response to one video monkey. These clusters suggest that some videos contained signals that compelled a reflexive redirection of the observer's attention. Theoretically, viewers could produce 4-5 interactive, JAGF saccades per second. In our data, even in clusters with a high probability of JAGF, the frequency did not exceed 1.5 interactive saccades/s (viewer C: 1.03 ± 0.416 Hz, n=32 clusters; viewer D: 1.14 ± 0.37 Hz, n=37 clusters; and viewer P: 1.36 ± 0.43 Hz, n=17 clusters). Furthermore, the movie frames that elicited the JAGF saccades within significant clusters overlapped only 1.3% of the time across the three observers and 7.96% of the time across two of the three observers, therefore 90.7% of the time the clusters were unique to each observer. It is unlikely, therefore, that the videos contained "irresistible" signals that triggered automatic stereotypical behaviors. On the contrary, the distribution of the JAGF saccades suggest more complex processing. All three viewers showed sequences of joint-attention saccades by switching back and forth between the two video monkeys resulting in bi-directional gaze interactions or "check-backs". We found 36 cases of these "check-backs" between paired clusters (viewer D: n= 15, C: n= 14, P: n= 7). These observations argue for more socially elaborate, mentalizing processes that guide the eye movements of third-party observers.

Disclosures: **T. Champ:** None. **S. Lee:** None. **A.B. Martin:** None. **C.M. Bolles:** None. **S. Kim:** None. **K.M. Gothard:** None.

Poster

145. Neural Circuits and Encoding of Emotional Behaviors

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 145.15

Topic: G.04. Emotion

Support: 1R56MH115681-01
R01MH121009

Title: Social context can be decoded from baseline firing rates in the primate amygdala.

Authors: *M. CARDENAS[1], K. ANDERSON[1], A. I. BOWMAN[1], A. B. MARTIN[1], S. J. BENSMAIA[2], A. FUGLEVAND[1], K. GOTHARD[1];
[1]Univ. of Arizona, Univ. of Arizona, Tucson, AZ; [2]Univ. of Chicago, Univ. of Chicago, Chicago, IL

Abstract: Social context constrains the perceived significance of external stimuli and informs behavior in ongoing social interactions. Reciprocal grooming in macaques creates a social context that induces behavioral changes (e.g., closed eyes, relaxed musculature, low vigilance) and autonomic changes (reduced heart rate and increased vagal tone) in the recipient. We

hypothesized that neurons in the amygdala would respond differently in this low vigilance state when compared to a higher vigilance state. We re-created the low vigilance, parasympathetically dominated state in a laboratory setting by delivering gentle grooming touches from trusted human partners. We compared the effect of these stimuli to non-social tactile stimuli delivered to the same areas of the skin by an automatic airflow system. Alternating blocks lasting around 10 minutes each of social and non-social stimuli allowed the monkeys to remain in a low-vigilance, low-arousal state during grooming compared to high arousal blocks with airflow stimuli. We recorded neural activity from the amygdala of three macaque monkeys alongside heart rate, which we used as an index of arousal and vigilance. We observed small but significant changes in the baseline firing rate of neurons in the amygdala between the two conditions. On average, baseline rates changed by 11% (n=400 cells) between contexts and ongoing context could be extracted from baseline firing rates in 147 individual neurons (t-test $p < 0.05$). Next we used a linear classifier (a support vector machine) to test the ability to decode ongoing context from the population activity. We find that 1-s bins of baseline activity can be accurately assigned to either the airflow or the grooming blocks when all 400 neurons were included in the model (99.7%). We also found that randomly selected subsets of only 119 neurons were always sufficient to decode context in 95% of bins. Finally, using principal component analysis we discovered that the variance in the baseline firing rates of all cells was best explained by the first component, which spanned the context dimension, yet the explained variance was only 6% of the total variance in the baseline activity. Thus, small variations in baseline firing rates transmitted information about context that was retained over long timescales. These prolonged changes in the baseline firing rates found in a large proportion of neurons in the amygdala are likely to generate sustained changes in downstream areas, possibly acting as the substrate of affective states and mood.

Disclosures: M. Cardenas: None. **K. Anderson:** None. **A.I. Bowman:** None. **A.B. Martin:** None. **S.J. Bensmaia:** None. **A. Fuglevand:** None. **K. Gothard:** None.

Poster

145. Neural Circuits and Encoding of Emotional Behaviors

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 145.16

Topic: G.04. Emotion

Title: A meta-analytic reevaluation of the primate amygdala's role in affective processing

Authors: *J. A. CHARBONNEAU[1,2], K. S. QUIGLEY[4,5], L. F. BARRETT[4,6], E. BLISS-MOREAU[3,2];
[1]Neurosci. Grad. Program, [2]California Natl. Primate Res. Ctr., [3]Dept. of Psychology, Univ. of California Davis, Davis, CA; [4]Dept. of Psychology, Northeastern Univ., Boston, MA; [5]VA Bedford Healthcare Syst., Bedford, MA; [6]Athinoula A. Martinos Ctr. for Biomed. Imaging, Massachusetts Gen. Hosp. and Harvard Med. Sch., Charlestown, MA

Abstract: Beliefs about the amygdala's role in detecting and processing threatening stimuli in the environment are among the most pervasive beliefs that exist in neuroscience and related fields. For decades, non-human primate models—primarily macaque monkeys—have been used to test the primate amygdala's causal role in threat processing. Such studies have produced heterogeneous results. We conducted a meta-analytic assessment of results from 26 experiments across 15 studies to test whether the macaque amygdala is necessary for responding to threat. In all studies, adult macaques received selective lesions of the amygdala and were compared to neurologically-intact control monkeys. Our data represent 195 unique monkeys (103 amygdala-lesioned), providing substantially more statistical power than any individual study could and allowing the opportunity to investigate the moderating impact of many different variables including outcome measures recorded, lesion extent, and lesion laterality. Our first major finding was that both monkeys with amygdala lesions (Cohen's d = 0.565) and control monkeys (d = 1.388) exhibited affective responses to threatening (compared to neutral) stimuli which differed significantly from 0; while the controls exhibited more intense and frequent responses, the amygdala was not necessary for threat responding. Effect sizes representing the contrast between responses to threatening and neutral stimuli were less variable in controls than monkeys with amygdala lesions, suggesting that the amygdala may play an important role in allowing for behavioral variability. Our second major finding was that across outcome measures reported, latency and frequency to retrieve food rewards from beside threatening objects consistently resulted in the largest contrast between amygdala-lesioned and control monkeys' responses to threat (d = 1.219), with amygdala-lesioned monkeys retrieving rewards faster and more frequently. This pattern—fast and frequent reward retrieval from near a threatening object—has traditionally been interpreted an indicator of a less robust (or not present) threat response. Our finding suggests that the historical association between amygdala and threat responding may actually be confounded by the amygdala's known role in reward valuation. Finally, we found significant evidence of a bias to publish studies reporting effects of amygdala lesions at conventional levels of statistical significance. Taken together, our results support a reconsideration of the necessity and role of the amygdala in processing threat.

Disclosures: J.A. Charbonneau: None. **K.S. Quigley:** None. **L.F. Barrett:** None. **E. Bliss-Moreau:** None.

Poster

145. Neural Circuits and Encoding of Emotional Behaviors

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 145.17

Topic: G.04. Emotion

Support: NIH/NIMH R01MH121009
P50 MH100023

Title: Saccade-related neural activity in the macaque amygdala and hippocampus is modulated by the social status of observed conspecifics

Authors: *S. LEE[1,2], A. B. MARTIN[1], U. RUTISHAUSER[3,4,5], K. M. GOTHARD[1];
[1]Dept. of Physiol., [2]Dept. of Electrical & Computer Engin., The Univ. of Arizona, Tucson, AZ;
[3]Dept. of Neurosurg., [4]Ctr. for Neural Sci. and Med., Cedars-Sinai Med. Ctr., Los Angeles, CA;
[5]Div. of Biol. and Biol. Engin., Caltech, Pasadena, CA

Abstract: The role of the primate amygdala in social behavior is demonstrated by selective neural responses to face identity, facial expressions, gaze direction, and social status. The amygdala is also involved in allocation of visual attention to stimuli of high socio-emotional salience. During natural social behaviors, high status individuals receive more attention than low status individuals. A recent phenomenon that has been identified in both humans and macaques is that ongoing theta oscillations in the hippocampus are phase reset by saccades. Further, in humans, these phase resets are particularly prominent for saccades that land on faces. The role of these phase resets in the processing of social information remains unknown. To examine this question, we tested the hypothesis that local field potentials in the non-human primate amygdala and hippocampus differentiate between saccades toward high status and low status individuals. We recorded eye movements and neural activity from the amygdala and hippocampus of a monkey while he watched one of three types of videos: (1) a video of a simulated hierarchical interaction between a high-status and low-status macaque, (2) a video of two moving objects, and (3) a video of natural scenes including macaques. The local field potentials elicited by saccades while scanning these three types of videos were compared to control saccades of similar length and duration produced while the viewer looked at a black screen. The eye-movement related component of the event-related potentials (ERPs) (recorded from 32 contacts spanning the distal 6-mm of two V-probes advanced each into the amygdala and hippocampus) was removed by subtracting from all channels the signal corresponding to the common average reference. The shapes of the resulting ERP's were nucleus- specific (amygdala) and layer-specific (hippocampus). In 49 of 59 contacts in the amygdala and 12 of 29 contacts in the hippocampus the magnitude of the saccade-onset aligned ERP's was higher for saccades originating from high-status compared to low-status individuals. Although this effect was relatively small (between 2-25 microvolts), it survived the additional control of removing the ERPs resulting from saccades while watching the black screen. These preliminary results suggest that looking at individuals of high-social status engages mesoscale neural populations in the non-human primate amygdala and hippocampus more so than when viewing low-social status individuals. Ongoing studies explore oscillatory and coupling effects between the amygdala and hippocampus during these viewing behaviors.

Disclosures: S. Lee: None. **A.B. Martin:** None. **U. Rutishauser:** None. **K.M. Gothard:** None.

Poster

145. Neural Circuits and Encoding of Emotional Behaviors

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 145.18

Topic: G.04. Emotion

Support: JSPS Grand JP20H03391

Title: Claustral neural circuits involved in the control of stress-induced anxiety responses

Authors: *A. KASAI, M. TANUMA, M. NIU, H. UENO, J. OHKUBO, R. YOKOYAMA, K. SEIRIKI, H. HASHIMOTO;
Osaka Univ., Osaka Univ., Suita, Japan

Abstract: The processing of stress responses involves brain-wide communication among cortical and subcortical regions. We have recently demonstrated that the claustrum (CLA) receives strong inputs from stress-responsive neurons in subcortical regions, including the basolateral amygdala (BLA), and that a CLA-BLA circuit is important for the control of stress-induced anxiety-related behaviors. However, the interrelationship between stress information input to the CLA and BLA is still unknown. Here, we show collateral projections from stress-responsive neurons in the dorsomedial prefrontal cortex (dmPFC) to the CLA and BLA using a whole-brain imaging system and an immediate early gene reporter system. In the $Fos^{2A\text{-}iCreERT2}$ knock-in mice, also known as TRAP2 mice, which allow activity-dependent genetic labeling, we injected retrograde adeno-associated virus vectors expressing Cre recombinase-dependent red fluorescent protein mCherry into the BLA and Cre-recombinase-dependent green fluorescent protein EGFP into the CLA. Then, the TRAP2 mouse was subjected to a single round of social defeat stress in the presence of tamoxifen to label stress-activated neurons. Whole-brain imaging of the TRAP2 mouse revealed that the CLA has strong inputs from social defeat stress-activated neurons in the anteroventral part of the BLA and the dmPFC. In addition, we found that a few stress-responsive neurons in the dmPFC have collateral projections to the BLA and CLA. These results suggest that neuronal connections among CLA, BLA and dmPFC would be important for the control of stress-induced anxiety responses.

Disclosures: A. Kasai: None. **M. Tanuma:** None. **M. Niu:** None. **H. Ueno:** None. **J. Ohkubo:** None. **R. Yokoyama:** None. **K. Seiriki:** None. **H. Hashimoto:** None.

Poster

145. Neural Circuits and Encoding of Emotional Behaviors

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 145.19

Topic: G.04. Emotion

Support: Washington Research Foundation Postdoctoral Fellowship (ERS)
NIDA 4R00DA045662-02 (SAG)
NARSAD Young Investigator Award 27082 (SAG)
NIDA R01DA054317 (SAG)
NIDA UG3DA053802 (SAG)

Title: Sensitization of a claustrum-amygdalar-accumbens neural system precedes incubation to palatable food craving

Authors: *E. R. SZELENYI[1], R. MADANGOPAL[4], V. T. TSAI[2], R. CHEN[5], S. A. GOLDEN[3];
[2]Biol. Structure, [3]Dept. of Biol. Structure, [1]Univ. of Washington, Seattle, WA; [4]Neuronal Ensembles in Addiction Section, NIH, NIDA IRP, Baltimore, MD; [5]Sch. of Med., Univ. of Maryland, Baltimore, MD

Abstract: Background: In rodent models, reward seeking progressively increases across abstinence in a phenomenon known as 'incubation of craving'. We recently established a mouse model of incubation of palatable food craving and applied unbiased single-cell activity mapping to demonstrate that incubation is associated with wide-spread neural activity beyond canonical reward centers (Madangopal, Szelenyi et al, 2022). From these data we hypothesize that select neural systems are sensitized as a function of abstinence duration that primes the brain towards incubation of craving and relapse. Here, we extend our analyses of a recently generated 'incubation of craving' whole-brain activity dataset and apply advanced image processing and statistical approaches to probe for sensitization of neural systems evoked by food craving. **Methods**: We used our previously published Fos+ whole-brain activity dataset capturing the brain-wide signature of incubation of food craving in mice. In the first set of analyses, we used segmentation bias-free voxelization of cell densities to identify the neural system correlates of relapse behavior. Image statistics were post-processed using cluster-based thresholding, and the distribution of significant voxels across ~1000 anatomical regions were segmented and identified post-hoc. We then determined the functional connectivity changes over the course of abstinence using UPGMA hierarchical clustering on Pearson R matrices derived from non-voxelized regionally segmented cell densities. **Results:** Early food craving induced a significant increase in activation clusters across a temporally conserved neural system consisting of the ventral claustrum (vCl), basomedial amygdala (BMA), and the hedonic nucleus accumbens (hNAc). This effect was sensitized as a function of abstinence duration, recruiting proximal to adjacent regions. Expansion of the vCl-BMA-hNAc food craving system corresponded with increased functional connectivity defined by a recruitment of early abstinence modular connectivity hubs into a singular hub at late incubation. **Conclusion:** Incubation of food craving is preceded by a systems-level sensitization process. Early abstinence from palatable food initialized and maintained activation of a vCl-BMA-hNAc neural system. vCl-BMA-hNAc undergoes a recruited sensitization of brain activation as a function of abstinence duration, leading to a complete functionally connected brain state and induction of incubation. These results provide critical insight into the neural mechanisms driving relapse to palatable food and offer novel therapeutic entry points into the dysregulation of reward seeking behavior.

Disclosures: E.R. Szelenyi: None. **R. Madangopal:** None. **V.T. Tsai:** None. **R. Chen:** None. **S.A. Golden:** None.

Poster

145. Neural Circuits and Encoding of Emotional Behaviors

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 145.20

Topic: G.04. Emotion

Support: NIDA R00DA045662
NIDA P30DA048736
5T32NS099578-05

Title: Operant chronic social defeat stress

Authors: *J. NAVARRETE, K. N. SCHNIDER, B. SMITH, Y. ZHANG, E. GROSS, V. TSAI, S. A. GOLDEN;
Univ. of Washington, Seattle, WA

Abstract: Background: A key challenge in developing new treatments for depression - a disease defined by social deficits - stems from a disconnect between preclinical models and the complexity of human social behavior. Chronic social defeat stress (CSDS) is used to induce depression-like behavior in mice, highlighted by the presence or absence of social avoidance in stress susceptible and resilient mice, respectively. CSDS uses exploratory investigation during involuntary interactions to stratify populations. We propose to incorporate voluntary social decision-making in preclinical models to identify translational mechanisms that promote stress resiliency. Towards this goal, we develop an operant social stress (oCSDS) procedure in male and female mice, where lever presses are reinforced by social contact after stress, to capture stress-related dynamic social-seeking behavior.

Methods: Experimental male and female outbred C57BL/6J mice trained to socially self-administer (SA) sex and age-matched conspecific partners using a fixed-ratio (FR1) reinforcement schedule over ten 12-trial sessions. Next, experimental male and female mice were subjected to repeated social or witness defeat, respectively, and each defeat session followed access to social SA testing (oCSDS). We tested social reward seeking before and after 10 days of oCSDS using non-reinforced sessions, followed by a social-reinforced progressive ratio test. Lastly, mice underwent social interaction (SI) tests with familiar C57BL/6J or novel CD-1 targets.

Results: Male and female mice acquired social SA prior to the stress phase. Witness female mice maintained social SA across the stress phase, males split into susceptible and resilient that reduced and maintained SA, respectively. Following social stress, susceptible mice attenuated and resilient mice maintained social reward seeking. Witness mice increased social reward seeking. Next, social-reinforced progressive ratio test yielded decreased lever pressing in defeated males and an increase in witness female mice. For SI, susceptible mice exhibited social avoidance of the novel CD-1 target while resilient mice showed no change with the novel CD-1 or familiar targets. Witness females showed no change in SI compared to their controls.

Conclusions: Female mice exhibited no changes in reinforced social SA but did increased social reward seeking and motivation for social-reinforced progressive ratio testing. Males followed a similar pattern as those reported in classic CSDS experiments. This shows oCSDS can reveal the temporal dynamics of stress susceptibility and resilience under volitional conditions in male and female mice.

Disclosures: **J. Navarrete:** None. **K.N. Schnider:** None. **B. Smith:** None. **Y. Zhang:** None. **E. Gross:** None. **V. Tsai:** None. **S.A. Golden:** None.

Poster

145. Neural Circuits and Encoding of Emotional Behaviors

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 145.21

Topic: G.04. Emotion

Support: NIDA R01DA054317
NIDA UG3DA053802
Foundation for Anesthesia Education and Research MRTG

Title: Mapping cellular resolution whole brain activity in mice under anesthetized and emerging states of isoflurane anesthesia

Authors: *A. D. MURRY[1], E. SZELENYI[2], S. A. GOLDEN[2], M. HESHMATI[1];
[1]Biol. Structure, Anesthesiol. and Pain Med., [2]Biol. Structure, Univ. of Washington, Seattle, WA

Abstract: Background: We aim to investigate the effects of isoflurane anesthesia on whole brain activity in order to identify novel anesthesia-activated circuitry at cellular resolution. We use cFos immediate early gene expression and light sheet microscopy to construct a whole brain functional connectome of isoflurane anesthesia in mice. Our goal is to explore both deeply anesthetized and emerging states of anesthesia in order to better understand transitions in anesthetized to awake neural circuitry.
Methods: Male and female, 2-5 month-old C57BL6/J mice underwent habituation to the anesthetic chamber and served as control mice or underwent isoflurane exposure. In Experiment 1, mice were exposed to 90-180min of 1.2% isoflurane. Another group was allowed to regain restoration of the righting reflex with isoflurane maintained at 0.3-0.4%, modeling a state of light anesthesia/emergence. In Experiment 2, experimental mice were deeply anesthetized for 300 minutes at 1.2% isoflurane. After isoflurane exposure, mice underwent transcardial perfusion. Brains were cleared and immunolabeled for cFos using a modified iDISCO+ protocol. Whole brain images were acquired on an UltraMicroscope II light-sheet microscope and processed using a volumetric registration pipeline called Clearmap. Each dataset was processed using cell detection optimization parameters and registered to a corresponding annotation file and anatomical atlas to determine the mean cell density for each brain region.
Results: Preliminary results demonstrate increased subcortical activity in isoflurane-exposed animals compared to control mice that display consistent cortical activity. Differential activity patterns between emerging and deeply anesthetized mice are also evident. Anesthesia-activated regions include those previously identified to be modulated by isoflurane like the central amygdala, paraventricular nucleus, ventral tegmental area, and locus coeruleus. Future studies will be aimed at functional manipulations of the identified neural circuits to determine their causal role in maintenance and emergence from isoflurane anesthesia.

Discussion: Millions of patients undergo anesthesia each year, while the mechanisms mediating the effects of general anesthesia on the brain are still unclear. Emergence is an unpredictable period in anesthesia care with few therapies available to directly alter emergence. An improved understanding of anesthesia-activated neural circuitry will better elucidate mechanisms of anesthetic action in the brain and help to identify possible therapeutic targets to modify emergence.

Disclosures: **A.D. Murry:** None. **E. Szelenyi:** None. **S.A. Golden:** None. **M. Heshmati:** None.

Poster

145. Neural Circuits and Encoding of Emotional Behaviors

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 145.22

Topic: G.04. Emotion

Support: NIDA R00DA045662
NIDA P30DA048736

Title: Role of Nucleus Accumbens Neuroligin-2 in Mediating Aggressive Behaviors

Authors: *N. HOFFMAN[1], N. GOODWIN[1], V. TSAI[1], S. A. GOLDEN[2], M. HESHMATI[2];
[2]Biol. Structure, [1]Univ. of Washington, Seattle, WA

Abstract: Neuroligins are a family of postsynaptic cell adhesion proteins that are essential to the formation and proper functioning of synapses and play a critical role in maintaining neural excitation/ inhibition balance. Neuroligin mutations are linked to several neuropsychiatric disorders like autism and depression, although their role in maladaptive social behavior remains unclear. Inappropriate aggression and agitation are often comorbid with neuropsychiatric disease and understanding the neural pathways underlying aggressive behavior may help to identify potential therapeutic targets. Neuroligin-2 (NLGN-2) specifically supports inhibitory synapse function and plays a key role in regulating social stress behaviors. Here, we examine the role of NLGN-2 in mediating adaptive and maladaptive aggressive behavior in adult male outbred CD-1 mice. In Experiment 1, we use immunohistochemistry to localize and quantify NLGN-2 in Fos-positive cells in nucleus accumbens of mice following resident-intruder reactive aggression. In Experiment 2, we train mice in an operant aggression self-administration procedure and examine changes in NLGN-2 in nucleus accumbens Fos-positive neurons following appetitive, or rewarding, aggression. In Experiment 3, we selectively knockdown NLGN-2 in nucleus accumbens in a neural circuit-specific manner to determine the functional effects of NLGN-2 manipulation on adaptive and maladaptive aggressive behavior. Through these studies, we find that NLGN-2 is downregulated in the nucleus accumbens of mice exhibiting higher levels of aggression. NLGN-2 levels significantly correlated with increased number of attack bouts independent of lever presses, indicating a significant role for nucleus accumbens NLGN-2 in

reactive and not appetitive aggression reward seeking. Together, these data demonstrate an important role for nucleus accumbens NLGN-2 in the spectrum of aggressive behavior.

Disclosures: **N. Hoffman:** None. **N. Goodwin:** None. **V. Tsai:** None. **S.A. Golden:** None. **M. Heshmati:** None.

Poster

145. Neural Circuits and Encoding of Emotional Behaviors

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 145.23

Topic: G.04. Emotion

Support: NIDA R00DA045662
NIDA P30DA048736

Title: An assessment of sensory and physical interaction during trial based social self-administration procedures.

Authors: *Y. ZHANG[1], J. NAVARRETE[2], K. N. SCHNEIDER[1], N. GOODWIN[2], V. S. TSAI[1], L. KUO[1], S. A. GOLDEN[1];
[1]Dept. of Biol. Structure, Univ. of Washington, Seattle, WA; [2]Univ. of Washington Grad. Program in Neurosci., Seattle, WA

Abstract: Background: Social interaction is a strongly reinforcing behavior. Recently, several operant procedures have been developed for assessing affiliative social motivation using trial-based designs. However, these operant procedures are split between variants that use either direct physical contact or purely sensory contact (via barriers) following operant responses. There are benefits and caveats to both approaches. Physical contact requires extensive experimenter involvement to both introduce and remove social intruders during each trial, but allows for clear observation and interpretation of the consummatory aspect of social interaction. Sensory contact requires minimal investigator involvement and is high throughput, but removes the consummatory social component and makes interpretation difficult. Here, using a novel automated operant procedure, we compare the consequences of physical or sensory contact (or a combination of both) during operant social self-administration on subsequent social seeking and interaction behaviors.

Methods: Both male and female inbred C57BL/6J mice were trained to lever press for age and sex-matched familiar conspecifics using a trial-based design. All experiments used 12 trials per day for 10 days, preceded by magazine training with physical contact for base social interaction behavior and followed by non-reinforced social reward seeking tests. For all trials, an automated delivery system provided physical or sensory intruder access to the resident experimental mouse. All trials were video recorded for later behavioral classification using supervised machine learning approaches (SimBA). In Experiment 1, mice were trained using physical contact where

lever presses resulted in the introduction of a familiar intruder into the operant chamber. In Experiment 2, mice were trained using sensory contact where lever presses resulted in sensory contact with a familiar intruder across a barrier. In Experiment 3, mice were trained with physical contact and then transitioned to and maintained on sensory contact.

Results: Preliminary results show potential differences in social self-administration depending on physical or sensory contact, as well as on social reward seeking. Similarly, the type of social behaviors displayed during social interactions were dependent on training parameters. Together, these data suggest that social self-administration using physically or sensorily reinforced trials may result in divergent social profiles for experimental mice.

Disclosures: Y. Zhang: None. **J. Navarrete:** None. **K.N. Schneider:** None. **N. Goodwin:** None. **V.S. Tsai:** None. **L. Kuo:** None. **S.A. Golden:** None.

Poster

145. Neural Circuits and Encoding of Emotional Behaviors

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 145.24

Topic: G.04. Emotion

Support: NIDA R00DA45662
NIDA P30DA048736

Title: Distinctive neuronal ensembles characterizing reactive and appetitive aggression

Authors: *V. S. TSAI[1], N. L. GOODWIN[2,3,4], S. A. GOLDEN[2,4];
[2]Dept. of Biol. Structure, [3]Grad. Program in Neurosci., [4]UW Ctr. for Excellence in Neurobio. of Addiction, Pain, and Emotion, [1]Univ. of Washington, Seattle, WA

Abstract: BACKGROUND: Maladaptive aggression is often symptomatic or characteristic of neuropsychiatric disorders. In humans, aggression manifests in two forms—reactive (defensive) or appetitive (rewarding)—and treatment differs between the two. However, despite clinical awareness of their differences, a preclinical characterization of the neural correlates distinguishing the aggression presentations does not yet exist. To examine differences in brain-wide recruitment of neuronal ensembles between reactive and appetitive aggression phenotypes, we used a coactivational analysis framework on single-cell c-Fos expression data from mice that combined machine learning clustering methods with network graph theory visualization. METHOD: Brain registration, anatomical annotation, and cell segmentation were performed using ABBA (Aligning Big Brains to Atlases) and QuPath. Our analytical framework consisted of unsupervised and supervised machine learning. The unsupervised method utilized two open-source programs: (*i*) CytoMAP, a spatial analysis toolkit with unsupervised *k*-means clustering and *t*-distributed stochastic neighbor embedding capabilities, and (*ii*) Cytoscape, a network analysis program that allowed us to visualize the anatomical organization of regions that

underwent statistically significant changes in activation compared to control in hierarchical network diagram form. The supervised method, used to validate and assess the results of the unsupervised approach, utilized hierarchical clustering. RESULTS: Preliminary results suggest subtle, but significant, differences in coactivational networks characterizing reactive and appetitive aggression. CONCLUSION: Preliminary results indicate reactive and appetitive aggression engage distinctive brain-wide neuronal ensembles. Future studies will aim to relate these findings to brain-wide *in situ* hybridization data to gain insight into the contributions of specific receptors and cell types to each aggression phenotype.

Disclosures: V.S. Tsai: None. **N.L. Goodwin:** None. **S.A. Golden:** None.

Poster

146. Behavioral Phenotypes and Neural Mechanisms of Relevance to Psychiatric Illness

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 146.01

Topic: G.05. Mood Disorders

Support: Hope for Depression Research
NIMH Grant R01MH051399
NIMH Grant P50MH096890

Title: Persistent transmission of paternal stress phenotypes to offspring show brain region-specific transcriptomic signatures

Authors: *A. M. CUNNINGHAM[1], D. M. WALKER[2], A. RAMAKRISHNAN[1], O. ISSLER[1], H. M. CATES[3], L. SHEN[1], E. J. NESTLER[1];
[1]Neurosci., Icahn Sch. of Med. At Mount Sinai, New York, NY; [2]Behavioral Neurosci., Oregon Hlth. and Sci. Univ., Portland, OR; [3]Adelphi Univ., Garden City, NY

Abstract: Depression risk has long been known to be highly influenced by both genetic and environmental factors. More recently, it has been proposed that intergenerational epigenetic mechanisms may also contribute, representing a third basis of risk. Previous studies on intergenerational trauma in rodents from our lab have shown that resilient and susceptible fathers exposed to chronic social defeat stress (CSDS) have different patterns of behavioral transmission and transcriptional changes in sperm (Cunningham et al., 2021). However, no studies to date have examined the persistent transmission of stress phenotypes to multiple litters in fathers from resilient and susceptible lineages. To study this, F0 male mice were exposed to 10 days of CSDS and subjected to social interaction testing to assess paternal phenotype (resilient or susceptible). Resilient, susceptible, or control F0 males were allowed to mate 30 days after stress to produce F1 “Litters 1” and again 60 days following stress to produce F1 “Litters 2”. We found that while both resilient and susceptible fathers persistently transmitted altered stress phenotypes to female F1 offspring, only susceptible fathers persistently transmitted altered stress phenotypes to male offspring. To better understand how the transcriptome in brain regions involved in stress

response may be differentially responding to stress in F1 offspring from stress lineages compared to controls, we conducted RNA-sequencing of the prefrontal cortex (PFC) and nucleus accumbens (NAc). We found that the PFC but not the NAc shows stress lineage-specific dynamic changes in gene expression in response to stress in F1 offspring. Finally, using a combination of bioinformatic techniques we identify key genes in the PFC that may be involved in regulating the behavioral phenotypes seen in male and female offspring from stress lineages. Taken together, these studies advance our understanding of the intergenerational epigenetic transmission of behavioral experience.

Disclosures: **A.M. Cunningham:** None. **D.M. Walker:** None. **A. Ramakrishnan:** None. **O. Issler:** None. **H.M. Cates:** None. **L. Shen:** None. **E.J. Nestler:** None.

Poster

146. Behavioral Phenotypes and Neural Mechanisms of Relevance to Psychiatric Illness

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 146.02

Topic: G.05. Mood Disorders

Support: NIMH Grant P50MH096890
Hope for Depression Research Foundation

Title: Role of H3K27me1 and H3K27me2 in Conferring Susceptibility to Stress Across the Lifespan

Authors: *A. TORRES BERRIO[1], M. ESTILL[1], A. RAMAKRISHNAN[1], H. KRONMAN[1], A. M. MINIER-TORIBIO[1], O. ISSLER[1], C. J. BROWNE[1], F. MARTÍNEZ-RIVERA[1], Y. VAN DER ZEE[1], E. M. PARISE[1], S. RAMIREZ[2], S. SIDOLI[3], L. SHEN[1], E. J. NESTLER[1]; [1]Icahn Sch. of Med. At Mount Sinai, Friedman Brain Inst., New York, NY; [2]Hunter Col., New York, NY; [3]Albert Einstein Col. of Med., Bronx, NY

Abstract: A life history of stress is the strongest risk factor for several psychiatric disorders. Indeed, stress is known to "scar" the brain, leading to persistent transcriptional alterations in regions involved in reward and mood regulation, such as the nucleus accumbens (NAc). Here, we characterized the enduring changes in histone modifications in the NAc of mice exposed to stress, either in early life or in adulthood, and assessed their role in mediating life-long behavioral and transcriptional dysregulation. We exposed female and male mice to early life stress (ELS), a paradigm known to heighten vulnerability to stress in adulthood, by combining maternal separation and reduced bedding during postnatal days (PND) 10 to PND 17. Tissue from the NAc was collected at PND21 and PND60 and processed for histone profiling via mass spectrometry. In parallel, we mapped the genome-wide enrichment of the most changed histone modifications using CUT&RUN followed by sequencing. Our results show that ELS alters the methylation (me) dynamics of lysine (K) 27 of the histone variant H3.3—the predominant form of H3 present in adult brain neurons. Specifically, we found an increase in the abundance of

H3.3K27me1, and a decrease in the abundance of H3.3K27me2, in the NAc immediately after ELS exposure (PND21) that lasted into adulthood (PND60). To determine whether this effect could also be observed in another model of stress, we exposed an independent cohort of adult male mice to chronic social defeat stress (CSDS), and separated mouse populations into susceptible (SUS) and resilient (RES) outcomes based on a social interaction test. We observed that SUS mice to CSDS also exhibit an increased abundance of H3.3K27me1 in NAc, accompanied by a decrease in H3.3K27me2. Genomic distribution shows that H3.3K27me1 is primarily enriched in gene bodies and proximal promoters, and correlates positively with gene expression, whereas H3.3K27me2 negatively correlates with gene expression and is weakly deposited across intergenic regions. Finally, we observed that changes in H3.3K27me1 and H3.3K27me2 are associated with elevated expression of SUZ-12, a protein that controls H3K27 methylation by guiding the polycomb repressive complex 2 to precise genomic sites. We are currently manipulating SUZ-12 expression in an age-dependent and cell-type-specific manner to assess their impact on H3.3K27 methylation and stress-induced persistent behavioral alterations. Together, these results suggest that H3.3K27me1 and H3.3K27me2 are important epigenetic "scars" that may mediate stress susceptibility across the lifespan, and point to the NAc as a key region that is highly sensitive to the effects of ELS.

Disclosures: **A. Torres Berrio:** None. **M. Estill:** None. **A. Ramakrishnan:** None. **H. Kronman:** None. **A.M. Minier-Toribio:** None. **O. Issler:** None. **C.J. Browne:** None. **F. Martínez-Rivera:** None. **Y. van der Zee:** None. **E.M. Parise:** None. **S. Ramirez:** None. **S. Sidoli:** None. **L. Shen:** None. **E.J. Nestler:** None.

Poster

146. Behavioral Phenotypes and Neural Mechanisms of Relevance to Psychiatric Illness

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 146.03

Topic: G.05. Mood Disorders

Support: P50MH096890
R01MH051399
R01MH114882
R01MH127820
R01MH104559

Title: Stress-resilient mice optimize subjective value and food security on an economic foraging task

Authors: *R. DURAND-DE CUTTOLI, F. J. MARTINEZ-RIVERA, L. LI, A. MINIER-TORIBIO, S. J. RUSSO, E. J. NESTLER, B. M. SWEIS;
Neurosci., Icahn Sch. of Med. at Mount Sinai, New York, NY

Abstract: Economic stress can often serve as a “second-hit” for those who have already accumulated a history of stressful experiences. This can precipitate significant changes in behavior that may be adaptive or maladaptive depending on one’s unique stress-response predispositions. How an individual recovers from a setback is a core feature of resilience but is seldom captured in animal studies. Here, we challenged mice in a novel two-hit stress model by first exposing animals to chronic social defeat stress (first hit) - a protocol known to separate individual differences in stress-resilient versus stress-susceptible phenotypes. Mice were then tested longitudinally across two months on the neuroeconomic task termed “Restaurant Row” during which mice foraged daily for their sole source of food while on a limited time budget. An abrupt transition into a reward-scarce environment on this task elicits an economic crisis (second hit) precipitating a massive drop in food intake that mice must respond to in order to survive. We found that stress-resilient mice mounted the most robust behavioral response to this economic challenge and readily renormalized food intake back to baseline levels faster compared to stress-susceptible and non-defeated control mice. This was achieved through an efficient increase in effort expenditure and a redistribution in how time was allocated among competing opportunities. Interestingly, stress-resilient mice learned to accomplish this while simultaneously maximizing subjective value by re establishing flavor preferences that approximated yield previously obtained in a reward-rich environment. These findings suggest that a resilient individual’s capacity to “bounce back” following economic stress while foraging entails the development of a multi-pronged strategy that not only ensures food security necessary for survival but also prioritizes other aspects of well-being including subjective value, highlighting a motivational balance that may be impaired in depression.

Disclosures: R. Durand-de Cuttoli: None. **F.J. Martinez-Rivera:** None. **L. Li:** None. **A. Minier-Toribio:** None. **S.J. Russo:** None. **E.J. Nestler:** None. **B.M. Sweis:** None.

Poster

146. Behavioral Phenotypes and Neural Mechanisms of Relevance to Psychiatric Illness

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 146.04

Topic: G.05. Mood Disorders

Support: NIMH Grant R01MH051399
Brain & Behavior Research Foundation Grant 30609
Hope for Depression Research Foundation

Title: Expression of the Astrocyte-Specific Extracellular Matrix Gene Htra1 Regulates Susceptibility to Stress in a Sex-Specific Manner

Authors: *E. M. PARISE[1], T. M. GYLES[1], O. K. SIAL[2], A. GODINO[1], C. J. BROWNE[1], L. F. PARISE[1], A. TORRES-BERRÍO[1], M. SALERY[1], R. DURAND-DE CUTTOLI[1], L. HOLT[1], T. MARKOVIC[1], F. CATHOMAS[1], J. B. GARON[1], C. TEAGUE[1], O. ISSLER[1], P. J. HAMILTON[3], C. A. BOLANOS-GUZMAN[2], S. J. RUSSO[1], E. J. NESTLER[1];

[1]Nash Family Dept. of Neurosci., Icahn Sch. of Med. at Mount Sinai, New York, NY; [2]Dept. of Psychology, Texas A&M Univ., College Station, TX; [3]Virginia Commonwealth Univ. Hlth. Syst., Virginia Commonwealth Univ. Hlth. Syst., Richmond, VA

Abstract: While the underlying pathophysiology of major depressive disorder (MDD) is poorly understood, convergent evidence from preclinical and clinical research supports the notion that MDD is related to impaired structural and synaptic plasticity in key limbic regions. The extracellular matrix (ECM) of the brain represents a novel domain for study as it not only provides structural support, but also is intimately involved in regulating synaptic plasticity and remodeling. We analyzed transcriptional profiles of ECM-related genes from the nucleus accumbens (NAc) in postmortem brain tissue of humans with MDD as well as in mice exhibiting a depression-related behavioral abnormalities after exposure to chronic variable stress (CVS). We identified *Htra1*, an astrocyte-enriched secreted serine protease, as being significantly down-regulated in the NAc of males and up-regulated in females across both species. We found that selective manipulation of the *Htra1* gene in astrocytes within the mouse NAc bidirectionally controls susceptibility to stress in a sex-specific manner. Furthermore, direct manipulation of *Htra1* in astrocytes of the NAc, in conjunction with sub-threshold stress, influences medium spiny neuron physiological activity both in brain slices and in vivo. Our findings reveal a pivotal role of astroglia as well as the brain's ECM in mediating stress vulnerability that is impacted in a sex-specific manner and set the stage for novel therapeutic approaches for MDD.

Disclosures: E.M. Parise: None. **T.M. Gyles:** None. **O.K. Sial:** None. **A. Godino:** None. **C.J. Browne:** None. **L.F. Parise:** None. **A. Torres-Berrío:** None. **M. Salery:** None. **R. Durand-De Cuttoli:** None. **L. Holt:** None. **T. Markovic:** None. **F. Cathomas:** None. **J.B. Garon:** None. **C. Teague:** None. **O. Issler:** None. **P.J. Hamilton:** None. **C.A. Bolanos-Guzman:** None. **S.J. Russo:** None. **E.J. Nestler:** None.

Poster

146. Behavioral Phenotypes and Neural Mechanisms of Relevance to Psychiatric Illness

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 146.05

Topic: G.05. Mood Disorders

Support: NIMH
HDRF

Title: Blood miR-144-3p: A Novel Diagnostic and Therapeutic Tool for Depression

Authors: Y. Y. DER ZEE[1,2], L. M. T. EIJSSEN[2], P. MEWS[1], A. RAMAKRISHNAN[1], K. ALVAREZ[1], C. L. LARDNER[1], H. M. CATES[1], D. M. WALKER[1], A. TORRES-BERRÍO[1], C. J. BROWNE[1], A. CUNNINGHAM[1], F. CATHOMAS[1], H. KRONMAN[1], E. M. PARISE[1], L. DE NIJS[2], L. SHEN[1], J. W. MURROUGH[1], B. P. F. RUTTEN[2], E. NESTLER[1], ***O. ISSLER**[1];

[1]Mount Sinai Sch. of Med., New York, NY; [2]Dept. of Psychiatry and Neuropsychology, Maastricht Univ., Maastricht, Netherlands

Abstract: Depression is a prevalent psychiatric disorder and one of the leading causes of disability worldwide. There is an urgent need for objective biomarkers to diagnose this highly heterogeneous syndrome, assign treatment, and evaluate treatment response and prognosis. MicroRNAs (miRNAs) are short non-coding RNAs detected in body fluids that have emerged as potential biomarkers of many disease conditions. The present study explored the possible use of miRNAs as biomarkers for depression and the response to divergent classes of antidepressant drugs. We profiled the expression levels of circulating blood miRNAs from male mice collected before and after exposure to chronic social defeat stress (CSDS), an extensively validated mouse model used to study depression, and after repeated imipramine or a single-dose ketamine treatment. We observed robust differences in blood miRNA signatures between stress-resilient and stress-susceptible mice after an incubation period but not immediately after exposure to the stress. Furthermore, ketamine treatment was more effective than imipramine at re-establishing baseline miRNA expression levels, but only in mice that responded behaviorally to the drug. We identified the red blood cell-specific miR-144-3p as a candidate biomarker to aid depression diagnosis and predict ketamine treatment response in stress-susceptible mice. To probe the translational relevance of this finding, we used blood samples from a human depression cohort and indeed validated that miR-144-3p is a predictor of depression severity and ketamine treatment response. Lastly, we demonstrate that systemic knockdown of miR-144-3p via subcutaneous administration of a specific antagomir is sufficient to reduce the depression-related phenotype in stress-susceptible mice. RNA-sequencing analysis of blood after such miR-144-3p knockdown revealed a blunted transcriptional stress signature as well. These findings identify miR-144-3p as a novel target for the diagnosis of depression and antidepressant treatment and highlight the importance of the regulatory process governed by non-coding RNAs in depression translational research.

Disclosures: Y.Y. der Zee: None. **L.M.T. Eijssen:** None. **P. Mews:** None. **A. Ramakrishnan:** None. **K. Alvarez:** None. **C.L. Lardner:** None. **H.M. Cates:** None. **D.M. Walker:** None. **A. Torres-Berrío:** None. **C.J. Browne:** None. **A. Cunningham:** None. **F. Cathomas:** None. **H. Kronman:** None. **E.M. Parise:** None. **L. de Nijs:** None. **L. Shen:** None. **J.W. Murrough:** None. **B.P.F. Rutten:** None. **E. Nestler:** None. **O. Issler:** None.

Poster

146. Behavioral Phenotypes and Neural Mechanisms of Relevance to Psychiatric Illness

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 146.06

Topic: G.05. Mood Disorders

Support: P50MH096890
R01MH051399
R01MH114882

R01MH127820
R01MH104559

Title: Chronic social stress induces isolated deficits in reward anticipation on a neuroeconomic foraging task

Authors: *B. M. SWEIS, R. DURAND-DE CUTTOLI, F. J. MARTINEZ-RIVERA, L. LI, A. M. MINIER-TORIBIO, S. J. RUSSO, E. J. NESTLER;
Neurosci., Icahn Sch. of Med. at Mount Sinai, New York, NY

Abstract: Anhedonia describes a loss of interest or pleasure in rewarding activities and can manifest in the form of decreased motivation to engage in reward-seeking behaviors. Deficits in reward anticipation comprise one aspect of anhedonia. Levels of motivation, however, are highly dynamic and can be altered, for example, due to fluctuations in different physiological states of an individual or as a result of environmental circumstances. Measuring reward anticipation distinct from other aspects of reward value, including costs required to obtain a reward or the intrinsic hedonic value of consuming the reward itself, can be difficult to disentangle. Here, we tested mice previously exposed to chronic social defeat stress, a well-validated animal model used for the study of depression, on a translational neuroeconomic self-paced foraging paradigm, termed “Restaurant Row.” On this task, mice were tested longitudinally and foraged daily for their sole source of food. While on a limited time budget, mice made serial decisions navigating between reward sites making accept versus reject decisions for offers that varied based on cost (delays) and subjective preferences (flavor). This task provides a rich framework to operationalize reward value and motivation-related processes among several domains of complex behavior separated across space and time. By analyzing travel behavior between reward patches, we found that the speed with which mice traveled was invigorated when approaching more preferred reward sites - a metric of reward anticipation that was independent of other aspects of reward value including willingness to wait, consummatory behaviors, or place preferences measured within the same trial. Following exposure to chronic social defeat stress, we found that only stress-susceptible but not stress-resilient mice revealed deficits in this metric after consuming but not after rejecting a reward on the previous trial, indicating that blunted anticipation in these animals is state-dependent, or punctuated by recent reward receipt. After increasing economic pressure and task demands by transitioning mice from a reward-rich to a reward-scarce environment, locomotion was globally invigorated and, in turn, masked stress-related deficits in reward anticipation. These findings suggest that the ability to detect changes in specific aspects of motivational deficits after chronic stress depends on an interaction between the state of an individual, recent reward history, and environmental circumstances.

Disclosures: B.M. Sweis: None. **R. Durand-De Cuttoli:** None. **F.J. Martinez-Rivera:** None. **L. Li:** None. **A.M. Minier-Toribio:** None. **S.J. Russo:** None. **E.J. Nestler:** None.

Poster

146. Behavioral Phenotypes and Neural Mechanisms of Relevance to Psychiatric Illness

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 146.07

Topic: G.05. Mood Disorders

Support: NIH R01MH051399
NIH T32-MH087004
Hope for Depression Research Foundation

Title: Gprin1 expression within the nucleus accumbens mediates resilience to chronic stress in mice

Authors: *T. M. GYLES, E. PARISE, A. GODINO, T. MARKOVIC, E. NESTLER;
Icahn Sch. of Med., Icahn Sch. of Med., New York, NY

Abstract: Major depressive disorder (MDD) is the leading cause of disability and a leading contributor to suicide according to the World Health Organization. Unfortunately, close to half of all patients diagnosed with MDD are at least partly resistant to available antidepressant treatments. Both genetic and environmental factors, including exposure to chronic social stress, play a role in the development of MDD and related syndromes. The chronic social defeat stress (CSDS) paradigm in mice has proven to be a highly useful animal model for studying depression-related behavioral abnormalities. Importantly, this paradigm allows for the identification of animals that develop such abnormalities, termed susceptible, from those that maintain mostly normal behavioral function, termed resilient. To better understand the potential genes underlying the resilient phenotype, we performed RNA-sequencing on mice exposed to CSDS and compared gene expression changes within the nucleus accumbens (NAc) between resilient and susceptible mice. Using weighted gene co-expression network analysis (WGCNA), we deduced several gene expression modules that are associated uniquely with resilience. We identified three genes (*Gprin1*, *Bcr*, and *Stx1a*) that were predicted to be key drivers (predicted to regulate other genes) within a highly significant, resilient-specific module. Our current focus is on investigating how changes in the expression of G protein-regulated inducer of neurite outgrowth 1 (GPRIN1) influences depression-related behaviors following stress. We confirmed that mice exposed to CSDS exhibit increased *Gprin1* mRNA levels in the NAc. We are now testing the consequences of virally manipulating GPRIN1 within the medium spiny neuron subtypes of this brain region. Bilateral overexpression of GPRIN1 in all NAc neurons prior to CSDS produces a pro-resilient effect. The same effect is seen using a cell-type-specific infection of medium spiny neurons that express the dopamine 1 receptor (DRD1). Ongoing work is investigating this effect in DRD2 neurons, as well as characterizing how higher GPRIN1 levels change NAc neuronal and circuit function to promote behavioral resilience. This study provides new insight into molecular mechanisms that underlie stress resilience which can help guide future antidepressant drug discovery efforts.

Disclosures: T.M. Gyles: None. **E. Parise:** None. **A. Godino:** None. **T. Markovic:** None. **E. Nestler:** None.

Poster

146. Behavioral Phenotypes and Neural Mechanisms of Relevance to Psychiatric Illness

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 146.08

Topic: G.05. Mood Disorders

Support: NIH Grant F30MH124269
NIH Grant K99MH125016
NIH grant R01 MH114923
NIH grant T32GM008152
Davee Foundation

Title: Hippocampal mechanisms of ketamine's acute and sustained antidepressant effects

Authors: *R. RAWAT, E. TUNC-OZCAN, J. A. KESSLER;
Northwestern Univ., Chicago, IL

Abstract: Major Depressive Disorder (MDD) is a leading contributor to global disease burden. Antidepressant medications are limited by their efficacy and delayed therapeutic onset; by contrast, even in antidepressant-resistant patients, a single dose of ketamine decreases depressive symptoms within hours and its effects last up to weeks. Ketamine use itself carries significant risks, and its mechanisms are unclear, highlighting the need for mechanistic research to inform new therapeutics with similar speed and magnitude. We hypothesized that the rapid and sustained effects represent two separate processes. We demonstrated that 1) the activity of adult-born immature granule neurons (ABINs) in the hippocampal dentate gyrus is both necessary and sufficient for ketamine's rapid antidepressant effects and 2) the sustained effects of ketamine may share a mechanism with the sustained effects of other first-line antidepressants. Using both male and female mice, we determined that ketamine treatment preferentially activates ABINs within 24 hours, and chemogenetic inhibition of ABIN activity blocks the antidepressant effects of ketamine in mice exposed to Unpredictable Chronic Mild Stress (UCMS). Conversely, chemogenetic activation of ABINs without any change in neuronal numbers mimics both the cellular and the behavioral effects of ketamine, indicating that increased ABIN activity is sufficient for rapid antidepressant effects. We have also determined the time course of ketamine's sustained effects in mice exposed to UCMS, and found that neurogenic signaling may underlie the sustained antidepressant effects of ketamine, similar to what we have observed with different classes of first line antidepressants. We thus identify potential mechanisms by which the hippocampal neurogenic niche regulates ketamine's unique antidepressant properties.
All experiments were conducted in both male and female 8-10 week old C57/BL6 mice; sex differences were assessed in all tests prior to grouping. All analyses were performed by experimenters blinded to experimental groups. All experiments and behavioral paradigms were performed with at least three independent cohorts of all groups.

Disclosures: R. Rawat: None. **E. Tunc-ozcan:** None. **J.A. Kessler:** None.

Poster

146. Behavioral Phenotypes and Neural Mechanisms of Relevance to Psychiatric Illness

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 146.09

Topic: G.05. Mood Disorders

Support: R01MH051399
1F99NS129172-01
Hope for Depression Research Foundation

Title: Approach-avoidance dynamics sensitive to social stress

Authors: *A. MINIER-TORIBIO, F. J. MARTINEZ, C. AZIZIAN, A. GODINO, L. LI, L. ROYCHOWDHURY, A. AUBRY, C. J. BROWNE, A. TORRES-BERRÍO, G. ROJAS, S. J. RUSSO, E. J. NESTLER;
Nash Family Dept. of Neurosci. and Friedman Brain Inst., Icahn Sch. of Med. at Mount Sinai, New York, NY

Abstract: Approach-avoidance conflicts impose decision-making demands to evaluate concurrent rewards and threats. This critical cognitive process is severely affected by stress-related disorders such as major depressive disorder (MDD), where patients often show a blunted approach to rewards to avoid irrelevant threats. Despite the prevalence of this maladaptation, little progress has been made to elucidate its underlying neurobiology. Here, we combined mouse models to study this approach-avoidance imbalance relevant for depression-associated phenotypes at the behavioral, cellular, and molecular levels. First, we exposed mice to chronic social defeat stress (CSDS mice), a well-validated model used to study MDD, which reveals resilient (RES) or susceptible (SUS) phenotypes as compared with naïve control mice. We then tested these groups on a novel adapted platform-mediated avoidance (PMA) task (Bravo-Rivera et al. 2014) to assess their approach-avoidance biases. In the PMA, mice learn to avoid a tone signaling a footshock by losing access to a lever signaling saccharine-water reward (approach). While we did not observe significant approach or avoidance differences during conditioning among groups, SUS mice showed elevated tone-evoked freezing. Subsequent extinction training revealed that SUS mice display extinction deficits by showing elevated freezing and avoidance, and reduced approach. Capitalizing on these behavioral findings, ongoing experiments aim to establish the role of different neurons in key brain areas signaling approach, avoidance, and stress processes, such as the nucleus accumbens (NAc). We are now capturing *in vivo* temporospatial dynamics of NAc cells by performing fiber photometry recordings of medium spiny neurons (MSNs) expressing D1 or D2 receptors during PMA testing, in naïve and CSDS mice. Moreover, we are using chemogenetic manipulations of D1 or D2 neurons to test their causal role in signaling approach-avoidance biases. Our preliminary results indicate that avoidance is bidirectionally regulated by D1 and D2 MSNs in the NAc, where D2 activity seems to particularly promote avoidance extinction in RES mice. Additional studies are directed at performing iDISCO+ to map brain-wide active neurons via FOS immunohistochemistry in naïve and CSDS mice after PMA. Together, this work provides a neurobehavioral profile of maladaptive decision-making after social stress, highlighting novel neurobiological targets to alleviate specific stress-induced behavioral abnormalities.

Disclosures: **A. Minier-Toribio:** None. **F.J. Martinez:** None. **C. Azizian:** None. **A. Godino:** None. **L. Li:** None. **L. Roychowdhury:** None. **A. Aubry:** None. **C.J. Browne:** None. **A. Torres-Berrío:** None. **G. Rojas:** None. **S.J. Russo:** None. **E.J. Nestler:** None.

Poster

146. Behavioral Phenotypes and Neural Mechanisms of Relevance to Psychiatric Illness

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 146.10

Topic: G.05. Mood Disorders

Support: KBRI 22-BR-02-02
NRF-2018M3C7A1024150

Title: Stress resilient role of mGluR5 in BLA target neurons

Authors: *J. KIM[1], S. KANG[2], T.-Y. CHOI[3], K.-A. CHANG[4], J. KOO[1];
[1]Korea Brain Res. Inst., Korea Brain Res. Inst., Daegu, Korea, Republic of; [2]Gachon Univ., Gachon Univ., Incheon, Korea, Republic of; [3]Korea Brain Res. Inst. (KBRI), Korea Brain Res. Inst. (KBRI), Daegu, Korea, Republic of; [4]Gachon Univ, Colleage of Med., Gachon Univ, Colleage of Med., Incheon, Korea, Republic of

Abstract: The metabotropic glutamate receptor 5 (mGluR5) has been implicated in stress-related psychiatric disorders, particularly major depressive disorders. Although growing evidence supports the pro-resilient role of mGluR5 in corticolimbic circuitry in the depressive-like behaviors following chronic stress exposure, the underlying neural mechanisms, including circuits and molecules, remain unknown. We measured the c-fos+ expression and probability of neurotransmitter release in and from the basolateral amygdala (BLA) neurons projecting to the medial prefrontal cortex (BLA to PFC), and ventral hippocampus (BLA to HPC) after chronic social defeat stress (CSDS). The role of the BLA projections in depressive-like behaviors was assessed using optogenetic manipulations, and the underlying molecular mechanisms of mGluR5 and downstream signaling were investigated by Western blotting, viral-mediated gene transfer, and pharmacological manipulations. CSDS disrupted the neural activity and glutamatergic transmission in both BLA to PFC and BLA to HPC projections. Optogenetic activation of the BLA projections reversed the detrimental CSDS effects on depressive-like behaviors and mGluR5 expression in mPFC and vHPC. Conversely, inhibition of the BLA projections of mice undergoing subthreshold social defeat stress-induced a susceptible phenotype and mGluR5 reduction. These two BLA circuits appeared to act in an independent way. Importantly, we demonstrate that mGluR5 overexpression in mPFC or vHPC was pro-resilient, while the mGluR5 knockdown was pro-susceptible and that the pro-resilient effects of mGluR5 are mediated through distinctive downstream signaling pathways in the mPFC and vHPC. These findings identify mGluR5 in the mPFC and vHPC that receive BLA inputs as a critical mediator of stress-resilience, highlighting circuit-specific signaling for depressive-like behaviors.

Disclosures: **J. Kim:** None. **S. Kang:** None. **T. Choi:** None. **K. Chang:** None. **J. Koo:** None.

Poster

146. Behavioral Phenotypes and Neural Mechanisms of Relevance to Psychiatric Illness

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 146.11

Topic: G.05. Mood Disorders

Support: Iowa Osteopathic Education and Research Funds (V.D.)

Title: Genetic profiling of the hippocampus during peripheral chronic inflammatory pain

Authors: A. GARMAN, A. ASH, E. KOKKINOS, D. NERLAND, *L. WINTER, V. DURIC; Des Moines Univ., Des Moines, IA

Abstract: Adam Garman, Allison Ash, Ellie Kokkinos, Dakota Nerland, Lori Winter, Vanja Duric Department of Physiology and Pharmacology, Des Moines University, Des Moines, IA 50312, USA
AbstractAltered mood and other psychiatric disorders are commonly associated with all types of chronic pain conditions. Recent neuroimaging studies indicate that pain exposure activates neural networks associated with cognitive and emotional aspects of pain, independent of sensory pain processing; however, brain mechanisms linking chronic pain conditions and development of comorbid clinical depression are still largely unknown. Here, we used a genome-wide RNA sequencing (RNAseq) analysis to examine the genetic profile of the hippocampus, a limbic region that regulates mood and stress responses, from male rats exposed to 35 days of inflammatory pain. Pain animals were further separated into either ‘resilient’ or ‘susceptible’ to development of enhanced behavioral emotionality based on behavioral testing (i.e., sucrose preference test, novelty suppressed feeding test, open field test). Bioinformatic analysis of the RNAseq data, followed by secondary confirmation using qPCR, revealed dysregulation of hippocampal genes involved in neuroinflammation and blood brain barrier integrity. Specifically, ADAM Metallopeptidase Domain 8 (ADAM8) and Aurora Kinase B (AurkB), genes with functional roles in the activation of the NLRP3 inflammasome and microgliosis, respectively, were significantly upregulated in the hippocampus of ‘susceptible’ animals expressing increased behavioral emotionality. In addition, genes associated with blood brain barrier integrity, such as the tight junction proteins Claudin 4 (Cldn4) and Claudin 5 (cldn5), were also significantly dysregulated between ‘resilient’ and ‘susceptible’ pain groups. Furthermore, the ongoing studies are focused on characterization of expression of these genes in rodent stress models (i.e., oral corticosterone, chronic restraint stress) as well as responsiveness to rapid antidepressant treatment with ketamine following exposure to chronic pain. Overall, the results of our RNAseq study continues to strengthen the idea that dysregulation of genes involved in neuroinflammatory process with the hippocampus and the integrity of the blood brain barrier may be associated with the increased behavioral emotionality found often expressed in chronic pain states.

Keywords: chronic pain, depression, gene, hippocampus, ADAM8, *Supported by Iowa Osteopathic Education and Research Funds (V.D.)*

Disclosures: **A. Garman:** None. **A. Ash:** None. **E. Kokkinos:** None. **D. Nerland:** None. **L. Winter:** None. **V. Duric:** None.

Poster

146. Behavioral Phenotypes and Neural Mechanisms of Relevance to Psychiatric Illness

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 146.12

Topic: G.05. Mood Disorders

Support: NIMH Grant 5R01MH126137
Pritzker Neuropsychiatric Disorders Research Consortium
Taubman Institute Biomedical Scholars Fund

Title: Studying the longitudinal effects of chronic stress using a novel digital behavioral box system

Authors: *A. GHIMIRE[1], D. KIRCA[1], P. HALE[1], I. CERDA[1,2], P. J. FITZGERALD[3], N. OGNJANOVSKI[4], S. MARINO[5], D. KIM[4], P. VIJAYAKUMAR[4], B. O. WATSON[4]; [1]Dept. of Psychiatry, Univ. of Michigan, Ann Arbor, Ann Arbor, MI; [2]Harvard Univ., Cambridge, MA; [3]Psychiatry, [4]Dept. of Psychiatry, [5]Univ. of Michigan, Ann Arbor, MI

Abstract: Stress in humans can lead to mental health conditions such as depression and anxiety. In rodents, we have powerful neuroscientific tools that are not available in humans, allowing for the study of neurobiologic circuitry that underlie mental health disorders in humans. While the behavior of mice exposed to chronic stress has been well studied, most prior work in this field has used relatively short-term tests (with a duration of minutes to hours) and does not measure behavior longitudinally or in conjunction with simultaneous brain electrophysiology. Furthermore, prior work utilizes experimenter-defined behavior tests, rather than assaying naturalistic behavior in the homecage. This is of particular importance given that depression and stress in humans manifest as changes to daily life including eating habits, energy level, motivation, sleep, and other symptoms. Such symptoms in humans are typically assessed using verbal reports. Efforts to more objectively quantify them use a “Digital Phenotyping" approach with the help of smartphones and activity trackers. Here we present our “Digital Homecage”(DH) system for mice and rats which allows us to track sucrose preference, weight, activity, preference for high-fat food pellets vs. regular pellets, and running wheel activity. We also acquire continuous video recordings, which are processed with commercial software (HomeCageScan, Cleversys Inc.) to provide objective behavioral scoring. Finally, we have designed this system to work in conjunction with simultaneous brain electrophysiological recording. We are able to score electrophysiological data into wake/REM/nonREM states, as well as quantify spectral, LFP and spiking events. All of this data is recorded 24/7 for multiple

weeks while discriminating behavior at sub-second resolution. Our results thus far demonstrate that sucrose preference in our system demonstrates response to both ambient lighting conditions and to acute stress. Ongoing work will quantify responses to chronic stress.

Disclosures: A. Ghimire: None. **D. Kirca:** None. **P. Hale:** None. **I. Cerda:** None. **P.J. Fitzgerald:** None. **N. Ognjanovski:** None. **S. Marino:** None. **D. Kim:** None. **P. Vijayakumar:** None. **B.O. Watson:** None.

Poster

146. Behavioral Phenotypes and Neural Mechanisms of Relevance to Psychiatric Illness

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 146.13

Topic: G.05. Mood Disorders

Support: Canadian Institute for Health Research 201903PJT-419517-PT

Title: Investigating Cross-Resilience to Chronic Social Defeat and Learned Helplessness Stress

Authors: *L. PENNEY, G. FAKHFOURI, M. BAIRACHNAYA, B. GIROS;
Psychiatry, McGill Univ., Montréal, QC, Canada

Abstract: The chronic social defeat (CSDS) and learned helplessness (LH) rodent models of stress have facilitated investigation of the molecular mechanisms underlying resilience and susceptibility to major depressive disorder (MDD) and post-traumatic stress disorder (PTSD). In this study, we wanted to determine whether there is a shared resilience to these two distinct paradigms of chronic stress: CSDS and LH, a trauma-type stress. 2-3 months old C57BL/6J mice were subjected to 10 days of CSDS, resulting in depression-like phenotypes in susceptible individuals, followed by a 30-day LH protocol using inescapable foot shocks. Our research combines several behavioural techniques and suggests that there is a cross-resilience to these two types of stress in both males and females. We found that a higher proportion of mice that were resilient following CSDS were also resilient following LH, compared to individuals that were CSDS susceptible and non-defeated controls. We also identified different patterns of resilience for males and females, with defeated females acquiring resilience to LH stress earlier than defeated males. These results point to a cross-resilience to chronic social and trauma-type stress, which is relevant to the understanding of the underlying mechanisms of resilience to MDD and PTSD.

Disclosures: L. Penney: None. **G. Fakhfouri:** None. **M. Bairachnaya:** None. **B. Giros:** None.

Poster

146. Behavioral Phenotypes and Neural Mechanisms of Relevance to Psychiatric Illness

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 146.14

Topic: G.05. Mood Disorders

Support: Partially supported by PRONACES-CONACYT grant 194171
VIEP-BUAP 2021-2022 to CA in Neuroendocrinología (BUAP-CA-288)
Fellowship from CONACYT No. 885936

Title: Sertraline had differential antidepressant effects in high- and low-yawning sublines of Sprague-Dawley rats

Authors: *D. BRAVO DURÁN[1], J. R. EGUIBAR[2], C. CORTES[3];
[1]Inst. of Physiol., Benemerita Univ. Autonoma De Puebla, Puebla, Mexico; [2]Intl. Office, Inst. of Physiol., Benemerita Univ. Autonoma De Puebla, Puebla, Pue., Mexico; [3]Inst. of Physiol., Benemerita Univ. Autonoma de Puebla, Puebla, Mexico

Abstract: Depression is the most prevalent mental disorder in the world, and it has been shown that high levels of stress are linked to an increased susceptibility to suffer anxiety and/or depression. In our laboratory, we selectively inbred two sublines from Sprague-Dawley (SD) rats, the high-yawning (HY) with 20 yawns/h and low-yawning (LY) with just 2 yawns/h. These sublines differ in the stress and anxiety responses in different psychobiological paradigms, being the LY rats more susceptible to stress with respect to HY that are resilient. The aim of this study was to assess the effect of sertraline (2.5 and 5 mg/Kg) on depressive behavior on both sublines using the forced swim test. We used adult male HY and LY rats (n = 6 per dose) that were housed in standard conditions with free access to rodent pellets and water. All subjects (Ss) had two swim-sessions in two consecutive days, the first with 15 min duration and, 24 h later, a second session of 5 min. The Ss received a chronic administration scheme with i.p. injections of sertraline at 23.5, 5 and 1 h before the second test. We scored the following behaviors: immobility, swimming, climbing, diving, number of grooming and head shakes, the last two behaviors are anxiety related. Our results show that with 2.5 mg/Kg dose of sertraline significantly decrease the immobility time in the HY rats with respect to LY rats ($p < 0.05$). Only swimming was increased significantly in HY rats ($p< 0.05$); and head shakes decreased significantly in HY rats ($p < 0.05$). In conclusion, these results show that HY rats are not only resilient to depression, but also that lower doses of sertraline have a greater antidepressant effect supporting that they are more sensible to serotonin uptake blockers.

Disclosures: D. Bravo Durán: None. **J.R. Eguibar:** None. **C. Cortes:** None.

Poster

146. Behavioral Phenotypes and Neural Mechanisms of Relevance to Psychiatric Illness

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 146.15

Topic: G.05. Mood Disorders

Support: National Science Centre Poland (Research grant UMO-2016/23/B/NZ4/01562), statutory funds of the Institute of Pharmacology Polish Academy of Sciences

Title: Trait sensitivity to negative feedback determines the effects of chronic stress and chronic mirtazapine treatment on anxiety and stress-coping strategy in rats

Authors: *P. SURÓWKA, K. NOWORYTA, A. CIEśLIK, R. RYGUłA;
Maj Inst. of Pharmacol. Polish Acad. of Sci., Krakow, Poland

Abstract: In this study, we examined whether trait sensitivity to negative feedback (NF) can interact with the effects of chronic stress and antidepressant treatment on anxiety and stress-induced coping strategies in rats. To accomplish this goal, the animals were screened in a series of probabilistic reversal learning tests and in this way each rat was classified into one of the 2 groups: NF insensitive or NF sensitive. Subsequently, the animals were subjected to chronic, restraint stress and parallel chronic treatment with antidepressant drug mirtazapine. Since the sensitivity to NF seems to theoretically interact with individual levels of anxiety and the ability to cope with stressful situations, the intergroup differences in the effects of stress and antidepressant treatment on anxiety-like behaviors and coping strategies were investigated using light/dark box and forced swim (FST) tests. Results of the conducted experiments indicated, that animals displaying trait insensitivity to NF, were more prone to develop stress-induced anxiety than their NF sensitive conspecifics. Moreover, an analysis of the behavioral patterns displayed by the NF insensitive animals during the FST, revealed complementary (anxiety-driven) effects of trait sensitivity to NF on the strategy of coping with an acute, stressful situation. Finally, an analysis of the interactions between NF sensitivity and the effects of antidepressant drug - mirtazapine revealed, that in animals subjected to chronic stress, the effects of the drug on anxiety and coping strategies differ significantly between animals classified as NF insensitive and NF sensitive. The present results suggest, that NF sensitivity screening could be potentially used to determine individual vulnerability to development of affective disorders and effectivity of their treatment.

Disclosures: P. Surówka: None. **K. Noworyta:** None. **A. Cieślik:** None. **R. Ryguła:** None.

Poster

146. Behavioral Phenotypes and Neural Mechanisms of Relevance to Psychiatric Illness

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 146.16

Topic: G.05. Mood Disorders

Support: NIH Grant 5R01MH106500-08

Title: Impact of social defeat stress on microglia and neuron cytoarchitecture in the nucleus accumbens

Authors: *D. FRANCO[1], B. M. SIEMSEN[1], S. L. KEY[1], P. DAS[1], M. S. HINGMIRE[1], M. E. FOX[2], M. LOBO[1];
[1]Anat. and Neurobio., Univ. of Maryland Baltimore, Baltimore, MD; [2]Anesthesiol. and Perioperative Med., Pennsylvania State Univ. Col. of Med., Hershey, PA

Abstract: Exposure to chronic stress in mice, a known risk factor for depression, produces long-lasting changes to the nucleus accumbens (NAc). Specifically, dendritic atrophy of dopamine receptor type 1 (D1), but not type 2 (D2) expressing medium spiny neurons (MSNs) is necessary and sufficient for chronic stress-induced deficits in motivational behavior. Emerging evidence implicates microglia as potential mediators of neuronal atrophy and motivational deficits after social stress. Since microglia can interact with neurons and facilitate neuronal dysfunction and cell death, they are prime candidates for investigating the relationship between chronic stress and D1-MSN atrophy. We hypothesized that D1-MSN atrophy would be associated with increased contact of D1-MSNs by microglia processes, facilitating dendritic atrophy. Male D1-CX3CR1-GFP and D2-CX3CR1-GFP mice were subjected to 10 days of CSDS, during which subjects were socially defeated by a male aggressor. A social interaction test determined susceptible (avoids interaction) and resilient (approaches interaction) groups. 3D reconstruction analyses of D1- or D2-MSNs and adjacent microglia were performed on confocal Z-stacks to quantify microglia morphology and MSN contact. CSDS reduced overall microglia contact at D1-MSNs, but not D2 MSNs, but microglia-MSNs contact in stressed animals negatively predicted CSDS-induced decreases in social interaction. Mice displaying the greatest social avoidance showed the greatest microglia-D1 MSN contact. CSDS decreased microglia density in the area occupied by D1-MSN dendrites, yet the average volume of microglia somas (an index of activated microglia) was increased by CSDS, which also negatively predicted CSDS-induced social avoidance. Reconstruction analyses of individual microglia within the region occupied by D1-MSNs revealed that only animals susceptible to CSDS displayed reduced microglia complexity. This adds to the growing body of literature implicating microglia in disease states. Future studies will focus on causally linking microglia alterations to stress-related neuropsychiatric disease. Upcoming experiments seek to characterize CD68 expression, a phagocytic marker, in socially defeated mice. Microglia mechanisms contributing to altered neuronal dendritic morphology and subsequent maladaptive behavioral phenotypes can pinpoint novel therapeutic targets for stress-related disorders and improve current treatments.

Disclosures: D. Franco: None. **B.M. Siemsen:** None. **S.L. Key:** None. **P. Das:** None. **M.S. Hingmire:** None. **M.E. Fox:** None. **M. Lobo:** None.

Poster

146. Behavioral Phenotypes and Neural Mechanisms of Relevance to Psychiatric Illness

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 146.17

Topic: G.05. Mood Disorders

Support: NIH Grant R01MH114882 (S.J.R.)
NIH Grant R01MH127820 (S.J.R.)
NIH Grant R01MH104559 (S.J.R.)
NIH Grant R01MH120514 (S.J.R.)
NIH Grant R01MH120637 (S.J.R.)
Brain & Behavior Research Foundation (30233)(L.L.)
Brain & Behavior Research Foundation (29104) (F.C.)

Title: Traumatic social experience engages lateral septum neurotensin circuitry to occlude social reward

Authors: *L. LI, R. DURAND-DE CUTTOLI, A. V. AUBRY, J. BURNETT, F. CATHOMAS, L. F. PARISE, K. CHAN, C. MOREL, C. YUAN, Y. SHIMO, H.-Y. LIN, J. WANG, S. J. RUSSO;
Icahn Sch. of Med. at Mount Sinai, New York, NY

Abstract: In humans, traumatic social experiences can contribute to psychiatric disorders. It is suggested that social trauma impairs brain reward function such that social behaviour is no longer rewarding, leading to severe social avoidance. In rodents, the chronic social defeat stress (CSDS) model has been used to understand the neurobiology underlying stress susceptibility versus resilience after social trauma, yet little is known regarding its impact on social reward. Here we show that, following CSDS, a subset of male and female mice termed susceptible (SUS) avoid social interaction with non-aggressive same sex juvenile C57BL/6J mice and do not develop context-dependent social reward following encounters with them. Non-social stressors have no effect on social reward in either sex. Next, using whole brain cFos mapping, *in vivo* Ca^{2+} imaging and whole cell recordings we identified a population of stress/threat-responsive lateral septum neurotensin (NT^{LS}) neurons that are activated by juvenile social interactions only in SUS mice, but not resilient or unstressed control mice. Optogenetic and chemogenetic manipulation of NT^{LS} neurons and their downstream connections modulate social interaction and social reward. Together, these data suggest that previously rewarding social targets are possibly perceived as social threats in SUS mice, resulting from hyperactive NT^{LS} neurons that occlude social reward processing.

Disclosures: L. Li: None. **R. Durand-De Cuttoli:** None. **A.V. Aubry:** None. **J. Burnett:** None. **F. Cathomas:** None. **L.F. Parise:** None. **K. Chan:** None. **C. Morel:** None. **C. Yuan:** None. **Y. Shimo:** None. **H. Lin:** None. **J. Wang:** None. **S.J. Russo:** None.

Poster

146. Behavioral Phenotypes and Neural Mechanisms of Relevance to Psychiatric Illness

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 146.18

Topic: G.05. Mood Disorders

Support: Foundation for OCD Research
Berkelhammer Award for Excellence in Neuroscience

Title: Intercalated nuclei of the amygdala function is disrupted in a mouse model of OCD

Authors: *R. ST. LAURENT, K. M. KUSCHE, A. C. KREITZER;
GIND, Gladstone Inst., San Francisco, CA

Abstract: Patients with obsessive compulsive disorder (OCD) have debilitating symptoms consisting of persistent negative thoughts, compulsions, and anxiety. Using advanced tools only available in mice, we can probe neural circuits that are necessary for the generation of behaviors relevant to OCD. For example, compulsivity, anxiety, and negative reinforcement are abnormal in OCD patients and we can measure correlates of these in mice. We focus on the intercalated nuclei of the amygdala (ITC): clusters of inhibitory cells that mediate components of negative reinforcement learning, anxiety, and repetitive behavior. The ITC is well positioned to influence behavior because it integrates cortical, thalamic, and neuromodulatory inputs while acting as a gate for amygdala output regions. We hypothesized that upregulation of ITC activity could lead to OCD-like behavior and that ITC activity is disrupted in an OCD mouse model. We targeted the ITC in FoxP2-cre mice and found that chemogenetic or optogenetic ITC stimulation increased self-grooming in an open field, however measured no effect on anxiety in an elevated plus maze. Next, we trained mice in a platform-mediated avoidance task to evaluate extinction of avoidance behavior. Using fiber photometry recordings of GCamp6f in the ITC of FoxP2-cre mice, we found that ITC responds strongly to shock early in training but shifted to the warning tone later in training, and ITC responses dissipated in extinction. We next used FoxP2-cre mice crossed to the SAPAP3 knockout line, allowing us to perform circuit-specific manipulations of the ITC in an OCD mouse model. Recordings done in FoxP2-cre::SAPAP3 mice revealed diminished responses to footshock in knockout mice compared to wildtype littermates. In a separate cohort, we activated the ITC using channelrhodopsin in FoxP2-cre::SAPAP3 mice during warning tones. Optogenetic stimulation increased avoidance in SAPAP3 knockout mice only; elevated avoidance persisted in a recall test the following day. To further investigate the knockout-specific behavior effect, we measured synaptic strength in SAPAP3 mice. We performed ex vivo whole-cell recordings and found a decrease in AMPAR/NMDAR ratio at prefrontal cortex (PFC) to ITC synapses in slices from SAPAP3 knockout vs. wildtype mice. This suggests that synaptic deficits reported in striatum in SAPAP3 knockout mice also extend to the ITC. Future studies will examine a causal link between changes in synaptic strength and behavioral phenotypes in this OCD mouse model. Our results suggest that dysregulated ITC activity can generate OCD-like behaviors and ITC activity during negative reinforcement is affected in SAPAP3 knockout mice.

Disclosures: R. St. Laurent: None. **K.M. Kusche:** None. **A.C. Kreitzer:** A. Employment/Salary (full or part-time):; MapLight Therapeutics.

Poster

146. Behavioral Phenotypes and Neural Mechanisms of Relevance to Psychiatric Illness

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 146.19

Topic: G.05. Mood Disorders

Support: NIMH Grant 5R01MH106500-08

Title: Nucleus accumbens neuron subtype translatomes in social stressed females

Authors: *G. KUMAR[1], D. FRANCO[1], M. E. FOX[2], M. BASU[1], J. OLUSAKIN[1], M. D. TURNER[1], S. AMENT[1], M. LOBO[1];
[1]Univ. of Maryland Sch. of Med., Baltimore, MD; [2]Penn State Col. of Med., Hershey, PA

Abstract: Nucleus accumbens neuron subtype translatomes in social stressed femalesGautam Kumar, Daniela Franco, Megan E. Fox, Mahashwata Basu, Jimmy Olusakin, Makeda Turner, Seth Ament, Mary Kay Lobo Stress can impact vulnerability for mental illness including depression. While depression occurs in both sexes there is a higher prevalence in females. However, social stress paradigms in animals often include only male subjects. To overcome this limitation, we used the chronic witness social defeat stress (CWDS) in female subjects. We employed a social preference test with same sex conspecifics to demonstrate a susceptible group that displays reduced social preference and a resilient group with social preference similar to controls. To elucidate the molecular mechanisms that underlie these individual differences in females exposed to CWDS we employed translatome RNA-seq profiling in nucleus accumbens (NAc) projection neuron subtypes, the dopamine 1 and 2 expressing medium spiny neurons (D1-MSNs and D2-MSNs). Weighted gene coexpression analysis (WGCNA) identified gene network modules significantly regulated by stress in MSN subtypes, with both stress susceptible and resilient regulated modules in D1-MSNs and only stress susceptible regulated modules in D2-MSNs. Further analysis of the WGCNA modules revealed that more modules for the D1-MSNs are regulated in resilient mice and represent molecules involved in development and proliferation, mitochondrial activity, and immune responses. D2-MSN susceptible modules are enriched in molecules involved in transcription, metabolic processes, and synaptic processes. Consensus modules between D1- and D2-MSNs were also identified. Consensus modules involved in transcriptional regulation and protein processing were shown to be downregulated in the stress susceptible group while consensus modules involved in synaptic structures were upregulated. Collectively, our studies uncover altered molecular processes in NAc neuron subtypes that may underlie female stress response.

Disclosures: G. Kumar: None. **D. Franco:** None. **M.E. Fox:** None. **M. Basu:** None. **J. Olusakin:** None. **M.D. Turner:** None. **S. Ament:** None. **M. Lobo:** None.

Poster

146. Behavioral Phenotypes and Neural Mechanisms of Relevance to Psychiatric Illness

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 146.20

Topic: G.05. Mood Disorders

Support: NIH Grant 5R01MH111918
NIH Grant 5T32MH015174

Title: Comparing whole brain activation patterns in the preexisting and consolidated connectomes of male and female mice following social defeat stress.

Authors: *K. R. ANDERSON[1], C. LARDNER[4], A. LIPSHUTZ[5], P. ROGU[2], H. MCBRIDE[3], D. FORTUNA[3], A. MANGANARO[3], D. DUMITRIU[3];
[1]Home, Columbia Univ. Med. Ctr., NY, NY; [2]Columbia Univ. Med. Ctr., New York, NY; [3]Columbia Univ. Med. Ctr., NY, NY; [4]Columbia Univ., Columbia Univ., New York, NY; [5]Barnard College, Columbia Univ., New York, NY

Abstract: Stress is a risk factor for the development of many disorders. Despite substantial research and understandings, a gap remains. One factor is the heterogeneous behavioral and neurobiological outcomes across individuals to stress. Some are susceptible while others display natural resilience. The majority of rodent studies thus far have aimed to uncover mechanisms of stress on the brain and body after stress exposure in those who are susceptible and largely in males. We have recently shown the brain displays circuity differences prior to stress exposure. To address the connection between the two connectomes, we specifically examine stress-induced activation patterns during an initial stressor and compare to the activation patterns following chronic stress in the same individual to uncover how this relationship results in behavioral responses. To do this, we first developed a model of social defeat (SD) stress that includes males and females. In SD, aggressor male CD1 urine is applied to both male and female mice and a pair is exposed to an aggressor for 10 minutes followed by aggressor co-housing for 10 days. SD is followed by a social interaction (SI) test to determine susceptible (avoidant) and resilient (social preference) phenotypes. There is a reliable population spilt with 40% of females and of males displaying approach behavior. Second, we utilize the TRAP2 mouse model that confers the ability to temporally tag neurons along side of immediate early gene staining. The mice undergo SD with trapping at the first stress exposure to capture the pre-existing connectome and cFos staining after the final stress exposure to capture the consolidated connectome. Preliminary data shows region specific trends that generally demonstrate control mice have lower numbers of neurons activated at both timepoints with no increase following chronic stress and no overlap of neurons, defeated mice have an increase in the number of activated neurons following a chronic stress and defeated animals with avoidant behavior have a higher magnitude in this increase, and lastly there is a trend toward increased colocalization in the two activation patterns in animals that display approach behavior. This whole brain approach aims to uncover the neurocircuit mechanisms of how selective susceptibility or resiliency to stress emerges.

Disclosures: K.R. Anderson: None. **C. Lardner:** None. **A. Lipshutz:** None. **P. Rogu:** None. **H. McBride:** None. **D. Fortuna:** None. **A. Manganaro:** None. **D. Dumitriu:** None.

Poster

146. Behavioral Phenotypes and Neural Mechanisms of Relevance to Psychiatric Illness

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 146.21

Topic: G.05. Mood Disorders

Support: R21MH122862

Title: Vulnerability to postpartum anhedonia and underlying neuroimmune and resting state function in Sprague Dawley rats

Authors: *J. GIFFORD, J. M. SCHWARZ;
Univ. of Delaware, Newark, DE

Abstract: Approximately 60% of new mothers experience postpartum mood disturbances known as the “baby blues.” Fortunately, most new mothers recover within a few weeks but a significant subset (10-15%) go on to develop postpartum depression (PPD). The present study aimed to examine the onset of anhedonia and associated changes in neuroimmune and endocrine function as well as altered resting state brain function postpartum. First time dams underwent a series of sucrose preference tests (prior to breeding and postpartum) to examine depressive-like behavior. Previous data revealed pre-pregnancy, most rats exhibit a strong sucrose preference (>80%) but immediately postpartum approximately 40% of new mothers display anhedonia suggesting some mothers are susceptible and others resilient to this onset of postpartum anhedonia. To better understand these individual differences, brain tissue was collected from animals at either postnatal day 2 or 9 and assessed for neuroimmune function. Fecal samples were also collected and assayed for estradiol and corticosterone levels. Results indicated an increase in IL-6 in susceptible animals in the dorsal hippocampus and medial prefrontal cortex (mPFC) at P2 and P9 time points as well as decreased BDNF in the mPFC at P2 and P9. Increased corticosterone postpartum was observed in resilient animals while no differences were observed in estradiol. Further, results suggest susceptible animals have altered default mode network integration between P3 and P10. Overall, this work aims to better understand and predict susceptibility or resiliency to postpartum anhedonia with hopes to proactively identify risk factors associated with PPD to aid in the development of future targeted therapeutics.

Disclosures: J. Gifford: None. **J.M. Schwarz:** None.

Poster

146. Behavioral Phenotypes and Neural Mechanisms of Relevance to Psychiatric Illness

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 146.22

Topic: G.05. Mood Disorders

Support: College of Sciences Dean Start Up Funds
UL Lafayette Graduate Student Organization
Louisiana Board of Regents Research Competativeness Award

Title: Examination of Addiction Related Pathways in a Primate Model of Self Injurious Behaviors

Authors: J. BARUA[1], M. JACKSON[1], B. L. FORET[2], E. ROMERO[4], D. HASSELSCHWERT[4], J. FONTENOT[4], F. VILLINGER[5], ***K. SMITH**[3];
[1]Dept. of Biol., Univ. of Louisiana, Lafayette, Lafayette, LA; [2]Dept. of Biol., [3]Univ. of Louisiana At Lafayette, Lafayette, LA; [4]New Iberia Res. Ctr., [5]New Iberia Res. Ctr. and Biol., Univ. of Louisiana at Lafayette, New Iberia, LA

Abstract: Self-injurious behavior (SIB) is a health issue of global concern, affecting both humans and non-human primates (NHP). Also referred medically as Non-suicidal self-injury (NSSI), SIB is defined as the deliberate, self-inflicted destruction of body tissues that causes immediate damage without suicidal intent, and that is not part of a cultural ritual. Individuals with NSSI are at higher risk of suicide attempt. In NHPs and humans, NSSI is speculated to be addictive by inducing endogenous opioid release and alleviation of emotional distress. This model directly relates to the limbic system, particularly the amygdala and reward circuits including the Ventral Tegmental Area (VTA) and Nucleus Accumbens (NAc). Developing a critical understanding of the neurobiology of SIB may be strengthened by exploring pathways of endogenous opioid signaling in the amygdala and dopamine in reward circuits. Our study of spontaneously occurring self-injurious behaviors focused on brains from NHPs (Macaca mulatta) that were euthanized to alleviate suffering associated with SIB, and to prevent major wounding events. All animals had mild wounding events, but showed persistent SIB behaviors, not resolved by treatment with diazepam and enhanced environmental enrichment, and were considered at risk for increasing wounding events. Samples were donated by the New Iberia Research Center, to gain a better understanding of SIB and to aid in the development of future treatments that can address SIB in NHP and humans. Control NHP were healthy animals euthanized as part of a terminal research protocol. As found in previous studies, SIB is more common in male than female NHP at the NIRC. However, rates of SIB observed at the NIRC are approximately 1% of macaques, due to a robust behavioral enrichment program, and is lower than at other NHP facilities (SIB estimates as high as 14%). We examined endogenous opioid signaling molecules in the limbic system, including the amygdala of monkeys with SIB (12 males and 4 females with SIB) compared to age and sex matched controls (5 males and 4 females with no history of SIB). We have found a significant decrease in the expression levels of the mu opioid receptor (MOR) mRNA in the amygdala of NHPs with SIB by qRT-PCR. For immunohistochemistry studies, we have collected an additional 5 brains from control males and 15 brains of male NHPs with SIB that have been fixed in PFA. Current studies using immunoblotting and immunostaining with unbiased stereological cell counts of MOR+ cells, will focus on confirming the mu opioid receptor mRNA data with protein levels in the amygdala. We will also examine dopamine transporter expression the VTA and NAc.

Disclosures: **J. Barua:** None. **M. Jackson:** None. **B.L. Foret:** None. **E. Romero:** None. **D. Hasselschwert:** None. **J. Fontenot:** None. **F. Villinger:** None. **K. Smith:** None.

Poster

147. Treatment and Drug Discovery for Mood Disorders

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 147.01

Topic: G.05. Mood Disorders

Support: TRDRP 27FT-0022
TRDRP 27IP-0057
TRDRP T29IR0455
NIH GM-123582
NIH DA043829
NIH DA049140
NIH GM7616

Title: Selective serotonin reuptake inhibitors within and near cells: Resolution at the compartmental and temporal levels via genetically encoded biosensors

Authors: *A. L. NICHOLS[1], Z. BLUMENFELD[1,3], L. LUEBBERT[1,4], H. J. KNOX[2], A. K. MUTHUSAMY[2], J. S. MARVIN[5], C. H. KIM[1], S. N. GRANT[2], D. P. WALTON[2], B. N. COHEN[1], R. HAMMAR[6], L. L. LOOGER[5], P. ARTUSSON[6], D. A. DOUGHERTY[2], H. A. LESTER[1];
[1]Div. of Biol. and Biol. Engin., [2]Div. of Chem. and Chem. Engin., Caltech, Pasadena, CA; [3]Keck Sch. of Med., USC, Los Angeles, CA; [4]Inst. of Biol., Leiden Univ., Leiden, Netherlands; [5]Janelia Res. Campus, HHMI, Ashburn, VA; [6]Dept. of Pharm., Uppsala Univ., Uppsala, Sweden

Abstract: Selective serotonin reuptake inhibitors (SSRIs) are the most prescribed treatment for individuals experiencing major depressive disorder (MDD). Despite their widespread use, the mechanism that relieves MDD after SSRIs bind the serotonin transporter (SERT) is still not understood, partially because no method has existed to directly examine the cellular and subcellular pharmacokinetic properties of these compounds in living cells. Here, we studied movements of escitalopram and fluoxetine using several tools: new intensity-based drug sensing fluorescent reporters ("iDrugSnFRs"), targeted to the plasma membrane (PM), cytoplasm, and endoplasmic reticulum (ER); impermeant quaternary amine derivatives of these same SSRIs; and ~ 1 second solution changes, with cultured neurons and HeLa cells. For purified solutions of iDrugSnFRs and SSRIs, fluorescence signals are uncomplicated and reach completion within a few seconds; but the cellular measurements on the SSRIs and their iDrugSnFRs yield a rich set of kinetic phenomena, on time scales from a few seconds to ~10 min. In contrast, the membrane-impermeant quaternary derivatives showed simpler, faster signals; but they interact with SERT > 10-fold less strongly than the SSRIs. We interpret these data in light of previous reports that SSRIs both sequester within and perturb some membrane compartments and may reach SERT from the membrane phase. Although the time scale of our experiments is orders of magnitude slower than the "therapeutic lag" of SSRIs, the novel measurements presented here emphasize that pharmacokinetic properties of SSRIs, including their anomalously high volume of distribution, may play roles in both the therapeutic lag and the equally puzzling "antidepressant discontinuation syndrome".

Disclosures: A.L. Nichols: None. **Z. Blumenfeld:** None. **L. Luebbert:** None. **H.J. Knox:** None. **A.K. Muthusamy:** None. **J.S. Marvin:** None. **C.H. Kim:** None. **S.N. Grant:** None. **D.P.**

Walton: None. **B.N. Cohen:** None. **R. Hammar:** None. **L.L. Looger:** None. **P. Artusson:** None. **D.A. Dougherty:** None. **H.A. Lester:** None.

Poster

147. Treatment and Drug Discovery for Mood Disorders

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 147.02

Topic: G.05. Mood Disorders

Title: Discovery of novel 5-HT2A receptor modulators for the treatment of mood disorders

Authors: *C. A. BOWEN[1], T. A. KHAN[1], R. B. PERNI[1], R. SHIN[1], R. ARON[1], A. L. HALBERSTADT[2], B. R. DIFRANCESCO[3], A. E. BRERETON[3], S. RAO[1], G. F. SHORT, III[1]; [1]EntheogeniX Biosciences, Inc., Encinitas, CA; [2]UCSD, La Jolla, CA; [3]Cyclica Inc., Toronto, ON, Canada

Abstract: Therapeutics for mood disorders, including treatment-resistant depression, remain a significant unmet medical need. Accumulating clinical and preclinical research suggests the potential for serotonergic psychedelic compounds to exhibit rapid and lasting antidepressant activity after a single administration. Such compounds, including psilocybin and N, N-dimethyltryptamine, the active component of ayahuasca, are agonists of serotonin 5-HT2A receptors. The goal of the current research was to discover novel 5-HT2A receptor agonists with optimal drug-like properties that show in vitro and in vivo pharmacological effects consistent with psilocin, the active metabolite of psilocybin. Artificial intelligence-driven *de novo* drug design followed by medicinal chemistry structure-activity relationship development has identified a series of novel, potent, small molecule 5-HT2A receptor agonists with drug-like physicochemical properties. Compounds exhibited nanomolar potencies for in vitro activation of human and mouse 5-HT2A receptor signaling pathways and apparent agonist selectivity for human 5-HT2A over 5-HT2B receptors, suggesting the potential for improved cardiac safety compared to known serotonergic psychedelic compounds. Overall molecular target activity profiles were consistent with psilocin. Compounds also had favorable in vitro metabolic properties and high brain penetrance in rodents following multiple routes of administration. Like known serotonergic psychedelic compounds, novel compounds induced head twitch responses (HTR) in adult male mice, the potency of which correlates with hallucinogenic potencies in humans. Compound-induced HTR were attenuated by the selective 5-HT2A receptor antagonist, M100907, demonstrating mediation via activation of 5-HT2A receptors. In addition, the lead compound exhibited antidepressant-like activity in the forced swim test in adult male rats. Further in vivo characterization of lead compounds is in progress. These results demonstrate the potential for the discovery of novel, potent, small molecule 5-HT2A receptor agonists for the treatment of mood disorders. Furthermore, a preclinical screening paradigm has been established that also enables identification of non-hallucinogenic 5-HT2A receptor modulators with antidepressant-like activity.

Disclosures: **C.A. Bowen:** A. Employment/Salary (full or part-time):; Employee of atai Life Sciences, EntheogeniX Biosciences, Inc., is an atai platform company. **T.A. Khan:** A. Employment/Salary (full or part-time):; Employee of atai Life Sciences, EntheogeniX Biosciences, Inc., is an atai platform company. **R.B. Perni:** A. Employment/Salary (full or part-time):; Consultant for atai Life Sciences, EntheogeniX Biosciences, Inc., is an atai platform company. **R. Shin:** A. Employment/Salary (full or part-time):; Employee of atai Life Sciences, EntheogeniX Biosciences, Inc., is an atai platform company. **R. Aron:** A. Employment/Salary (full or part-time):; Employee of atai Life Sciences, EntheogeniX Biosciences, Inc., is an atai platform company. **A.L. Halberstadt:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Principal investigator for research contracted by atai Life Sciences, EntheogeniX Biosciences, Inc., is an atai platform company. **B.R. DiFrancesco:** A. Employment/Salary (full or part-time):; Employee of Cyclica Inc. **A.E. Brereton:** A. Employment/Salary (full or part-time):; Employee of Cyclica Inc. **S. Rao:** A. Employment/Salary (full or part-time):; Employee of atai Life Sciences, EntheogeniX Biosciences, Inc., is an atai platform company. **G.F. Short:** A. Employment/Salary (full or part-time):; Employee of atai Life Sciences, EntheogeniX Biosciences, Inc., is an atai platform company.

Poster

147. Treatment and Drug Discovery for Mood Disorders

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 147.03

Topic: G.05. Mood Disorders

Title: Methylone, a rapid-acting entactogen with robust antidepressant-like activity in the forced swim test

Authors: *J. WARNER-SCHMIDT[1], C. J. PITTENGER[2], M. STOGNIEW[1], B. MANDELL[1], S. J. OLMSTEAD[1], B. KELMENDI[3];
[1]Transcend Therapeut., New York, NY; [2]Psychiatry, Yale Univ., New Haven, CT; [3]Yale Univ. Sch. of Med., Hamden, CT

Abstract: Serotonin reuptake inhibitors (SRIs) represent the first line pharmacological treatment for a variety of neuropsychiatric illnesses, including post-traumatic stress disorder (PTSD) and major depressive disorder (MDD). They are slow-acting antidepressants (SAADs) with a delayed onset of action, so most patients do not show significant effects until at least 4 weeks, and often up to 8 weeks, of continuous treatment. SRIs are also associated with impairing side-effects and, even when optimally delivered, 40% of the patients do not respond. Methylone (3,4-methylenedioxy-N-methylcathinone; also known as MDMC, bk-MDMA and M1) is a beta-ketone analog of MDMA and a rapid-acting entactogen (RAE) that improved symptoms in 81% of patients in a clinical case series of 21 individuals with severe PTSD (Kelmendi et al., 2022). In the current study, we employ the Forced Swim Test (FST), a classic and widely used screen

for antidepressants, to explore the effect of methylone. Antidepressants consistently reduce immobility in the FST. Here, we investigate the antidepressant-like activity of methylone compared with the prototypical selective SRI (SSRI), fluoxetine, and with novel rapid-acting antidepressants such as ketamine, psilocybin, and MDMA. Results demonstrate that methylone produces a rapid, robust, dose-dependent antidepressant-like response in the FST. A single dose of methylone (15 mg/kg, IP) reduces immobility by 99% compared to controls ($p<0.001$) compared to a 54% reduction with three doses of fluoxetine (3 x 10 mg/kg, IP). At this dose, methylone also significantly increases swimming and not climbing behavior in the FST, consistent with serotonergic activity (Detke et al., 1995). In addition, the effect of a single dose of methylone persists for at least 72 hours post-dose compared with fluoxetine, which has a behavioral response that only lasts for 1-hour post-dose. We also explore effects of methylone on monoamine transporter binding, uptake, and release. Taken together, and consistent with the recent clinical case series, our results suggest that methylone may have clinical utility in the treatment of PTSD, MDD and other central nervous system disorders.

Disclosures: **J. Warner-Schmidt:** A. Employment/Salary (full or part-time):; Transcend Therapeutics. **C.J. Pittenger:** F. Consulting Fees (e.g., advisory boards); Transcend Therapeutics, Ceruvia Life Sciences, Freedom Biosciences, Biohaven Pharmaceuticals. **M. Stogniew:** A. Employment/Salary (full or part-time):; Transcend Therapeutics. **B. Mandell:** A. Employment/Salary (full or part-time):; Transcend Therapeutics. **S.J. Olmstead:** A. Employment/Salary (full or part-time):; Transcend Therapeutics. **B. Kelmendi:** F. Consulting Fees (e.g., advisory boards); Transcend Therapeutics, Ceruvia Life Sciences.

Poster

147. Treatment and Drug Discovery for Mood Disorders

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 147.04

Topic: G.05. Mood Disorders

Title: CYB003: A novel, orally active analog of psilocybin for the potential treatment of Major Depressive Disorder

Authors: *G. B. VARTY, M. MORGAN, J. KRAKOWSKY, C. CANAL, T. MUELLER, A. REICHELT, K. AVERY, P. PATHARE, J. HARTSEL, A. NIVOROZHKIN, M. PALFREYMAN;
Cybin, Toronto, ON, Canada

Abstract: Phase 2 clinical studies have demonstrated that short-term administration of psilocybin has beneficial effects on psychiatric conditions such as Major Depressive Disorder (MDD) and Treatment-Resistant Depression (TRD). While psilocybin is efficacious and inherently safe, literature shows that there is significant variability between patients in their psychedelic and side effect experiences. This variability is likely due to psilocybin acting as a pro-drug that requires de-phosphorylation to the psychoactive metabolite, psilocin. Once

metabolized, psilocin is absorbed across into the bloodstream and crosses the blood-brain barrier to interact with central serotonergic receptors. Improving the absorption, distribution, and elimination of psilocybin, while retaining its therapeutic effects, may offer significant benefits to the patient. CYB003 is a novel analog of psilocybin that may offer such benefits. The aim of these studies was to compare the pharmacological and pharmacokinetic (PK) profile of CYB003 to psilocybin and psilocin. Pharmacological profiles of CYB003 and psilocin were compared using serotonin (5-HT) receptor binding and functional assays. Additionally, both compounds were evaluated in the mouse head twitch response (HTR) model (a rodent model of psychedelic-like behavior). To compare the PK profile, CYB003 and psilocybin were administered orally to rats and plasma samples were collected at several time points post-dosing, with samples analyzed for levels of psilocin. CYB003 retains the pharmacological profile of psilocin by binding to, and activating the 5-HT_{2A} receptor, and inducing HTR in mice. CYB003 demonstrates potential advantages over psilocybin in terms of its PK profile. Specifically, compared to psilocybin, the rat plasma exposure profile of CYB003 has a shorter time to reach its peak effect, has a reduced half-life, and importantly, results in significantly less inter-subject variability. Finally, CYB003 was well-tolerated in safety studies conducted in both rodent and non-rodent species. These findings suggest that, compared to psilocybin, CYB003 may provide therapeutic benefit but across a shorter clinical visit and with improved dosing accuracy, resulting in improved tolerability. Based on these preclinical studies, CYB003 will progress into Phase 1/2a clinical studies in 2022.

Disclosures: **G.B. Varty:** A. Employment/Salary (full or part-time):; Cybin. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Cybin. **M. Morgan:** A. Employment/Salary (full or part-time):; Cybin. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Cybin. **J. Krakowsky:** A. Employment/Salary (full or part-time):; Cybin. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Cybin. **C. Canal:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Mercer University. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Cybin. **T. Mueller:** A. Employment/Salary (full or part-time):; Cybin. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Cybin. **A. Reichelt:** A. Employment/Salary (full or part-time):; Cybin. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Cybin. **K. Avery:** A. Employment/Salary (full or part-time):; Cybin. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Cybin. **P. Pathare:** A. Employment/Salary (full or part-time):; Cybin. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Cybin. **J. Hartsel:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Cybin. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Cybin. **A. Nivorozhkin:** A. Employment/Salary (full or part-time):; Cybin. E. Ownership Interest (stock,

stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Cybin. **M. Palfreyman:** A. Employment/Salary (full or part-time):; Cybin. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Cybin.

Poster

147. Treatment and Drug Discovery for Mood Disorders

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 147.05

Topic: G.05. Mood Disorders

Title: The preclinical safety, behavioural and pharmacokinetics properties of MSP-1014, a novel prodrug of psilocin.

Authors: *J. A. ARAUJO[1,2], G. A. HIGGINS[1], I. A. M. DE LANNOY[1], I. DEAN[2], J. ATKINSON[2], J. LANTHIER[2], M. SLASSI[2];
[1]InterVivo Solutions Inc., Fergus, ON, Canada; [2]Mindset Pharma Inc, Toronto, ON, Canada

Abstract: Psilocybin, a serotonergic hallucinogen, improved symptoms of depression in difficult to treat patient populations such as treatment resistant depression in phase II studies. Moreover, this effect was both rapid and long-lasting when delivery was combined with psychotherapy. Psilocybin is a prodrug of psilocin, which is thought to mediate these antidepressant effects primarily by activation of 5-HT2A receptors. The current study compared a novel prodrug of psilocin, MSP-1014, to psilocybin in preclinical studies evaluating safety, behavioural and pharmacokinetics properties of both psilocin prodrugs. While psilocin showed partial agonism at the 5-HT2A receptor, both psilocybin and MSP-1014 exhibited substantially reduced EC50 and Emax compared to psilocin. Metabolite identification studies in both human liver microsomes and hepatocytes showed that MSP-1014 is primarily metabolized to psilocin, with the majority of other metabolites identified overlapping with those of psilocin. Mouse and rat pharmacokinetics studies verified that MSP-1014 is rapidly and completely metabolized to psilocin, particularly by the oral (PO) route. Compared to psilocybin, psilocin Cmax was 40% lower and tmax delayed by 0.5 h, which may potentially improve tolerability. Behavioural evaluation of psilocybin (0-10 mg/kg) in the mouse showed that the head twitch response, which is a behavioural correlate of 5-HT2A target engagement, was increased following subcutaneous administration of MSP-1014 compared to psilocybin at the same doses. Moreover, at 3 and 10 mg/kg, both locomotor activity (LMA) and core body temperature (BT) were reduced following administration of psilocybin, but not MSP-1014. MSP-1014 was also evaluated in a drug discrimination assay in which rats were trained to discriminate a psilocybin cue from saline. MSP-1014 displayed complete generalization to the psilocybin cue and similar ED50 (0.3 mg/kg for psilocybin) and duration of action (~4 hr) at equimolar doses. Lastly, the safety of a single administration of MSP-1014 was compared to equimolar doses of psilocybin (1, 5 and 30 mg/kg doses of psilocybin PO). The safety profile of both drugs was similar with transient decreases in both LMA and BT being the primary behavioural observation. No change in clinical pathology parameters were observed for

either drug and the no observable adverse effect level exceeded the doses tested. These data indicate that MSP-1014 is a rapidly metabolized prodrug of psilocin and is likely to exert similar effects to psilocybin in humans. The attenuation of reduced LMA and BT compared to psilocybin in mice suggests that tolerability of MSP-1014 may be superior to psilocybin.

Disclosures: **J.A. Araujo:** A. Employment/Salary (full or part-time):; InterVivo / Mindset. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); InterVivo / Mindset. **G.A. Higgins:** A. Employment/Salary (full or part-time):; InterVivo. F. Consulting Fees (e.g., advisory boards); Mindset. **I.A.M. de Lannoy:** A. Employment/Salary (full or part-time):; InterVivo. F. Consulting Fees (e.g., advisory boards); Mindset. **I. Dean:** A. Employment/Salary (full or part-time):; Mindset. **J. Atkinson:** A. Employment/Salary (full or part-time):; Mindset. **J. Lanthier:** A. Employment/Salary (full or part-time):; Mindset. **M. Slassi:** A. Employment/Salary (full or part-time):; Mindset.

Poster

147. Treatment and Drug Discovery for Mood Disorders

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 147.06

Topic: G.05. Mood Disorders

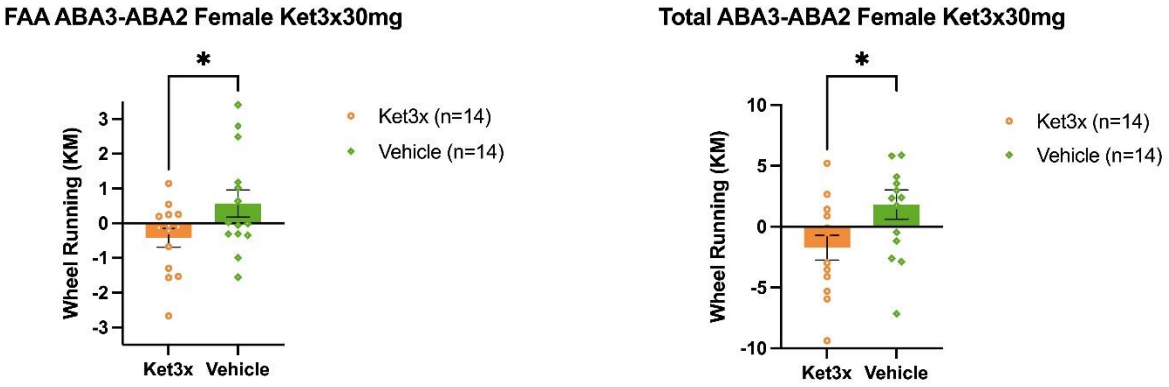
Support: Vulnerable Brain Project Grant
NIH Grant 2R25NS080686
NSF Grant DBI-1950649
NIH Grant P30 EY13079

Title: Multiple injections of ketamine during the second induction of activity-based anorexia in late adolescence attenuate hyperactivity of female mice and elevate exploratory behavior of male mice during the third induction of activity-based anorexia

Authors: *Y. DONG[1,2], S. GOODWIN-GROEN[2], C. J. AOKI[2];
[1]Columbia Univ., New York, NY; [2]Ctr. for Neural Sci., New York Univ., New York, NY

Abstract: Anorexia nervosa (AN) is a complex neurobehavioral disorder with no known effective pharmacological treatment. A previous study on activity-based anorexia (ABA) animal model showed that a single injection of ketamine (KET) during mid-adolescence prolonged resilience in female ABA mice by increasing food consumption and decreasing wheel running activity along with reduced anxiety-like behavior (doi.org/10.1002/eat.22937). However, a single injection of KET during late adolescence was ineffective (doi.org/10.1007/978-1-0716-0924-8_15). We asked whether multiple KET injections during late adolescence may be more effective by giving ABA mice (N = 61, 25 males, 36 females) 3 KET injections (Ket3x, 10 or 30 mg/kg) 24 hours apart or vehicle, during ABA2 (P55-59, late adolescence). Hyperactivity was measured hourly as wheel running; anxiety-like behavior was measured by elevated plus-maze (EPM) on

P77 after recovery from ABA3. 10 days after KET, during ABA3, the female Ket3x30mg group decreased food anticipatory activity (FAA) and total running relative to ABA2 when compared to the female vehicle group (p = 0.0475 for FAA; p = 0.0332 for Total), reflecting reduced ABA vulnerability. This effect was absent in the female Ket3x10mg group, or the male Ket3x10/30mg groups, indicating sex and dose dependence. In ABA2, there was a negative correlation between the percentage of frequency in the open arms of the EPM and the average ABA wheel activity in both male and female vehicle groups (p = 0.002, r = -0.63) indicating that wheel-running was driven by anxiety. This relationship was removed by Ket3x30mg for both sexes. Moreover, in ABA3, there was a positive correlation in the male Ket3x30mg group (p = 0.003, r = 0.919), indicating that wheel running reflected exploratory behavior, rather than anxiety. These behavior findings will be compared to food consumption and body weight data of these ABA mice in another poster (Goodwin-Groen et al). Multiple injections may be needed for late adolescence due to decreased neuroplasticity and NR2B-NMDAR channels.



Disclosures: **Y. Dong:** None. **S. Goodwin-Groen:** None. **C.J. Aoki:** None.

Poster

147. Treatment and Drug Discovery for Mood Disorders

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 147.07

Topic: G.05. Mood Disorders

Support: AMED JP20dm0107122 (H.H.)
AMED JP20dm0207061 (H.H.)
JSPS JP20H00492 (H.H.)
JSPS JP20H03392 (Y.A.)

Title: The agranular insular cortex mediates the antidepressant actions of arketamine

Authors: ***R. YOKOYAMA**[1], Y. AGO[2], A. KASAI[1], M. TANUMA[1], M. HAYASHIDA[1], Y. SHIMAZAKI[1], M. HIGUCHI[1], H. IGARASHI[1], K. SEIRIKI[1], S. YAMAGUCHI[3], T.

NAKAZAWA[4], K. HASHIMOTO[5], H. HASHIMOTO[1];
[1]Osaka Univ., Osaka, Japan; [2]Hiroshima Univ., Hiroshima, Japan; [3]Gifu Univ., Gifu, Japan; [4]Tokyo Univ. Agri., Tokyo, Japan; [5]Chiba Univ. Ctr. Forensic Mental Hlth., Chiba, Japan

Abstract: The NMDA receptor antagonist (*R,S*)-ketamine exerts rapid and potent antidepressant effects, and one of the enantiomers (*S*)-ketamine (esketamine) has been approved for treatment-resistant depression. Additionally, an increasing number of preclinical studies have revealed that another enantiomer (*R*)-ketamine (arketamine) has greater potency and longer-lasting antidepressant-like effects than esketamine in rodents. Although many studies provide insights into the molecular mechanisms of the effects of ketamine, the antidepressant mechanism of ketamine enantiomers is not fully understood. In the present study, we aimed to identify brain regions that contribute to the difference in antidepressant action between ketamine enantiomers by brain-wide mapping of immediate early gene expression. We found that post-weaning social isolation increased the immobility time of male C57BL6/J mice in the forced swim test and arketamine showed a greater potency of antidepressant-like effect than esketamine in isolation-reared mice. Whole-brain imaging revealed that both arketamine and esketamine increased neuronal activity in cortical and subcortical regions in isolation-reared Arc-dVenus mice which expresses a destabilized fluorescent reporter protein dVenus under the promoter of immediate-early gene *Arc*. Then, the machine learning classifiers with brain-wide activation mapping identified several candidates of brain areas including the agranular insular cortex (aIC) that may contribute to the antidepressant-like effect of arketamine and discrimination between the effects of arketamine and esketamine. Furthermore, we found that a temporary suppression of neuronal activity by the Gi-DREADD system in the aIC blocked the antidepressant-like effect of arketamine, but not of esketamine, and conversely Gq-DREADD activation of neurons in the aIC induced antidepressant-like effects in isolation-reared mice. These findings suggest that ketamine enantiomers have different neural mechanisms and that activation of the aIC is necessary to exert the antidepressant-like effects of arketamine.

Disclosures: R. Yokoyama: None. **Y. Ago:** None. **A. Kasai:** None. **M. Tanuma:** None. **M. Hayashida:** None. **Y. Shimazaki:** None. **M. Higuchi:** None. **H. Igarashi:** None. **K. Seiriki:** None. **S. Yamaguchi:** None. **T. Nakazawa:** None. **K. Hashimoto:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Dr. Kenji Hashimoto declares that he has received research support and consultant fees from Sumitomo Dainippon Pharma Co., Ltd., Otsuka Pharmaceutical Co., Ltd., and Taisho Pharmaceutical Co., Ltd.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Dr. Kenji Hashimoto is the inventor of filed patent applications 'The use of (R)-ketamine in the treatment of psychiatric diseases' by Chiba University. **H. Hashimoto:** None.

Poster

147. Treatment and Drug Discovery for Mood Disorders

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 147.08

Topic: G.05. Mood Disorders

Support: NIH Grant R43MH122063

Title: Inhibition of group II metabotropic glutamate receptors for the treatment of anhedonia: evidence from behavioral and in vivo electrophysiological studies in rats

Authors: *F. FAZIO[1], P. ASSAKURA-MIYAZAKI[1], C. M. STEELE[1], D. J. SHEFFLER[2], J. H. HUTCHINSON[2], L. TAUTZ[2], N. D. P. COSFORD[2], R. A. GADIENT[3], G. VELICELEBI[3], A. DER-AVAKIAN[1];
[1]Dept. of Psychiatry, Univ. of California San Diego, La Jolla, CA; [2]Cancer Metabolism & Signaling Networks Program, NCI-Designated Cancer Ctr., Sanford Burnham Prebys Med. Discovery Inst., San Diego, CA; [3]Camino Pharma, San Diego, CA

Abstract: Major depressive disorder (MDD) is a debilitating condition characterized by anhedonia, the loss of interest in rewarding events. Adapting one's behavior to maximize the probability of rewarding outcomes (i.e., reward learning) is impaired in MDD and other psychiatric disorders and can be measured in humans and rodents using the Probabilistic Reward Task (PRT). Deficits in reward learning, as measured by the PRT, have been demonstrated in humans with MDD and healthy humans and rats following transient suppression of dopamine transmission. Here, we assessed whether reward learning deficits in rodents could be reversed with antidepressant treatments and with pharmacological compounds that inhibit the Group II metabotropic glutamate receptors ($mGlu_{2/3}$) and are hypothesized to have antidepressant-like effects. We also assessed the frontal electrophysiological profiles of those treatments using *in vivo* electroencephalogram (EEG). Adult male and female Wistar rats were tested in the PRT following co-administration of the dopamine D_2/D_3 receptor agonist pramipexole (0 and 0.1 mg/kg), that suppresses striatal dopamine transmission, together with: 1) ketamine (0 and 10 mg/kg); 2) fluoxetine (0 and 5 mg/kg); 3) the $mGlu_{2/3}$ orthosteric antagonist LY341495 (0 and 1 mg/kg); or 4) a novel $mGlu_{2/3}$ negative allosteric modulator (NAM) (0, 5, and 10 mg/kg) using a within-subjects Latin-square design in separate cohorts of rats for each compound. In additional cohorts of rats, we recorded EEG activity from a frontal electrode after co-administration of pramipexole and ketamine or the $mGlu_{2/3}$ NAM at the same doses described above. Pramipexole suppressed reward learning in all cohorts and enhanced frontal delta (0-4 Hz) oscillations. Acute treatment with ketamine, LY341495, and the $mGlu_{2/3}$ NAM, but not fluoxetine, reversed the pramipexole-induced impairment in reward learning. Ketamine also attenuated the pramipexole-induced enhancement of frontal delta oscillations and potentiated frontal gamma (30-100 Hz) oscillations, while the $mGlu_{2/3}$ NAM suppressed frontal delta and normalized frontal gamma oscillations that were altered by pramipexole. These findings suggest that acute treatment with ketamine or inhibition of $mGlu_{2/3}$ can normalize frontal low- and high-frequency EEG activity, suggesting that EEG activity may be used as a biomarker for treatment response. Further, inhibition of $mGlu_{2/3}$ is as effective as ketamine in reversing reward learning impairments commonly observed in MDD and other psychiatric disorders characterized by anhedonia, but with fewer psychotomimetic effects, making it a potentially safer alternative treatment for anhedonia.

Disclosures: **F. Fazio:** None. **P. Assakura-Miyazaki:** None. **C.M. Steele:** None. **D.J. Sheffler:** None. **J.H. Hutchinson:** None. **L. Tautz:** None. **N.D.P. Cosford:** None. **R.A. Gadient:** None. **G. Velicelebi:** None. **A. Der-Avakian:** None.

Poster

147. Treatment and Drug Discovery for Mood Disorders

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 147.09

Topic: G.05. Mood Disorders

Support: FIS2018, PI18 00576, Spanish Ministry of Health

Title: Fast antidepressant-like effects of cannabidiol in the chronic mild stress model in mice

Authors: *M. GARCÍA-GUTIÉRREZ[1,2,3], A. AUSTRICH OLIVARES[1], D. NAVARRO[1,4], J. MANZANARES[1,5];
[1]Inst. De Neurociencias, Univ. Miguel Her, Inst. de Neurociencias, Univ. Miguel Her, San Juan De Alicante, Spain; [2]Red Temática de Investigación Cooperativa en Salud (RETICS), Red de Trastornos Adictivos,Instituto de Salud Carlos III, MICINN and FEDER, Madrid, Spain; [3]Inst. de Investigación Sanitaria y Biomédica de Alicante (ISABIAL), Alicante, Spain; [4]Red Temática de Investigación Cooperativa en Salud (RETICS), Red de Trastornos Adictivos Inst. de Salud Carlos III, MICINN and FEDER, Madrid, Spain; [5]Red Temática de Investigación Cooperativa en Salud (RETICS), Red de Trastornos Adictivos, Inst. de Salud Carlos III, MICINN and FEDER, Madrid, Spain

Abstract: Studies conducted over the last few years show that CBD presents antidepressant properties. Here, we aimed to further examined if CBD, alone or in combination with current antidepressant drugs, as the selective reuptake inhibitor (SSRI) sertraline (STR), modulates behavioral alterations induced by the unpredictable chronic mild stress model (UCMS) in ICR mice. Once the UCMS was established, mice were randomly divided into the following groups: STR (10 mg/kg-1, p.o., 24h), CBD (20 mg/kg, i.p., 12h), STR+CBD or Veh+Veh, receiving treatment for a total of 4 weeks. Anxiety- and depressive-like behaviors, cognitive alterations and anhedonia were evaluated at different time points (4, 7, 18 and 26 days) by the light-dark box (LBD), tail suspension (TST), elevated plus maze (EPM), object recognition (OR) and sucrose intake (SI) tests. Gene expression levels of the brain-derived neurotrophic factor (BDNF) and serotonin transporter reuptake (Scl6a4) were evaluated in the hippocampus (HIPP) and dorsal raphe (DR), respectively, by real-time PCR. BDNF immunoreactivity was also examined in the DG of the HIPP. The results revealed that CBD, alone or in combination with STR, reduced anxiogenic and depressogenic-like behaviors in the LDB and TST only after 4 and 7 days of treatment, respectively. In contrast, 14 days of treatment were necessary for STR to take effect in the EPM; notwithstanding, the anxiolytic-like effects of CBD were higher than STR. Moreover, CBD improved cognitive impairment and anhedonia more than the STR and STR+CBD combination.Gene expression studies revealed that CBD and CBD+STR increased

the Slc6a4 gene expression in the DR to a greater degree than STR. CBD alone was the only treatment increasing BDNF gene expression in the HIPP. In addition, BDNF immunoreactivity was higher in UCMS mice treated with CBD. In summary, CBD displays a fast antidepressant-like effect with significant changes in Scl6a4 and BDNF. Notably, CBD effects were superior that STR or the combination CBD+STR. These results suggest that CBD may be a potential new option for treating depressive disorders with a more rapid onset of antidepressant action.

Disclosures: **M. García-Gutiérrez:** None. **A. Austrich Olivares:** None. **D. Navarro:** None. **J. Manzanares:** None.

Poster

147. Treatment and Drug Discovery for Mood Disorders

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 147.10

Topic: G.05. Mood Disorders

Support: La Caixa Foundation (LCF/PR/HP17/52190001)

Title: Pivotal role of adenosine A_{2A}receptors in the amygdala in the control of repeated stress-induced alterations

Authors: S. G. FERREIRA, A. SIMÕES, P. M. CANAS, N. GONCALVES, A. Q. NUNES, N. J. MACHADO, C. SOUZA, V. LOURENÇO, C. LEMOS, I. AMARAL, M. P. KASTER, H. B. SILVA, J. LOPES, A. R. TOMÉ, P. AGOSTINHO, ***R. A. CUNHA**;
Univ. of Coimbra, Coimbra, Portugal

Abstract: Caffeine consumption correlates inversely with the incidence of depression and suicide ideation (*Arch Intern Med* 171:1571, 2011) and polymorphisms of adenosine A_{2A} receptors (A_{2A}R-caffeine's main targets) are associated with major depression (*Purinergic Signal* 15:37, 2019). Accordingly, caffeine and A_{2A}R blockade prevent mood and memory impairment in mice subjected to chronic unpredictable stress (*PNAS* 112:7833, 2015). We now tested which brain circuits are controlled by A_{2A}R to prevent chronic stress-induced maladaptive alterations.In 3 rat models of repeated stress (restraint stress, social defeat, forced treadmill running), mood and memory alterations were abrogated by the systemic (ip) administration of a selective A_{2A}R antagonist (SCH58261 0.5 mg/kg) and the amygdala displayed the more consistent upregulation of A_{2A}R and alteration of synaptic markers (compared to accumbens, prefrontal cortex or hippocampus). The bilateral injection in the basolateral amygdala (BLA) of lentivectors encoding a A_{2A}R-silencing short hairpin (*Nature Comm* 7:11915, 2016), but not encoding a control non-targeted sequence, to male adult Wistar rats, prevented the restraint stress (4h daily during 14 days)-induced despair-based depression (forced-swimming), reward-based deficits (splash), anhedonia (sucrose intake), increased anxiety (elevated plus-maze), hampered memory (modified Y-maze, object displacement), altered density of synaptic proteins and exacerbated amygdala LTP. Conversely, overstimulation of BLA-A_{2A}R signalling in male adult Wistar rats

injected in the BLA with AAV5-CaMKIIα-optoA_{2A}R-mcherry (chimera to light-activate A_{2A}R transducing systems; *Mol Psychiatry* 20:1339, 2015), but not with AAV5-CaMKIIα-mcherry (control), upon light stimulation through implanted optic fibers targeting the BLA, for 6 consecutive days (8 trains each with 3000 light pulses of 50 ms duration over 5 min, 10 min inter-train interval), triggered increased anxiety, anhedonic-like and depressive-like behaviour, impaired spatial working memory and increased BLA-LTP magnitude.This shows a pivotal role of amygdala A_{2A}R controlling repeated stress-induced modifications and prompts A_{2A}R as targets to manage mood-related disorders.

Disclosures: **S.G. Ferreira:** None. **A. Simões:** None. **P.M. Canas:** None. **N. Goncalves:** None. **A.Q. Nunes:** None. **N.J. Machado:** None. **C. Souza:** None. **V. Lourenço:** None. **C. Lemos:** None. **I. Amaral:** None. **M.P. Kaster:** None. **H.B. Silva:** None. **J. Lopes:** None. **A.R. Tomé:** None. **P. Agostinho:** None. **R.A. Cunha:** None.

Poster

147. Treatment and Drug Discovery for Mood Disorders

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 147.11

Topic: G.05. Mood Disorders

Support: Seed Grant from Texas A&M University (SE)
NIH grant R35 CA197707 (RSC)
Allen Endowed Chair in Nutrition & Chronic Disease Prevention (RSC)

Title: Sex-dependent differences in the stress mitigating and antidepressant effects of selective aryl hydrocarbon receptor modulators

Authors: C. A. MADISON, R. A. DEBLER, N. I. VARDELEON, L. HILLBRICK, A. JAYARAMAN, S. SAFE, R. S. CHAPKIN, *S. EITAN;
Texas A&M Univ., College Station, TX

Abstract: Major depressive disorder is a severe and debilitating disorder that affects approximately 280 million people worldwide. Although multiple pharmacological and behavioral treatments are currently available, about two-thirds of patients need to try multiple different medications, a process that takes months, before they experience symptom relief. Moreover, some do not respond or experience remission following any existing medication. Thus, there is still a critical need to improve our understanding of the underlying causes of depression and to provide improved medications for individuals who do not respond as well to current medications.
Our recently published study demonstrated that selective aryl hydrocarbon receptor (AhR) modulators (SAhRMs) act as antidepressants in female mice exposed to unpredictable chronic mild stress (UCMS). Given that some AhR effects are known to be mediated via estrogen receptor (ER) signaling and the interaction of certain SAhRMs with ERs, this study examined

sex differences in the effects of SAhRMs on stress-related changes in depression-like behavior, emotional state, and cognition.
Mice were fed with vehicle or 20 mg/kg 4-Dihydroxy-2-naphthoic acid (DHNA), a SAhRM, for three weeks prior to four weeks of unpredictable chronic mild stress (UCMS). Mice were examined for depression-like behaviors (sucrose preference, forced swim test, splash test, and tape groom test), emotional state (open-field test, novelty-induced locomotion, light/dark test, marble burying, novelty-induced hypophagia, and elevated-plus maze), and cognition (object location recognition, novel object recognition, Morris water maze).
In females, UCMS decreased sucrose preference and increased immobility time in the FST; both effects were prevented by DHNA. No significant effects were observed in the anxiety and cognitive tests. In males, UCMS increased immobility time in the FST, and increased the latency to groom in the splash test; DHNA did not mitigate these effects. However, DHNA prevented the following UCMS-induced effects: increased novelty-induced locomotion, increased time spent in the light compartment in the light/dark test, and increased time spent with an object in a novel location.
Our findings further confirm the potential of SAhRMs to act as antidepressants in females. In contrast, SAhRMs did not appear to act as antidepressants in males; however, SAhRMs may still mitigate stress effects and reactivity in males. Together, these results hint at a role of ER signaling in the antidepressant effects of SAhRMs in females. Future studies are necessary to determine the molecular mechanisms underlying the effects of SAhRMs.

Disclosures: C.A. Madison: None. **R.A. Debler:** None. **N.I. Vardeleon:** None. **L. Hillbrick:** None. **A. Jayaraman:** A. Employment/Salary (full or part-time):; Texas A&M University. **S. Safe:** A. Employment/Salary (full or part-time):; Texas A&M University. **R.S. Chapkin:** A. Employment/Salary (full or part-time):; Texas A&M University. **S. Eitan:** A. Employment/Salary (full or part-time):; Texas A&M University.

Poster

147. Treatment and Drug Discovery for Mood Disorders

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 147.12

Topic: G.05. Mood Disorders

Title: Robust hippocampal and cortical target engagement induced by ABX-002, a novel thyromimetic in development for major depressive disorder (MDD)

Authors: *D. A. MACKENNA, M. B. WOERNER, A. ALAVI, A. KLOVA, B. A. STEARNS; Autobahn Therapeut., San Diego, CA

Abstract: Thyroid hormone has pleotropic effects in vivo which may be harnessed for therapeutic treatment of neuropsychiatric diseases. Hypothyroidism results in depressive behavior in rodents with measurable defects in hippocampal neurogenesis and function (Montero-Pedrazuela 2006; Glombik 2021). T3 and T4 are used clinically to augment existing

therapies for depression regardless of metabolic status of the patient. However, they are dose-limited due to peripheral effects on the heart, bone and liver.
ABX-002 is a thyromimetic prodrug with enhanced delivery to the brain that may further augment efficacy in patients with treatment resistant depression (TRD). ABX-002 crosses the blood brain barrier and is activated to the active metabolite, LL-340001, by fatty acid amide hydrolase (FAAH), an enzyme enriched in the brain. LL-340001 binds to thyroid hormone receptors with 16x preference for TRb compared with TRa.
The purpose of these studies is to evaluate the relative potency of ABX-002 on regulation of gene expression in the brain vs. heart in both mice and non-human primates (NHP) that were administered ABX-002 orally for up to 7 days. Relative potencies of ABX-002 were compared with T3 in mice while known T3 target genes were compared in heart and brain for NHP. In mouse, hemi-brain samples were analyzed along with sub-samples harvested in cortex, hippocampus and cerebellum. In NHP, samples were harvested from 7 regions of the CNS including cortex, hippocampus, cerebellum, corpus callosum, hypothalamus, optic nerve and spinal cord.
Within the brain, ABX-002 was most potent at inducing target gene regulation in the hippocampus and cortex compared with cerebellum and other regions in both the mouse and NHP. This was partially explained by differences in prodrug metabolism with cortex and hippocampus having 1.5 to 2-fold higher tissue concentrations than other brain regions.
The difference in prodrug metabolism between brain and periphery was more dramatic across both species. In mouse, ABX-002 had a ~5x greater window between changes in gene expression in the brain vs. heart compared with T3. T3 was not evaluated in NHP; however, similar to mouse, a large window occurs between the brain and heart, where gene expression changes were observed in brain at doses as low at 30 ug/kg while 300-1000 ug/kg was required to detect measurable changes in the heart.
Taken together, ABX-002 enhances thyromimetic activity in the hippocampus and cortex. Both regions represent areas key to known pathophysiology in depression. Thus, ABX-002 is a novel approach to treatment of TRD.

Disclosures: **D.A. MacKenna:** A. Employment/Salary (full or part-time):; Autobahn Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Autobahn Therapeutics, Blade Therapeutics, Galecto. **M.B. Woerner:** A. Employment/Salary (full or part-time):; Autobahn Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Autobahn Therapeutics. **A. Alavi:** A. Employment/Salary (full or part-time):; Autobahn Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Autobahn Therapeutics. **A. Klova:** A. Employment/Salary (full or part-time):; Autobahn Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Autobahn Therapeutics. **B.A. Stearns:** A. Employment/Salary (full or part-time):; Autobahn Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Autobahn Therapeutics.

Poster

147. Treatment and Drug Discovery for Mood Disorders

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 147.13

Topic: G.05. Mood Disorders

Support: Janssen
Ontario Research Fund
Ontario Brain Institute

Title: Baseline immune predictors of relapse in major depressive disorder

Authors: *A. FIEVOLI[1], S. ASBURY[1], C. MATTHEWS[1], B. N. FREY[1], R. LAM[2], R. MILEV[3], S. E. ROTZINGER[4], C. N. SOARES[3], R. UHER[5], G. TURECKI[6], S. KENNEDY[4,7], J. A. FOSTER[1];
[1]Dept. of Psychiatry & Behavioural Neurosciences, McMaster Univ., Hamilton, ON, Canada; [2]Dept. of Psychiatry, Univ. of British Columbia, Vancouver, BC, Canada; [3]Dept. of Psychiatry, Providence Care, Queen's Univ., Kingston, ON, Canada; [4]St Michael's Hospital, Li Ka Shing Knowledge Institute, Ctr. for Depression and Suicide Studies, Toronto, ON, Canada; [5]Dept. of Psychiatry, Dalhousie Univ., Halifax, NS, Canada; [6]Douglas Mental Hlth. Univ. Institute, Dept. of Psychiatry, McGill Univ., Montreal, QC, Canada; [7]Dept. of Psychiatry, Univ. of Toronto, Toronto, ON, Canada

Abstract: A major challenge in the treatment of major depressive disorder (MDD) is relapse, which is defined as the return of depressive symptoms during a period of remission. Relapse rates in MDD are high, with approximately 50% of individuals relapsing following treatment of their first depressive episode, therefore early intervention to prevent relapse is crucial. There is evidence suggesting that immune dysregulation may contribute to depressive symptomology. However, it is currently unknown whether inflammation can predict future relapse in MDD. Therefore, the objective of this project was to identify potential immune biomarkers of relapse in participants that responded to a treatment or a combination of treatments for MDD. This project is a part of the Wellness Monitoring for Major Depressive Disorder longitudinal study (NCT02934334) of responders to antidepressant treatment at 6 clinical sites across Canada. Montgomery Asberg Depression Rating Scale (MADRS) scores were used to assess depression severity. Protocol relapses (MADRS >22) were clinically validated. In addition, symptom profiles were reviewed to identify additional relapses. Participants were categorized into ultrastable, unstable, and relapse groups. Ultrastable participants maintained a MADRS score <14 throughout the study and were not considered to be in relapse. Unstable participants were those whose MADRS score were above the inclusion criterion of 14 but were below the protocol defined criterion for relapse of 22. A total of 96 MDD participants (62% male) were included in the analysis. Relapses were confirmed in 25 participants. 31 participants were classified as unstable and 40 participants were ultrastable. Plasma immune profiles were generated using the following LEGENDplex immunoassays: Human Neuroinflammation Panel 1, Human Th Cytokine Panel, and Human Macrophage/Microglia Panel. Univariate analysis of individual immune proteins did not show differences between ultrastable, unstable, or relapse groups.

Ongoing principal component analysis (PCA) and hierarchical clustering will determine if data-driven immune subtypes predict relapse.

Disclosures: **A. Fievoli:** None. **S. Asbury:** None. **C. Matthews:** None. **B.N. Frey:** None. **R. Lam:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Allergan, Asia-Pacific Economic Cooperation, Canadian Network for Mood and Anxiety Treatments, Healthy Minds Canada, Janssen, Lundbeck, Lundbeck Institute, Unity Health, Otsuka, Pfizer. F. Consulting Fees (e.g., advisory boards); BC Leading Edge Foundation, CIHR, Michael Smith Foundation for Health Research, MITACS, Myriad Neuroscience, Ontario Brain Institute, Otsuka, Pfizer, VGH-UBCH Foundation. **R. Milev:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; CAN-BIND, CIHR, Janssen, Lallemand, Lundbeck, Nubiyota, OBI, OMHF. F. Consulting Fees (e.g., advisory boards); AbbVie, Allergan, Eisai, Janssen, KYE, Lallemand, Lundbeck, Otsuka, Sunovion. **S.E. Rotzinger:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); "Teneurin C-Terminal Associated Peptides (TCAP) and methods and uses thereof. Inventors: David Lovejoy, R.B. Chewpoy, Dalia Barsyte, Susan Rotzinger.". **C.N. Soares:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Ontario Research Fund-Research Excellence (ORF-RE), AHSC AFP Innovation Fund. F. Consulting Fees (e.g., advisory boards); Otsuka. **R. Uher:** None. **G. Turecki:** None. **S. Kennedy:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Ontario Brain Institute, Ontario Research Fund, Otsuka, Pfizer, Servier, Brain Canada, CIHR, Sunovion, Lundbeck, Janssen. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Field Trip Health. F. Consulting Fees (e.g., advisory boards); Abbott, Alkermes, Abbvie, Janssen, Lundbeck, Lundbeck Institute, Xian-Janssen. **J.A. Foster:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Ontario Brain Institute, CIHR, NSERC, Ontario Research Fund, Brain Canada, Canadian Foundation For Innovation. F. Consulting Fees (e.g., advisory boards); Takeda Canada, Rothman, Benson & Hedges Inc, MRM Health NL, Klaire Labs, Novozymes, AlphaSights.

Poster

147. Treatment and Drug Discovery for Mood Disorders

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 147.14

Topic: G.05. Mood Disorders

Support: JSPS KAKENHI, Grant Number 16K19257

Title: Intra-individual state-dependent comparison of plasma mitochondrial DNA copy number and IL-6 levels in patients with bipolar disorder

Authors: *Y. KAGEYAMA[1], Y. DEGUCHI[2], K. INOUE[2], T. KASAHARA[3], M. TANI[4], K. KURODA[5], T. KATO[6];
[1]Dept. of Neuropsychiatry,, Osaka Metropolitan University, Grad. Sch. of Med., Osaka, Japan; [2]Osaka Metropolitan Univ. Grad. school of Med., Dept. of Neuropsychiatry, Grad. Sch. of Medicine, Osaka Metropolitan Univ., Osaka, Japan; [3]Career Develop. Program, RIKEN Ctr. for Brain Sci., Wako-shi, Japan; [4]Tani Mental Clin., Osaka, Japan; [5]Dept. of Psychiatry, Hannan Hosp., Osaka, Japan; [6]Dept. of Psychiatry & Behavioral Sci., Juntendo Univ. Grad. Sch. of Med., Tokyo, Japan

Abstract: Background: Though depressive patients with bipolar disorder (BD) reportedly show elevated plasma IL-6 levels, its molecular mechanism is not understood. Since mitochondrial dysfunction associated with the accumulation of partially deleted mitochondrial DNA (ΔmtDNA) is implicated in BD, we hypothesized that plasma circulating cell-free mtDNA (ccf-mtDNA) released from the brain causes inflammation as damage-associated molecular patterns. First, we determined whether brain-derived mtDNA can be detected in plasma using neuron-specific mutant *Polg1* transgenic (Tg) mice accumulating ΔmtDNA only in the brain. Second, we investigated whether the plasma ccf-mtDNA is elevated in association with increased cytokine levels in depressive patients with BD. **Methods:** Mouse plasma ccf-mtDNA levels were measured using real-time PCR targeting two regions of the mtDNA (*CO1* and *D-loop*) in Tg mice and non-Tg littermates. The amount of ΔmtDNAs was determined from the copy number ratio of the *CO1* and *D-loop* regions, which were lost and preserved, respectively, in ΔmtDNA. Human plasma ccf-mtDNA levels were measured using real-time PCR targeting two regions of the mtDNA (*ND1* and *ND4*) and IL-6 levels were evaluated in 10 patients in different states (depressed and remitted) of BD in a longitudinal manner and 10 healthy controls. **Results:** The mouse plasma *CO1/D-loop* ratio was significantly lower in Tg than non-Tg mice ($P = 0.0029$). Human plasma ccf-mtDNA copy number, *ND4/ND1* ratio, and IL-6 levels were not significantly different between dBD and rBD. Human plasma ccf-mtDNA levels showed a nominal significant correlation with delusional symptoms ($P = 0.033$, $\rho = 0.68$). **Conclusions:** The analysis of Tg mice revealed that brain-derived mtDNA, which lacks the *CO1* region, could be present in peripheral blood. The present findings did not support our hypothesis that plasma ccf-mtDNA differentiates the cytokine levels between dBD and rBD, patients with elevated cytokine levels should be examined to test our hypothesis. We found that the plasma ccf-mtDNA level showed a nominal positive correlation with delusional symptoms in patients with dBD. It was reported that delusional symptoms were significantly associated with neuroinflammation (Schiavone and Trabace, 2017). Plasma ccf-mtDNA might have a potential link with delusional symptoms.

Disclosures: Y. Kageyama: None. **Y. Deguchi:** None. **K. Inoue:** None. **T. Kasahara:** None. **M. Tani:** None. **K. Kuroda:** None. **T. Kato:** None.

Poster

147. Treatment and Drug Discovery for Mood Disorders

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 147.15

Topic: G.05. Mood Disorders

Support: Nubiyota LLC

Title: Investigating the short and long-term effects of microbial ecosystem therapeutic-2 intervention on sleep disturbances in individuals with depression

Authors: *H. BROMLEY[1], A. CHINNA MEYYAPPAN[2], C. SGARBOSSA[1], R. MILEV[1]; [1]Neurosci., [2]Queen's Univ., Niagara Falls, ON, Canada

Abstract: Approximately 90% of patients with depression experience some form of sleep disturbances. Sleep symptoms have a major impact on quality of life as well as increase the risk factor for suicide. While sleep disturbances were traditionally considered a symptom of depression, current evidence suggests that most sleep-related symptoms remain unresolved following treatment and may precede depression. Recently, it has been proposed that probiotics, fecal microbiota transplant, and other microbial therapies can interact with intestinal microbiota to benefit individuals suffering from various psychiatric disorders. Evidence suggests that the gut microbiome may be able to regulate sleep and mental states through the microbiota gut-brain-axis. This study investigates the use of a novel gut repopulation treatment, Microbial Ecosystem Therapeutic (MET)-2, as a therapeutic intervention against sleep disturbances in depression. MET-2 contains 40 bacterial strains from a healthy donor and is administered daily as an oral capsule. The primary aim of this study is to assess sleep behaviour changes in individuals with depression before, during, and after MET-2 administration. The secondary aims are to assess the long-term effects of MET-2 treatment on sleep behaviours in individuals with depression. In this phase 2, double-blind, placebo-controlled, randomized controlled trial, treatment-naïve individuals between 18 and 45 years old with depression will be randomized into treatment or placebo groups. Patients will orally consume either the MET-2 product or placebo alternative once daily for 6 weeks. As a primary outcome measure, participants' sleep disturbances will be assessed using the Pittsburgh Sleep Quality Index (PSQI) at baseline, week-2, week-4, and week-6 of treatment. Participants who have completed at least 5-weeks of MET-2 treatment will be invited to participate in a follow-up study to assess lasting changes of MET-2 on sleep. Of the ten (n=10) participants included in this study to date, the majority of individuals (n=8) displayed an improvement in PSQI scores from baseline to the week-6 visit. Of the participants who have completed the follow-up study (n=3), one participant (n=1) maintained an improvement in PSQI scores from baseline to the week-12 visit. Given that the study is double-blind in nature and not yet completed, we are unable to state any significance at this time but are hopeful with the current results. This study is the first to examine MET-2 efficacy on sleep disturbances in depression. We hope these results will contribute to a growing body of research assessing gut repopulation as a therapeutic for a variety of psychiatric illnesses.

Disclosures: **H. Bromley:** None. **A. Chinna Meyyappan:** None. **C. Sgarbossa:** None. **R. Milev:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; RM has received consulting and speaking honoraria from AbbVie, Allergan, Eisai, Janssen, KYE, Lallemand, Lundbeck, Neonmind, Otsuka, and Sunovion, and research grants from CAN-BIND, CIHR, Janssen, Lal.

Poster

147. Treatment and Drug Discovery for Mood Disorders

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 147.16

Topic: G.05. Mood Disorders

Title: Probiotic supplementation with lactate-producing bacteria induces anxiolytic- and antidepressant-like effects

Authors: *A. CARRARD[1], N. BOUZOURÈNE[1], P. J. MAGISTRETTI[2], J.-L. MARTIN[1]; [1]Ctr. For Psychiatric Neurosci., Ctr. For Psychiatric Neurosci., Prilly, Switzerland; [2]King Abdullah Univ. of Sci. and Technol., Thuwal, Saudi Arabia

Abstract: Major Depressive Disorder (MDD) is a leading cause of disability worldwide. Importantly, approximately 30% of MDD patients do not respond to antidepressant medications. In recent years, we have shown that peripheral administration of lactate promotes antidepressant-like responses in different animal models (Carrard et al., Mol Psychiatry 2018). With regard to the underlying mechanisms, we have observed that adult hippocampal neurogenesis is required for the antidepressant effects of lactate (Carrard et al, Mol Psychiatry 2021). Over the last decade, increasing evidence has shown alterations of the gut microbiota composition in MDD patients. Consistent with these observations, fecal microbiota transplantation from depressed patients to healthy rodents induces depressive- and anxiety-like behavior. In animal models of depression, administration of specific bacterial strains induces changes in the gut microbiota composition and improves anxiety- and depressive-like behavior. Collectively, these observations led us to investigate whether Lacidofil, a commercial probiotic combination containing *L. rhamnosus* (95%) and *L. helveticus* (5%) (Lallemand Health Solutions), improved anxiety- and depressive-like behavior in the corticosterone model of depression. Chronic Lacidofil supplementation increased the relative abundance of *L. rhamnosus* in the caecum and feces of C57BL/6 treated mice compared to control animals. Analysis of depressive-like behavior in the corticosterone model of depression revealed that chronic Lacidofil supplementation reversed the effects of corticosterone on anhedonia and behavioral despair in the saccharin preference test and forced swim test, respectively ($n \geq 17$ from 2-3 independent experiments). The effects of Lacidofil on anxiety-like behavior were assessed using the light-dark box and marble burying tests. Chronic Lacidofil supplementation counteracted the decreased time spent in the light compartment and the increased number of buried marbles induced by corticosterone. Together, these data show that probiotic supplementation with

Lacidofil reverses anxiety- and depressive-like behavior induced by chronic treatment with corticosterone.

Disclosures: **A. Carrard:** None. **N. Bouzourène:** None. **P.J. Magistretti:** None. **J. Martin:** None.

Poster

147. Treatment and Drug Discovery for Mood Disorders

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 147.17

Topic: G.05. Mood Disorders

Support: Ontario Brain Institute
Hersh Foundation and the Rose Foundation

Title: Gut microbial communities enriched with butyrate producers are protective against symptoms of depression and anxiety

Authors: S. ASBURY[1], C. R. CHIN FATT[2,3], M. K. JHA[3,2], A. MINHAJUDDIN[2,3], S. SETHURAM[2,3], T. MAYES[2,3], S. H. KENNEDY[4,5], *J. A. FOSTER[2,1,3], M. TRIVEDI, M.D.[2,3]; [1]Psychiatry & Behavioural Neurosciences, McMaster Univ., Hamilton, ON, Canada; [2]Ctr. for Depression Res. and Clin. Care, [3]Psychiatry, UT Southwestern, Dallas, TX; [4]Psychiatry, Univ. of Toronto, Toronto, ON, Canada; [5]Ctr. for Depression Studies, St. Michael's Hosp., Toronto, ON, Canada

Abstract: Recent evidence has demonstrated links between the presence of specific gut microbiome taxa in individuals with depressive symptoms as well as those diagnosed with depression and anxiety. Traditional human microbiome analyses strategies suffer from multicollinearity of distinct microbes, given the presence of numerous related taxa. Community-based inference should be performed to identify co-occurrence networks implicated in the gut-brain axis. Here, we employed weighted correlation network analysis (WCNA) to interrogate gut microbial structure in a clinical population with depression. Our study includes 203 adult participants (n_{males} = 63, mean age = 45.6±15.9 years) diagnosed with unipolar or bipolar depression recruited via the Texas Resilience Against Depression (T-RAD) study. Participant's current depression, anxiety, and anhedonia symptom severity were assessed via the Patient Health Questionnaire (PHQ-9), General Anxiety Disorder - 7 item scale (GAD-7), and Dimensional Anhedonia Rating Scale, respectively. Fecal samples for 16S rRNA microbiome sequencing were collected within 1 to 6 weeks of clinical assessment. We developed a novel retain-resolve algorithm that maximizes taxonomic resolution by retaining amplicon sequence variants that meet prevalence and abundance thresholds, and resolving filtered taxa to genus-level (github.com/SarahAsbury/retainresolve). Associations between microbial communities and symptom severity were evaluated using WCNA, adjusting for age as a covariate. WCNA identified three stable gut microbial networks in depressed patients. One network was negatively

associated with GAD-7 and PHQ-9 scores. Network hub taxa were defined by 95-percentile network connectivity and represent potential network regulators. Hub taxa for the anxiety- and depression-associated network were: *Ruminococcaceae_UCG-010*, *Ruminococcaceae_UCG-005*, and *Christensenellaceae_R-7_group*. *Ruminococcaceae* are known butyrate producers and were enriched in both hub taxa and general network composition. Short-chain fatty acid metabolites have been previously implicated as gut-brain axis modulators, and our findings further support this hypothesis. *Christensenellaceae* are heritable taxa positively associated with metabolic disorders and BMI, suggesting overall gut metabolic health may modulate symptoms in depressed populations. Importantly, hub taxa *Ruminococcaceae_UCG-005*, and *Christensenellaceae_R-7_group* had high prevalence in the population (>70%) and may represent biomarkers and therapeutic targets for anxiety and depression symptom exacerbation in depressed patients.

Disclosures: S. Asbury: None. **C.R. Chin Fatt:** None. **M.K. Jha:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Acadia Pharmaceuticals, Neurocrine Bioscience, Navitor/Supernus, Janssen Research & Development, Psychiatry & Behavioral Health Learning Network. F. Consulting Fees (e.g., advisory boards); Eleusis Therapeutics US, Inc, Janssen Global Services, Janssen Scientific Affairs, Worldwide Clinical Trials/Eliem, Guidepoint Global, North American Center for Continuing Medical Education, Medscape/WebMD, Clinical Care Options, Global Medical Education. **A. Minhajuddin:** None. **S. Sethuram:** None. **T. Mayes:** None. **S.H. Kennedy:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Abbott, Brain Canada, CIHR, Janssen, Lundbeck, Ontario Brain Institute, Otsuka, Pfizer, SPOR. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Field Trip Health. F. Consulting Fees (e.g., advisory boards); Abbvie, Boehringer-Ingelheim, Janssen, Lundbeck, Lundbeck Institute, Merck, Otsuka, Pfizer, Sunovion, Servier. **J.A. Foster:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Ontario Brain Institute, NSERC, Ontario Research Fund, Brain Canada, Canadian Foundation For Innovation, CIHR. F. Consulting Fees (e.g., advisory boards); MRM Health NL, Klaire Labs, Takeda Canada, Rothman, Benson, Hedges Inc, Novozymes, AlphaSights. **M. Trivedi:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; NIMH, NIDA, NCATS, American Foundation for Suicide Prevention, Patient-Centered Outcomes Research Institute (PCORI), Blue Cross Blue Shield of Texas. F. Consulting Fees (e.g., advisory boards); Acadia Pharmaceuticals Inc, Alkermes Inc, Alto Neuroscience Inc, Axsome Therapeutics, Biogen MA Inc, Circular Genomics Inc, Compass Pathfinder Limited, GH Research Limited, GreenLight VitalSign6 Inc, Heading Health Inc, Janssen, Legion Health Inc, Merck Sharp & Dohme Corp., Mind Medicine (MindMed) Inc, Merck Sharp & Dhome LLC, Neurocrine Biosciences Inc, Noema Pharma AG, Orexo US Inc, Otsuka American Pharmaceutical Inc, Otsuka Canada Pharmaceutical Inc, Otsuka Pharmaceutical Development & Commercialization Inc,, Praxis

Precision Medicines Inc, SAGE Therapeutics, Signant Health, Sparian Biosciences Inc, Takeda Pharmaceutical Company Ltd, Titan Pharmaceuticals Inc, WebMD, Oxford University Press.

Poster

147. Treatment and Drug Discovery for Mood Disorders

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 147.18

Topic: G.05. Mood Disorders

Support: NuBiyota

Title: A longitudinal follow-up of microbial therapeutics as treatment for depression: protocol and preliminary results

Authors: *C. SGARBOSSA, A. CHINNA MEYYAPPAN, H. BROMLEY, R. MILEV; Psychiatry, Queen's Univ., Kingston, ON, Canada

Abstract: Rationale: Many conventional psychiatric treatment methods, particularly antidepressant medications, are often accompanied by a high rate of relapse and illness reoccurrence following discontinuation of treatment. In efforts to address this issue, innovative treatment methods for psychiatric illnesses such as microbial therapeutics are now being explored. Gut-repopulation techniques have long been used as treatment for chronic GI-related disorders such as inflammatory bowel disease, however recent research has highlighted the potential of these techniques to mediate mood through the gut-brain axis, due to their unique ability to repopulate the gut with bacteria from a healthy donor. However, given the novelty of utilizing microbe therapy to treat psychiatric symptoms, the long-term effects regarding sustained improvements in mood are unclear.
Methods: Microbial Ecosystem Therapeutic-II (MET-2) is an orally administered microbial capsule that is currently being assessed for its use as treatment for depression in a phase 2, double-blind, placebo-controlled, multi-centre, randomized controlled trial. Approximately 20 participants aged 18-45 who previously participated in the MET-2 trial will be recruited to the longitudinal follow-up. Participants will return 12- and 24-weeks post-MET-2 treatment to assess for any lasting changes in mood using validated clinical scales and provide a stool sample for microbial analysis using 16S rRNA sequencing.
Objectives:1.Assess the longitudinal efficacy of MET-2 treatment on symptoms of anxiety and depression using validated clinical scales from pre-, during, and post-treatment scores.2.Assess any longitudinal changes in microbiota composition and diversity in response to MET-2 treatment from pre-, during, and post-treatment analyses.
Results: To date, seven participants (n=7) have consented to the follow-up and three participants (n=3) have completed visits. Preliminary results exhibited mixed findings. Some participants had a sustained improvement in mood (n=2), while another had no sustained improvement and scores returned to baseline (n=1). Due to the double-blind nature of the study, whether the participants received placebo or active MET-2 product is unknown until the study reaches completion. For

these reasons, we are unable to state significance of preliminary results.
Conclusion: Due to the limited studies that have assessed the longitudinal effects of microbe therapy on mood, any results from this exploratory follow-up will provide valuable insight for evaluating the promise of gut-repopulation techniques as treatment for psychiatric illnesses such as depression.

Disclosures: C. Sgarbossa: None. **A. Chinna Meyyappan:** None. **H. Bromley:** None. **R. Milev:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; CAN-BIND, CIHR, Janssen, Lallemand, Lundbeck, Nubiyota, OBI and OMHF.. F. Consulting Fees (e.g., advisory boards); AbbVie, Allergan, Eisai, Janssen, KYE, Lallemand, Lundbeck, Neonmind, Otsuka, and Sunovion..

Poster

147. Treatment and Drug Discovery for Mood Disorders

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 147.19

Topic: G.05. Mood Disorders

Support: MITACS Accelerate Grant

Title: Microbial Ecosystem Therapeutic-2 (MET-2) for Symptoms of Major Depression and/or Generalized Anxiety Disorder: Clinical Findings and Future Directions

Authors: *A. CHINNA MEYYAPPAN[1,2,3], R. MILEV[1,2];
[1]Queen's Univ. Ctr. For Neurosci. Studies, Kingston, ON, Canada; [2]Providence Care Hosp., Kingston, ON, Canada; [3]Pharmacogenetics Res. Clin., Ctr. for Addiction and Mental Hlth., Toronto, ON, Canada

Abstract: Background/Objective: Analyses of the human gut microbiota have shown considerable individual variability in bacterial content which is hypothesized to influence brain function, and potentially mood and anxiety symptoms, through bidirectional biochemical signalling between the gut microbiota and the brain, also known as the gut-brain axis. Preclinical and clinical research examining these effects suggests that gut repopulation techniques such as fecal microbiota transplant (FMT) may aid in improving depression and anxiety symptoms and severity by recolonizing the gastrointestinal tract with healthy bacteria. The microbial therapeutic used in this study is an alternative treatment to FMT that is composed of various strains of gut bacteria from a health donor. The primary objective of this study was to assess subjective changes in mood and anxiety symptoms before, during, and after administration of the microbial therapeutic. Safety and tolerability of therapeutic were also assessed.
Method: Twelve treatment-naïve adults diagnosed with major depressive disorder or generalized anxiety disorder were recruited from the Kingston, Canada area. Participants orally consumed

once daily an encapsulated microbial therapeutic, containing 40 strains of bacteria purified and lab-grown from a single healthy donor stool, for 8 weeks. Participants underwent a series of clinical assessments measuring mood, anxiety, and GI symptoms using validated clinical scales and questionnaires. Molecular data was collected from blood and fecal samples to assess metabolic changes, neurotransmitter levels, inflammatory markers, and level of engraftment for fecal samples to predict outcomes in depression or anxiety.**Results:** Seven of twelve individuals responded to treatment (50% improvement in mood/anxiety symptom scores (MADRS/GAD-7 scales) since starting treatment). Over the 10 weeks, MET-2 significantly decreased MADRS and GAD-7 scores, $F(1,11)= 21.6121$, $p = 0.001$ and $F(1,11) = 18.088$, $p = 0.001$, respectively. Patients also showed a significant improvement in sleep quality and severity of illness. This improvement may be mediated by the recolonization of the gastrointestinal tract with healthy bacteria.**Conclusion**: These preliminary findings are the first to provide evidence for the role of microbial therapy in potentially treating depression and anxiety. This study has now transitioned into a larger randomized controlled trial with 60 patients being recruited across three sites in Southern Ontario.

Disclosures: **A. Chinna Meyyappan:** A. Employment/Salary (full or part-time):; Queen's University. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; CIHR CGS-D, Doctoral Recipient, MITACS Accelerate Scholarship, NuBiyota LLC, External Study Sponsor. **R. Milev:** A. Employment/Salary (full or part-time):; Queen's University, Providence Care Hospital. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; CAN-BIND, CIHR, Janssen, Lundbeck, NuBiyota, Ontario Brain Institute, OMHF. F. Consulting Fees (e.g., advisory boards); AbbVie, Allergan, Eisai, Janssen, KYE, Lallemand, Lundbeck, Neonmind, Otsuka, Sunovion.

Poster

147. Treatment and Drug Discovery for Mood Disorders

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 147.20

Topic: G.05. Mood Disorders

Support: NIH Grant AT010984
NIH Grant CA229451

Title: Discovery of microglial-targeted glutaminase inhibitors for the treatment of chronic stress-associated depression

Authors: *X. ZHU[1], C. TALLON[1], A. THOMAS[1], P. MAJER[2], T. TICHY[2], A. SHARMA[1], K. RANGARAMANUJAM[1], R. RAIS[1], B. SLUSHER[1];

[1]JHU, Baltimore, MD; [2]Inst. of Organic Chem. and Biochemistry, Acad. of Sci. of the Czech Republic, Prague, Czech Republic

Abstract: Major depressive disorder (MDD) is a common and debilitating psychiatric disorder with a high lifetime prevalence, imposing a severe economic burden on society. Despite several clinically effective treatments for MDD, many patients exhibit resistance to current antidepressants. Thus, novel interventions based on pathological mechanisms of MDD are needed. We recently discovered that glutaminase (GLS1), the enzyme which catalyzes the hydrolysis of glutamine to glutamate, is highly upregulated in activated microglia in the brain of mice subject to Chronic Social Defeat Stress (CSDS), a well-established rodent model used to study stress-induced mood disorders, including depression. We then reported that inhibiting the elevated glutaminase activity with JHU-083, our orally available and brain-penetrable glutamine antagonist prodrug, dramatically inhibited the stress-induced microglial glutaminase activity, inflammatory cytokine induction, and normalized the CSDS-induced social avoidance and anhedonia. Unfortunately, while JHU-083 showed robust therapeutic efficacy, its chronic dosing is known to cause gastrointestinal toxicity limiting its translational application. Given its significant clinical potential, we are addressing this limitation by directly targeting microglial glutaminase using a hydroxyl-dendrimer nanoparticle delivery system. Systemically administered hydroxyl-terminated poly(amidoamine) (PAMAM) dendrimers (~4-10 nm) are rapidly cleared from circulation under normal conditions but are selectively engulfed and retained by activated and phagocytic immune cells, such as microglia, under inflammatory conditions. Using a Cy5 fluorescently labeled PAMAM dendrimer (D-Cy5), we tested its brain penetration in mice after CSDS and found that D-Cy5 was selectively engulfed by activated microglia in mice after CSDS. In addition, we successfully synthesized and characterized Dendrimer-TTM020 (analog of JHU-083 designed for dendrimer conjugation) and showed that Dendrimer-TTM020 inhibited elevated microglial glutaminase activity in mice subjected to CSDS. We are currently evaluating the therapeutic and tolerability profile of D-TTM020 in the CSDS murine model. A successful Dendrimer-TTM020 conjugate ready for Investigational New Drug (IND)-enabling studies will support future clinical studies to combat chronic stress-associated depression.

Disclosures: X. Zhu: None. **C. Tallon:** None. **A. Thomas:** None. **P. Majer:** None. **T. Tichy:** None. **A. Sharma:** None. **K. Rangaramanujam:** None. **R. Rais:** None. **B. Slusher:** None.

Poster

147. Treatment and Drug Discovery for Mood Disorders

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 147.21

Topic: G.05. Mood Disorders

Support: R01GM134363-01

Title: Hemispheric differences in aperiodic activity interact with symptom chronicity in Major Depressive Disorder to predict Sertraline treatment response

Authors: *A. CHAPMAN[1], S. E. SMITH[2], B. VOYTEK[3,4,2,5];
[1]Psychology, [2]Neurosciences Grad. Program, [3]Cognitive Sci., [4]Halıcıoğlu Data Sci. Inst., [5]Kavli Inst. for Brain and Mind, UC San Diego, La Jolla, CA

Abstract: Major Depressive Disorder (MDD) is a neuropsychiatric condition that can be difficult to treat because of inconsistent responses to different antidepressant medications across patients. As a result, there have been growing pursuits for neurophysiological indicators that can help predict treatment response to antidepressant medication for MDD patients. Abnormal electroencephalogram (EEG) patterns have been present in patients with MDD, such as hemispheric asymmetry in alpha power. However, many EEG measures associated with MDD have failed to generalize or serve as indicators for depression treatment response, necessitating further investigation using novel quantitative methods and measures. One such measure is non-oscillatory "aperiodic" activity, which can be quantified by the "aperiodic exponent" using spectral parameterization. In this between-patients analysis leveraging open data from a large clinical study of Sertraline (SER) intervention for MDD, we show how hemispheric differences in aperiodic exponent at baseline predict clinical improvement in patients with chronic and non-chronic MDD. More specifically, we found that patients with chronic MDD that received SER treatment showed the most clinical improvement when the aperiodic exponent in the left hemisphere is greater at baseline. On the other hand, patients with non-chronic MDD that received SER treatment had the most clinical improvement when the aperiodic exponent in the right hemisphere is greater at baseline. This effect was not observed for patients receiving a placebo. These results suggest that hemispheric differences in the aperiodic exponent might be relevant to clinical improvement for patients with MDD. Additionally, these hemispheric differences in aperiodic activity can help indicate treatment response when taking into account symptom chronicity in MDD patients. These results identify hemispheric asymmetry in aperiodic activity as a promising subject for further investigations of treatment response in depression.

Disclosures: **A. Chapman:** None. **S.E. Smith:** None. **B. Voytek:** None.

Poster

147. Treatment and Drug Discovery for Mood Disorders

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 147.22

Topic: G.05. Mood Disorders

Support: Krembil Foundation
CAMH Discovery Fund
Labatt Family Network

Title: Inter-individual variability in rTMS target connectivity

Authors: *S. HARITA[1], D. MOMI[4], F. MAZZA[2], J. D. GRIFFITHS[3];
[1]Inst. of Med. Sci., [2]Physiol., [3]Univ. of Toronto, Univ. of Toronto, Toronto, ON, Canada;
[4]Krembil Ctr. for Neuroinformatics, Ctr. for Addiction and Mental Hlth., Toronto, ON, Canada

Abstract: *Background***:** Repetitive transcranial magnetic stimulation (rTMS) is an emerging alternative to existing treatments for major depressive disorder (MDD). Previously, rTMS target sites have focused on individual brain regions implicated in MDD, such as the dorsolateral prefrontal cortex (dlPFC) and orbitofrontal cortex (OFC). However, additionally considering the network connectivity of these sites (i.e. wider set of brain regions that are mono- or polysynaptically activated by rTMS stimulation) may be useful. *Hypothesis***:** Our hypothesis was that individual differences in functional brain dynamics would contribute more to variability in network engagement (implicated for dlPFC and OFC stimulation sites) than individual differences in cortical geometry associated with E-field patterns. *Methods***:** To determine the E-field, we created a tetrahedral head model from T1- and T2-weighted MR images for 121 subjects from the Human Connectome Project (HCP) database. We used the F3 and Fp1 10-20 EEG electrode system to target the left dlPFC and left OFC, respectively. We acquired the resting-state fMRI data for these subjects from the HCP database, to study the functional connectivity of rTMS targets. *Results***:** Three major functional networks were targeted across the dlPFC and OFC: the ventral attention, fronto-parietal and default-mode networks in the dlPFC and the fronto-parietal and default mode networks in the OFC. Furthermore, the degree to which each network is engaged varied on a subject-by-subject basis, highlighting inter-individual variability of rTMS application. *Conclusions***:** Our hope is that these insights prove useful as part of the broader effort by the psychiatry, neurology, and neuroimaging communities to help improve and refine rTMS therapy, through a better understanding of the technology and its neurophysiological effects.

Disclosures: S. Harita: None. **D. Momi:** None. **F. Mazza:** None. **J.D. Griffiths:** None.

Poster

147. Treatment and Drug Discovery for Mood Disorders

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 147.23

Title: WITHDRAWN

Poster

147. Treatment and Drug Discovery for Mood Disorders

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 147.24

Topic: G.05. Mood Disorders

Support: NIA Grant R01AG070873
NIA Grant R43AG071045
NIAAA Grant 75N94019C00010

Title: Characterization of antidepressant-like effects of two novel phosphodiesterase 2 inhibitors

Authors: Y. YAN[1], S. AVASTHI[1], W. WANG[2], F. DU[3], X. ZHU[4], J. M. O'DONNELL[5], ***Y. XU**[1];
[1]Rutgers, The State Univ. of New Jersey, Newark, NJ; [2]Univ. of Arizona, Tucson, AZ; [3]FD Neurotechnologies, Inc., FD Neurotechnologies, Inc., Columbia, MD; [4]Case Western Reserve Univ., Cleveland, OH; [5]Dept. of Pharmaceut. Sci., Univ. at Buffalo, The State Univ. of New York, Buffalo, NY

Abstract: PDE2A represents a novel target for new therapies addressing psychiatric disorders. To date, the development of PDE2A inhibitors suitable for human clinical evaluation has been hampered by the poor brain accessibility and metabolic stability of the available compounds. In our efforts to develop the functional activity of novel and small molecule inhibitors of PDE2A, two lead compounds Hcyb1 and Hcyb3 generated from chemical scaffolds optimized for both better brain bioavailability and greater metabolic stability have been synthesized and biologically characterized *in vitro* and *in vivo*. The IC_{50} values of Hcyb1 and Hcyb3 were 33.4 nM and 10.7 nM for PDE2A with >50-fold selectivity over other PDEs with excellent potency, acceptable B/P ratios, and improved brain penetration (i.e., AUC). The desired metabolic stability and half-life were also acceptable. The cell-based assay and *in vivo* study confirmed that Hcyb1 and Hcyb3 displayed the desired biochemical effects, i.e., increased cAMP/cGMP, phosphorylation of CREB and VASP, and BDNF levels in the hippocampal cells. Further behavioral tests showed that Hcyb1 and Hcyb3 exhibited antidepressant- and anxiolytic-like effects, as evidenced by decreased immobility time in the forced swimming and tail suspension tests, increased % of time spent and % of entrances into open arms in the elevated plus-maze, and increased hole visiting in the hole board test in mice. These findings extend the previous studies and validate PDE2A as a target for induction of depression- and anxiety-like behavior. Moreover, the chemical experience garnered from this study supports the idea that PDE2A is a tractable target for drug development in the treatment of mood disorders.

Disclosures: Y. Yan: None. **S. Avasthi:** None. **W. Wang:** None. **F. Du:** None. **X. Zhu:** None. **J.M. O'Donnell:** None. **Y. Xu:** None.

Poster

147. Treatment and Drug Discovery for Mood Disorders

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 147.25

Topic: G.05. Mood Disorders

Title: Monoaminergic influence of the glutamatergic rapid-acting antidepressant RO-25-6981 and its analogs

Authors: C. K. DAWES[1], N. K. GHAZIMORAD[2], J. WIRTZ[2], D. C. VALLS[2], J. NEWBY[2], J. JANSON[2], V. KLAHARN[2], R. D. KIRSH[3], C. H. SO[2], D. B. RAWLINS[2], *J. N. TALBOT[1]; [1]Col. of Grad. Studies, [2]Col. of Pharm., [3]Comparative Med. Unit, Roseman Univ. of Hlth. Sci., Henderson, NV

Abstract: Rational design of lead compounds targeting serotonergic and glutamatergic systems is critical to developing novel therapeutics for treating psychiatric disorders. The ketamine-like glutamatergic antagonist RO-25-6981 exerts both rapid and sustained antidepressant-like activity. The purpose of the current study is to develop RO-25-6981 analogs that delineate antidepressant-like mechanisms of NR2B-selective NMDA receptor antagonism and monoaminergic reuptake transporter inhibition in behavioral models. Wild-type C57BL/6J mice and heterozygous transgenic mice deficient in NR2b subunit expression of the NMDA receptor ($Grin2^{btm1.1(Grin2a)Bjha}$) were utilized in the study. To assess antidepressant-like behaviors, the tail suspension test (TST) and locomotor activity (LA) tests were performed using RO-25-6981 and its analogs with traditional antidepressant drugs, including the serotonin selective reuptake inhibitor fluoxetine and the tricyclic antidepressant desipramine, as positive controls for monoaminergic reuptake activity. In the TST, six RO-25-6981 analogs (TR-2, TR-4, TR-5, TR-6, TR-13, and TR-17) were found to exhibit antidepressant-like activity in wild-type mice following acute administration (i.p., 30 min) compared to vehicle-treated controls, with varying potency but similar efficacy comparable to RO-25-6981 and the traditional monoaminergic antidepressants fluoxetine and desipramine. Other TR analogs tested showed no antidepressant-like activity, despite possessing reported NMDA receptor antagonist activity via mid- to low-nanomolar binding affinity at the NR2B subunit. In contrast, increasing serotonin reuptake transporter inhibition via the addition of a tertiary amine increased antidepressant-like activity of TR-17. Interestingly, RO-25-6981, TR-5 and TR-17 exhibited similar antidepressant-like activity in wild-type and NR2B-deficient mice. Unlike RO-25-6981, all TR compounds profoundly limited motor activity suggesting independent psychotropic vs. generalized locomotor effects. Taken together, these data suggest that the antidepressant-like activity of RO-25-6981 and its analogs does not correlate with the degree of NMDA receptor antagonism. Furthermore, these data point to serotonergic reuptake inhibition contributing to the overall antidepressant-like activity of RO-25-6981 in animal models of mood.

Disclosures: C.K. Dawes: None. **N.K. Ghazimorad:** None. **J. Wirtz:** None. **D.C. Valls:** None. **J. Newby:** None. **J. Janson:** None. **V. Klaharn:** None. **R.D. Kirsh:** None. **C.H. So:** None. **D.B. Rawlins:** None. **J.N. Talbot:** None.

Poster

147. Treatment and Drug Discovery for Mood Disorders

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 147.26

Topic: G.05. Mood Disorders

Support: 2020M3E5D9080794

Title: Virtual screening of Tachykinin Receptor 1 Inhibitors using Machine-Learning

Authors: *H. YOO[1], C.-S. LEE[2], J.-I. HWANG[3], H. LEE[1], H. KIM[1];
[1]Dept. of Anat., [2]Med. Sci. Res. Ctr., [3]Dept. of Biomed. Sci., Korea Univ., Seoul, Korea, Republic of

Abstract: Substance P and Tachykinin receptor 1 (TACR1) have been one of the important antidepressant target molecules, and substance P is well-known to be elevated in major depressive disorder patients. However, no current TACR1 antagonist has a known effect on depressive symptoms after the phase 3 clinical trial failed. We used machine learning and in-silico docking to identify molecules that effectively antagonize TACR1. We collected the pChEMBL value ($-\log_{10}$IC50 or Ki) of 2499 ligands on TACR1 using the CHEMBL and NCBI databases and divided them into training (80%) and test set (20%). Using KNIME and Maestro (Schrodinger v2021-2), we compared six machine learning methods with 5-fold cross-validation and selected the model with the highest R^2 and lowest RMSE (root mean squared error) on average. Next, we used the best performing algorithm, Deepchem, to predict the pChEMBL value of 2.68 million ligands in the ENAMINE library. The prediction scores were binned into 20 categories, and ligands in the top 2 categories with high prediction scores were used for further analysis. The ligands were clustered using hierarchical clustering based on morgan fingerprint; we selected 15 ligands based on prediction score and clustering results. Each ligand and substance P was treated on TACR1-transfected HEK293 cells to measure the inhibitory effect of the ligand on TACR1. Using FLIPR Calcium 6-QF Assay, three ligands showed reduced F/F0 value in 50μM compared to 5μM, and dose-dependency was measured. This revealed the possibility of a noble structured TACR1 antagonist. For further study, we are trying to modify the structure of screened ligands and apply it to the depression animal model for in vivo study.

Disclosures: H. Yoo: None. **C. Lee:** None. **J. Hwang:** None. **H. Lee:** None. **H. Kim:** None.

Poster

147. Treatment and Drug Discovery for Mood Disorders

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 147.27

Topic: G.05. Mood Disorders

Support: NSERC CGS-D
Michael Smith Foreign Study Supplement

Title: Ipsc-derived neurons from treatment-resistant depression patients and healthy controls respond differently to reelin and (2r,6r)-hnk

Authors: J. N. JOHNSTON[1], B. QUINTANILLA[2], P. YUAN[3], H. J. CARUNCHO[1], M. YAVI[4], B. KADRIU[5], C. A. ZARATE, Jr.[4];
[1]Div. of Med. Sci., Univ. of Victoria, Victoria, BC, Canada; [2]UTHealth Houston, Houston, TX; [3]Biomarker Lab., NIMH/NIH, Bethesda, MD; [4]Exptl. Therapeut. and Pathophysiology Br., NIMH, Bethesda, MD; [5]Janssen Janssen Pharmaceut. Companies of Johnson & Johnson, San Diego, CA

Abstract: Major Depressive Disorder (MDD) is the leading cause of disability worldwide, with a lifetime prevalence rate around 16%. Despite this ubiquity, traditional antidepressants have a substantial therapeutic time delay and low efficacy rates. Ketamine has been discovered to have rapid antidepressant effects mediated through a transient activation of the mammalian target of rapamycin (mTOR) which promotes a sustained elevation of synaptic-strength related proteins. (2R,6R)-hydroxynorketamine (HNK), a major metabolite of ketamine, appears to produce similar rapid antidepressant effects in animal models without associated side effects. Reelin, a large glycoprotein, is an important mediator of synaptic plasticity which parallels some of the behavioural and biological effects of ketamine, warranting further investigation. Inducible pluripotent stem cells (iPSCs) were programmed from peripheral mononuclear blood cells from 5 treatment-resistant depression patients and 2 healthy controls. The STEMdiff^{TM} embryoid body protocol was followed to develop single-cell neural progenitor cells. Cells were supplemented and cultured for 10 weeks, then divided into 5 different conditions (vehicle; 5nM, 10nM, and 50nM reelin; 1μM (2R,6R)-HNK) at 2 timepoints (1 hr; 24 hr). Western blotting analyses were used to quantify mTOR, phosphorylated-mTOR (p-mTOR), PSD95, GluA1, Synapsin 1 (Syn-I), Disabled-1 (Dab1), tyrosine kinase receptor B (TrkB), extracellular signal-regulated kinase (ERK), and p-ERK. In HC, no significant differences were found in any treatment or time group. However in TRD cell lines at 1 hr, reelin and (2R,6R)-HNK significantly increased levels of PSD-95 (R50nM, $p<0.05$; HNK1μM, $p<0.01$), Syn-I (R10nM, $p<0.05$; R50nM, $p<0.01$; HNK1μM, $p<0.01$), Dab1 (R10nM, $p<0.05$; R50nM, $p<0.01$; HNK1μM, $p<0.01$), and p-ERK (R50nM, $p<0.05$; HNK1μM, $p<0.05$). With 24 hr application, these effects were reversed, demonstrating a significant down-regulation of expression of PSD-95 (R10nM, $p<0.05$; R50nM, $p<0.01$) and Syn-I (R10nM, $p<0.05$; R50nM, $p<0.01$; HNK1μM, $p<0.01$). Reelin and (2R,6R)-HNK have parallel effects both at 1 hr and 24 hr in iPSC-derived neurons from TRD patients, but no effect on those from HCs. HC cell lines may be better at mediating homeostasis after treatment as in TRD, the increased protein expression was reversed at 24 hours, suggesting a mechanistic shift between time points. This study is a forward step towards the development of leading-edge antidepressant therapeutics and the use of novel methodologies to improve the translatability of pharmacological research.

Disclosures: J.N. Johnston: None. **B. Quintanilla:** None. **P. Yuan:** None. **H.J. Caruncho:** None. **M. Yavi:** None. **B. Kadriu:** None. **C.A. Zarate:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Co-inventor on patent for use of ketamine in depression and suicidal ideation, assigned patent rights to U.S. government but shares percentage of royalties, Co-inventor on patent for use of (2R,6R)-HNK in depression and neuropathic pain, assigned patent rights to U.S. government but shares percentage of royalties, Co-inventor on patent for use of (S)-dehydronorketamine and other (R,S)-ketamine metabolites in depression and neuropathic pain, patent rights to U.S. government but shares percentage of royalties, Co-inventor on patent for use of (2R,6R)- and

(2S,6S)-HNK in depression, anxiety, anhedonia, suicidal ideation, and PTSD, assigned patent rights to U.S. government but shares percentage of royalties.

Poster

147. Treatment and Drug Discovery for Mood Disorders

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 147.28

Topic: G.05. Mood Disorders

Title: Antidepressant and anxiolytic properties of the extract and isolated compounds from Ziziphus abyssinica

Authors: *I. T. HENNEH[1], F. A. ARMAH[2], R. P. BINEY[3], M. EKOR[4];
[1]Dept. of Pharmacotherapeutics and Pharm. Practice, [2]Dept. of Biomed. Sci., [4]Dept. of Pharmacol., [3]Univ. of Cape Coast, Cape Coast, Ghana

Abstract: Rationale and Objectives: The diversity offered by natural products has timelessly positioned it as a good source for novel therapeutics for the management of various medical conditions, including anxiety and depressive disorders. This is an exploratory study that evaluated hydro-ethanolic root bark extract (ZAE) and isolated compounds from *Ziziphus abyssinica* for anxiolytic and antidepressant properties. **Methods and Results:** Established *in vivo* experimental models were adopted in assessing antidepressant (forced swim and tail suspension tests), as well as anxiolytic (elevated plus maze and open field tests) effects of ZAE and the isolated compounds. Each of the experiments utilized seven (7) groups of eight (8) weeks old male ICR mice with ten (10) mice in each group. Negative control groups were administered 10 mL/kg normal saline and positive control groups were either given fluoxetine (3, 10, 30 mg/kg, *p.o.*) or diaxepam (0.3, 1 or 3 mg/kg *p.o.*) respectively for depression and anxiety tests. Elucidation of structures of the isolated compounds was carried out using infra-red spectroscopy, mass spectrometry, nuclear magnetic resonance and X-ray crystallography. Two pentacyclic triterpenes, β-amyrin and polpunonic acid, were isolated from the plant. ZAE (30, 100 and 300 mg/kg, *p.o.*) as well as the isolated compounds, β-amyrin (3, 10 and 30 mg/kg, *p.o.*) and polpunonic acid (3, 10 and 30 mg/kg, *p.o.*), exhibited significant ($P < 0.05$) anxiolytic and antidepressant properties in murine models comparable to fluoxetine which was used as the positive control drug. **Conclusion:** The anxiolytic and antidepressant properties exhibited by the crude extract and isolated compounds from the plant suggest that they could be further investigated as alternatives or complements to the already available drugs. Mechanisms mediating these effects are currently on-going in our laboratories.

Disclosures: I.T. Henneh: None. **F.A. Armah:** None. **R.P. Biney:** None. **M. Ekor:** None.

Poster

147. Treatment and Drug Discovery for Mood Disorders

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 147.29

Topic: G.05. Mood Disorders

Support: USHBC

Title: Using blueberries as a treatment for individuals diagnosed with depression and anxiety in a rural Louisiana population: a pilot study

Authors: *K. VENABLE[1], P. KELLEY[2], H. J. CRULL[1], P. EBENEZER[1], S. O'BRYAN[3], C. LEE[1], J. FRANCIS[1];
[1]LSU, Baton Rouge, LA; [2]UCSF, San Francisco, CA; [3]UAB, Birmingham, AL

Abstract: Blueberries are a densely nutritional fruit with high antioxidant capacity and anti-inflammatory properties that potentially modulate serotonin and have demonstrated beneficial effects on health and multiple disease states, in numerous preclinical and clinical studies. Depression and anxiety are prevalent and costly psychiatric disorders in America and globally. Further, emerging evidence supports a relationship, bidirectional perhaps, between depression and the immune system, with chronic, low-grade, systemic inflammation observed in a subset of individuals diagnosed with major depressive disorder. To investigate how a medicinal dose of blueberries might support the physiological health and emotional wellbeing of individuals diagnosed with depression and anxiety, we collaborated with a Louisiana rural health clinic system, Louisiana Health Care Practitioners (LHCP), and designed and implemented a randomized, placebo-controlled, crossover study at 2 LHCP sites. This study consisted of two 12-week arms with baseline, mid, and post treatment assessments in each arm; in the first arm, participants were randomly assigned to either 24 g whole, freeze-dried blueberry powder ("blueberry first") or a calorie-matched placebo control powder ("placebo first") which they suspended in water and ingested each day (for 12 weeks). Between arms 1 and 2 there was a 4 week washout period, followed by treatment crossover in the second arm, so, those who were assigned to blueberry in the first arm switched to placebo in the second arm and vice versa. At all six timepoints we collected blood samples and MDI and GAD7, self-report measures probing depression and anxiety symptoms, respectively. At baseline and post assessments, we also administered the SIGH-D, a verbal interview utilizing the Ham-D scale and the IDSC. To elucidate physiological changes, we chose non-targeted metabolomics and will measure inflammatory cytokine expression in participant serum samples with MSD assays targeting IL-1β, TNF-α, Il-6, IL-10, IFNγ. We calculated changes from baseline to post assessment scores, and found blueberry treatment ameliorated symptoms of anxiety and depression compared to placebo, as measured by the GAD-7 and SIGH-D but not the MDI; these effects were most prominent in the first arm. We plan to use mixed effects modeling to analyze the relationship between blueberry treatment, inflammatory cytokine expression, metabolomics, and behavioral outcomes. This is a pilot study that lacked robust statistical power, but support the growing momentum toward more personalized forms of psychiatric treatment options for disorders as complex as depression and anxiety.

Disclosures: **K. Venable:** None. **P. Kelley:** None. **H.J. Crull:** None. **P. Ebenezer:** None. **S. O'Bryan:** None. **C. Lee:** None. **J. Francis:** None.

Poster

148. Stress, Depression, and Other Psychiatric Disorders

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 148.01

Topic: G.08. Other Psychiatric Disorders

Support: NHMRC Grant 1108092; 1116930; 2012929
DECRA DE190101244

Title: Role of the paraventricular thalamus to insular cortex glutamatergic projection in stress-induced binge eating in female mice

Authors: ***R. G. ANVERSA**[1], E. J. CAMPBELL[1], S. S. CH'NG[1], A. J. LAWRENCE[1], R. M. BROWN[2];
[1]Florey Inst. of Neurosci. and Mental Hlth., [2]Biochem. and Pharmacol., The Univ. of Melbourne, Melbourne, Australia

Abstract: Eating disorders have the 2nd highest mortality rate of all mental health disorders across the globe. Stress is a known trigger for the dysfunctional eating observed in obesity and eating disorders. Unfortunately, little is known about the neurobiology underlying stress-induced eating, particularly in females. This study aimed to investigate the neural pathways underlying stress-induced binge eating utilizing a newly stablished stress-induced binge eating protocol. Female vGlut2-Cre mice (n=27) were divided into 4 groups: naïve (n = 4), control (n = 8), stress minus reward (n = 8), and stress plus reward (n = 8). Stress groups animals underwent a stress-induced bingeing protocol, where the mouse could smell and see the highly palatable food but could not consume it for 15 minutes. Immediately afterwards the food was made available. Control mice were not subjected to the stress and were simply allowed to consume the food reward. 90 minutes after the frustration stress, animals were perfused for Fos protein immunohistochemistry. A second cohort received stereotaxic injections of either inhibitory DREADD (AAV-hSyn-DIO-hM4D(Gi)-mCherry, n = 20) or control virus (AAV-CAG-mCherry, n = 20) in the paraventricular nucleus of the thalamus (PVT), and bilateral cannula implants into the insular cortex. Mice were subjected to the stress-binge protocol described above. Binge-like behaviour was associated with increased Fos-protein expression in the insular cortex ($p < 0.0003$) and PVT ($p < 0.0009$). Furthermore, chemogenetic inhibition of excitatory vGlut2+ projecting neurons from the PVT to insular cortex reduced bingeing behaviour ($p < 0.0024$). Importantly, inhibition of this pathway had no effect on general locomotor activity and anxiety-like behavior in the light-dark test, nor affected eating behavior independent of stress. Collectively these data suggest a distinct thalamocortical pathway that gates stress-induced binge eating in female mice.

Disclosures: **R.G. Anversa:** None. **E.J. Campbell:** None. **S.S. Ch'ng:** None. **A.J. Lawrence:** None. **R.M. Brown:** None.

Poster

148. Stress, Depression, and Other Psychiatric Disorders

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 148.02

Topic: G.08. Other Psychiatric Disorders

Support: NHMRC project grant APP110892
ARC DECRA DE190101244
Melbourne Research Scholarship

Title: Episodic short access to a high-fat high-sugar diet induces compulsive behaviour, increased aggression and changes in glutamate protein expression in the striatum

Authors: *D. SKETRIENE[1,2], P. SINNAYAH[3], M. MAO[1,2], A. J. LAWRENCE[1,2], R. M. BROWN[1,2];
[1]Univ. of Melbourne, Melbourne, Australia; [2]Florey Inst. of Neurosci. & Mental Hlth., Parkville, Australia; [3]Victoria Univ., Melbourne, Australia

Abstract: **Introduction:** Time-limited and sporadic access to preferred diet models a common form of dieting, whereby a person episodically abstains from high-fat/high-sugar (HFHS) palatable foods while trying to eat less energy-dense and often less palatable foods. It was demonstrated that the cycling pattern of overeating junk food and episodes of self-restriction from it resembles the use-abstinence cycle observed in drug addiction. Moreover, such dieting is a risk factor for the development of binge eating disorder and could lead to obesity. Previously, we and others showed that in rats, the intermittent access to an HFHS diet leads to the development of a hallmark behavioural feature of drug addiction - compulsivity. In substance use disorders, increased compulsivity is be associated with a glutamatergic dysfunction in the striatum. Therefore, we hypothesised that compulsive-like eating induced by intermittent access to the HFHS diet would lead to changes in the expression of specific glutamate proteins in the striatum.
Methods: We compared male rats with episodic one-hour access and those with 24h access to the HFHS diet. Both groups had unrestricted access to standard rodent diet and water. A control group never had access to the "junk" food. Compulsive-like eating was assessed using a conditioned suppression paradigm where rats had an opportunity to eat HFHS food in the presence of an aversive signal (previously associated with a mild foot shock). In a different cohort of animals, we conducted elevated plus maze, open field, social interactions and hole board tests. Finally, we explored changes in the glutamatergic system in the different parts of the striatum using western blot, mass spectrometry and whole-cell patch electrophysiology.
Results: Total HFHS food intake and latency to start eating in the conditioned suppression task were reduced in all groups except the one with episodic access, confirming that random sporadic

access to the preferred diet could lead to the development of compulsive-like behaviour towards HFHS food. There were no differences between groups in anxiety-like behaviour, locomotion, and short and long-term memory. However, the episodic access group displayed heightened aggression. Brain analysis revealed increased levels of subunits of glutamate receptors (GluN2B, GluA1) in dorsal striatum.
Conclusion: Our findings suggest that an intermittent access schedule to HFHS is sufficient to promote compulsive-like eating behaviour associated with glutamatergic changes in the dorsal striatum and suggest new targets for a potential pharmacological intervention for better management of compulsive overeating.

Disclosures: D. Sketriene: None. **P. Sinnayah:** None. **M. Mao:** None. **A.J. Lawrence:** None. **R.M. Brown:** None.

Poster

148. Stress, Depression, and Other Psychiatric Disorders

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 148.03

Topic: G.08. Other Psychiatric Disorders

Support: JP21K15210
JP21H00311
JP22H02944
JP21wm0425010
21gm1510006
JP21H05694

Title: Effects of Importin α1(KPNA1) depletion and adolescent social stress on psychiatric disorder-associated behaviors in mice.

Authors: *K. SAKURAI[1,2], E. KASAHARA[3], T. OZAWA[1,2], T. MACPHERSON[1,2], Y. MIYAMOTO[4], Y. YONEDA[4], A. SEKIYAMA[3], M. OKA[4], T. HIKIDA[1,2];
[1]Inst. for Protein Res., Osaka Univ., Suita, Japan; [2]Dept. of Biol. Sciences, Grad. Sch. of Sci., Osaka Univ., Toyonaka, Japan; [3]Grad. Sch. of Pharmaceut. Sci., Osaka Univ., Suita, Japan; [4]Natl. Inst. of Biomed. Innovation, Hlth. and Nutrition, Osaka, Japan, Ibaraki, Japan

Abstract: Importins are a category of proteins that assist polypeptides to be transported from the cytoplasm to the nucleus. Importin αs (Impαs), otherwise known as KPNAs, bind to classical nuclear localization signals (cNLS) in the sequence of cargo proteins and assist their entry into the nucleus by acting as adaptors to Importin β (Impβ), which allow the Cargo-Impα-Impβ trimer to pass through the nuclear pore complex. In addition to their well-characterized role in canonical nucleocytoplasmic transport, more recent studies have suggested wider roles of Impαs including gene regulation and axonal transport, with various implications in humans and mice physiology. KPNA1(Human Importin α5/Mouse Importin α1) is a member of the Impα family

expressed highly in the brain, which has been shown to decrease anxiety-related behaviors through the nuclear transport of the MeCP2 transcription factor. Furthermore, a recent study has identified the *KPNA1* gene as a possible contributor to schizophrenia pathogenesis in humans. In addition to various genetic factors, it is well known that a plethora of environmental factors may induce behavioral deficits or enhance deficits caused by genetic factors. Such gene-environment (GxE) interactions between various factors are thought to underlie the complex mechanism of psychiatric disorder pathogenesis, and mouse models of genetic risk factors subjected environmental stress can be used as a model of GxE interaction in human patients. To investigate the effects of both environmental stress and KPNA1 deficiency on mouse behavior, we subjected male *Kpna1* knockout mice on a C57BL/6JJcl background to adolescent social isolation, a model for human adolescent psychosocial stress. Behavioral characterization including anxiety-related behaviors revealed effects of both KPNA1 deficiency and social isolation on aversive learning in the inhibitory avoidance test and depression-related behavior in the forced swim test. Moreover, analysis of biomarkers (signal molecules in plasma, brain monoamines) showed significant alterations as a result of KPNA1 deficiency and/or social isolation. Although the connections between KPNA1 depletion and behavior have not been fully understood, further investigations into the cellular and molecular mechanisms behind these altered behavioral phenotypes as a result of genetic (KPNA1 deficiency) and/or environmental (social isolation) risk factors may reveal the currently unknown mechanisms underlying GxE interaction in the pathogenesis of psychiatric disorders, possibly leading to new therapeutic approaches.

Disclosures: **K. Sakurai:** None. **E. Kasahara:** None. **T. Ozawa:** None. **T. Macpherson:** None. **Y. Miyamoto:** None. **Y. Yoneda:** None. **A. Sekiyama:** None. **M. Oka:** None. **T. Hikida:** None.

Poster

148. Stress, Depression, and Other Psychiatric Disorders

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 148.04

Topic: G.08. Other Psychiatric Disorders

Support: JSPS KAKENHI grants JP21K15210
JSPS KAKENHI grants JP21H05694
JSPS KAKENHI grants JP22H02944
JSPS KAKENHI grants JP21K15210
Japan Agency for Medical Research and Development (AMED) JP21wm0425010
Japan Agency for Medical Research and Development (AMED) 21gm1510006
JST SPRING under Grant Number JPMJSP2138

Title: Motivational increase and brain network variation based on functional connectivity in Importin α3 (KPNA3) deficient mice

Authors: *Y. AOMINE[1,2], K. SAKURAI[1,2], T. MACPHERSON[1,2], T. OZAWA[1,2], Y. MIYAMOTO[3], M. OKA[3], Y. YONEDA[4], T. HIKIDA[1,2];
[1]Inst. for Protein Research, Osaka university, Osaka, Japan; [2]Dept. of Biol. Sci., Grad. Sch. of Science, Osaka university, Osaka, Japan; [3]Natl. Inst. of Biomed. Innovation, Hlth. and Nutr. (NIBIOHN), Osaka, Japan; [4]The Res. Fndn. for Microbial Dis. of Osaka Univ., Osaka, Japan

Abstract: Importin α3 (Gene: *Kpna3*, ortholog of human Importin α4) is a member of the importin α family and participates in nucleocytoplasmic transport by forming trimeric complexes between cargo proteins and importin β1. Evidence from human studies has indicated that single nucleotide polymorphisms (SNP) in the *KPNA3* gene are associated with the occurrence of several psychiatric disorders accompanied by abnormal reward-related behavior, including schizophrenia, major depression, and substance addiction. However, the precise roles of KPNA3 in controlling reward processing and motivation are still unclear. In this study, we evaluated the behavioral effects of *Kpna3* knockout (KO) in mice (male C57BL/6N) on touchscreen operant chamber-based tasks. We used progressive ratio (PR) schedule test, in which the number of operant responses to obtain a reward increases with each reward collected, to evaluate the motivation of mice to instrumentally respond for a reward. In this schedule, the break point, defined as the number of responses needed to receive the last reward collected, allows assessment of how much effort (responses) mice are willing to expend for a single reward. KO mice showed a significantly increased motivation (increased break point) to instrumentally respond for sucrose. We additionally measured the number of c-Fos positive cells, a marker of neural activity, in 20 regions of the brain and identified a network of brain regions based on their interregional correlation coefficients (functional connectivity). Network and graph-theoretic analyses suggested that *Kpna3* deficiency enhanced overall interregional functional connectivity. In particular, functional connectivity was significantly increased in four regions (the medial posterior nucleus accumbens (NAcp-m), ventral pallidum (VP), anterior basolateral amygdala (BLAa), posterior lateral hypothalamus (LH-p)). In addition, centrality analysis on network identified three types of hub regions. In the first type, VP and BLAa showed high centralities in both WT and KO mice. In the second type, NAcp-m, LH-p, medial preoptic area (MPOA), and dorsal raphe nucleus (DR) showed high centrality only in KO mice, suggesting that these regions play a central role in the control of motivation following the deletion of *Kpna3*. Finally, in the third type, the lateral and ventral orbital area (LO/VO), medial orbital area (MO), and median raphe nucleus (MR) showed high centrality only in WT mice. These findings suggest the importance of *Kpna3* in motivational control, and indicate that *Kpna3* KO mice may be an attractive line for modeling motivational abnormalities associated with several psychiatric disorders.

Disclosures: Y. Aomine: None. **K. Sakurai:** None. **T. Macpherson:** None. **T. Ozawa:** None. **Y. Miyamoto:** None. **M. Oka:** None. **Y. Yoneda:** None. **T. Hikida:** None.

Poster

148. Stress, Depression, and Other Psychiatric Disorders

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 148.05

Topic: G.08. Other Psychiatric Disorders

Support: NIH Grant R25 NS 80686
Klarman Family Foundation Eating Disorders Research Grants Program

Title: Baseline anxiety is associated with vulnerability to activity-based anorexia in mice

Authors: *N. COLLIE-BEARD[1], S. HANIF[1], N. S. BURGHARDT[1,2];
[1]Dept. of Psychology, Hunter Col., New York, NY; [2]Psychology Program, Behavioral and Cognitive Neurosci., The Grad. Center, CUNY, New York, NY

Abstract: Up to 65% of patients with anorexia nervosa are also diagnosed with an anxiety disorder. However, it is unclear if anxiety is a risk factor for developing anorexia or if anxiety develops as a consequence of extreme malnutrition. Using activity-based anorexia (ABA), a commonly used model of anorexia in mice, we are testing whether there is a relationship between pre-existing levels of anxiety and vulnerability to this eating disorder. Individual differences in anxiety were first assessed in young adult C57/Bl6 female mice (postnatal day 63; n=19) with the open field test. Then ABA was tested for 10 days, during which mice were individually housed with unlimited access to a running wheel and restricted access to food. Although food was only available during the first 2 hours of the dark cycle, mice could consume an unlimited amount of food in that time. Mice were weighed daily and removed from the experiment if they lost at least 25% of their baseline weight. Consistent with our previously published study (Beeler et al., 2021), we found that a subset of mice was resilient to ABA, as demonstrated by a progressive increase in food consumption, a decrease in wheel running, and stabilization of body weight. In contrast, vulnerable mice increased wheel running during the light cycle without adapting their food intake, leading to life-threatening weight loss that required removal from the experiment. When we examined the relationship between measures of baseline anxiety and ABA vulnerability, we found a significant correlation between entries into the center of the open field and day of ABA removal ($r = 0.75$, $p=0.0002$), indicating that the most anxious mice (fewest entries) were most vulnerable (early removal). ABA removal also correlated with all other measures of anxiety-like behavior in the open field test, including center time ($r = 0.59$, $p = 0.007$) and center distance ($r = 0.70$, $p = 0.0008$). While there was a modest correlation between ABA removal and total distance ($r = 0.57$, $p = 0.01$), it was not as robust as the correlation with percentage of total distance traveled in the center ($r = 0.68$, $p = 0.001$). Given that we found no correlation between baseline running and the day of ABA removal ($r = 0.16$, $p = 0.52$), the association we find with open field behavior is likely driven by anxiety rather than activity level. Our preliminary results indicate that anxious individuals who diet and exercise may be at higher risk of developing anorexia nervosa. Understanding this relationship further may provide much needed insight into the biological substrates of this poorly understood eating disorder.

Disclosures: **N. Collie-Beard:** None. **S. Hanif:** None. **N.S. Burghardt:** None.

Poster

148. Stress, Depression, and Other Psychiatric Disorders

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 148.06

Topic: G.08. Other Psychiatric Disorders

Support: NYS Office for People with Developmental Disabilities

Title: Effects of stimulation of the endocannabinoid system on mouse behavior in the BTBR mice, a model of Autism Spectrum Disorder

Authors: *K. K. CHADMAN[1], W. FYKE[2], S. SAYAKKARA[3];
[1]NYS Inst. Basic Res., NYS Inst. Basic Res., Staten Island, NY; [2]SUNY Downstate, SUNY Downstate, New York, NY; [3]Biol., CUNY Col. of Staten Island, Staten Island, NY

Abstract: Autism Spectrum Disorder (ASD) is a developmental disability characterized by deficits in social communication, and repetitive/restricted behaviors with an occurrence of 1 in 54 children. ASD is diagnosed through clinical behavioral assessments, as there is no biomarker. The endocannabinoid system (ECS) is a neuromodulatory cell-signaling system that has been implicated in the pathology of ASD. The ECS consists of two main components: type 1 (CB1) and type 2 (CB2) receptors, and the endogenous molecules anandamide (AEA) and 2-arachidonoylglycerol (2-AG). The majority of the CB1 receptors are found in the brain, in the hippocampus, basal ganglia and cerebellum, while moderate levels are seen in the amygdala and hypothalamus. The ECS regulates sleep, appetite, memory and mood. Our hypothesis is that the ECS is understimulated in people with ASD, and stimulating it through either direct agonism (CP-55940) or by blocking the enzymatic degradation of 2-AG (JZL-184) will lead to improvements in the behaviors related to ASD. The effects of JZL-184 and CP-55940 were tested with the following behavioral tests: social approach, direct social interaction and contextual fear conditioning on male and female C57BL/6J mice (control group) and the BTBR mice (mouse models for ASD). CP-55940 led to a decrease in the total distance traveled by the C57BL/6J and BTBR mice, suggesting a sedative-like effect that interfered with the behavioral analysis. JZL-184 had modest effects, increasing sniffing of the novelty mouse and reducing social sniffing during the direct social interaction experiment. Overall, the endocannabinoids only expressed modest effects on behaviors in the ASD mouse model which could be a result of the doses used in these experiments.

Disclosures: K.K. Chadman: None. **W. Fyke:** None. **S. Sayakkara:** None.

Poster

148. Stress, Depression, and Other Psychiatric Disorders

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 148.07

Topic: G.08. Other Psychiatric Disorders

Title: Loss of non-canonical open reading frame within lncRNA TUNAR increased pre-pulse inhibition and depression-related behavior in mice

Authors: K. FUJII[1,2,3], Y. MORIWAKI[4], Y. KOSHIDAKA[2], M. ADACHI[2], Y. YANAGIBASHI[2], S. HONGO[2], Y. AIZAWA[5], ***K. TAKAO**[1,2,3,4];
[1]Dept. of Behavioral Physiology, Fac. of Med., [2]Life Sci. Res. Ctr., [3]Res. Ctr. for Idling Brain Sci., [4]Dept. of Behavioral Physiology, Grad. Sch. of Med. and Pharmaceut. Sci., Univ. of Toyama, Toyama, Japan; [5]Grad. Sch. of Biosci. and Biotech., Tokyo Inst. of Technol., Yokohama, Japan

Abstract: By definition, long noncoding RNAs (lncRNAs) do not contain protein-coding open reading frames (ORFs). Recent bioinformatics and high-throughput sequencing studies, however, reported that many lncRNAs possess short “non-canonical” ORFs (sORFs) encoding microproteins. In particular, Ribo-seq, a technology using deep-sequencing to identify the positions of ribosomes engaged in translation, revealed that lncRNA contains many sORFs previously considered to be untranslatable. These newly identified microproteins are expected to be novel factors that will contribute to our understanding of life science and are potential targets of drug discovery. The Tcl1 upstream neuron-associated RNA (*TUNAR*) was discovered as a lncRNA. The *TUNAR* sequence is remarkably conserved across vertebrates and is highly expressed in neural tissues. By *in silico* screening, we identified that *TUNAR* has a sORF region encoding a 48-amino acid polypeptide. The lncRNA *TUNAR* plays a vital role in pluripotency and neural differentiation of mouse embryonic stem cells. Whether or not the sORF is translated into a microprotein *in vivo*, and how *TUNAR* and the microprotein affect brain function and behaviors, however, remain unclear.
Here, we generated *TUNAR*-microprotein reporter mice and *TUNAR* sORF deletion mice on the C57BL/6J background using the CRISPR-Cas9 genome editing system. Utilizing *TUNAR*-microprotein reporter mice in which an epitope-tag coding sequence was inserted before the stop codon, we detected the epitope tag-specific stained cells in the mouse central nervous system (e.g., thalamus, inferior colliculus, pons). These findings suggested that the *TUNAR* sORF is translated into an endogenous protein. To investigate the function of *TUNAR* microprotein in the brain, we subjected *TUNAR* sORF deletion mice to a comprehensive behavioral test battery. *TUNAR* sORF deletion mice had significantly lower body weight than their wild-type (WT) littermates. In the rotarod test, *TUNAR* sORF deletion mice exhibited better motor coordination compared with WT mice. In the startle response/pre-pulse inhibition (PPI) test, while there was no significant difference in the acoustic startle response, *TUNAR* sORF deletion mice showed increased PPI compared with WT mice. In both the Porsolt forced swim test and tail suspension test, *TUNAR* sORF deletion mice exhibited increased depression-related behavior. These results suggest that the *TUNAR* sORF deletion induces a depressive effect. These findings together indicate that the non-canonical microprotein from *TUNAR* is translated in the brain and has a critical role in sensory-motor gating and depression-related behavior.

Disclosures: K. Fujii: None. **Y. Moriwaki:** None. **Y. Koshidaka:** None. **M. Adachi:** None. **Y. Yanagibashi:** None. **S. Hongo:** None. **Y. Aizawa:** None. **K. Takao:** None.

Poster

148. Stress, Depression, and Other Psychiatric Disorders

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 148.08

Topic: G.08. Other Psychiatric Disorders

Title: Dissecting the role of medial vs lateral orbitostriatal projections in regulating perseverative behavior.

Authors: *P. FENTON[1], A. M. LIBSTER[1], S. C. DULAWA[2];
[1]Univ. of California San Diego, San Diego, CA; [2]Phychiatry, Univ. of California - San Diego, La Jolla, CA

Abstract: Obsessive-Compulsive Disorder (OCD) is a psychiatric condition in which perseverative thoughts and actions occur in an unwanted, persistent, and often disabling fashion. Extensive evidence suggests that dysfunction in cortico-striato-thalamo-cortical (CSTC) loops, including the orbitofrontal cortex (OFC), plays a central role. Human neuroimaging studies have consistently identified aberrant activity in the orbitofrontal cortex (OFC) in OCD, and more recently the heterogeneity of the OFC has come under scrutiny. Studies have shown discreet, functional roles of the OFC along the mediolateral axis. Furthermore, it has been shown that this aberrant activity abating in response to successful treatment with serotonin reuptake inhibitors (SRIs), the most effective pharmacological monotherapy for OCD patients. However, approximately 40% of OCD patients do not respond to serotonergic interventions, necessitating further understanding of the neural circuits involved in the perseverative behaviors etiologically relevant to OCD and obsessive-compulsive spectrum (OCS) behaviors. The serotonin receptor 5-HT1D, an inhibitory GCPR located on axon terminals of both serotoninergic and non-serotoninergic neurons, has been implicated in modulating OC-symptoms in patient populations. Studies have demonstrated acute exacerbation of OC symptoms in response to administration of meta-Chlorophenylpiperazine (mCPP), a non-selective 5-HT agonist with high affinity for the 5-HT1D receptor, and Sumatriptan, a selective 5-HT1D agonist commonly prescribed to treat migraines. Here we use a previously validated pharmacological model of 5-HT1BR (5-HT1D murine equivalent) agonist-induced perseverative behaviors in the Delayed Alternation Task (DAT) and Open-Field Test (OFT). Our goal is to understand how orbitostriatal projections originating in the medial versus lateral OFC regulate perseverative behaviors etiologically relevant to OCD. Here, we apply fiber photometry to freely-behaving mice receiving rAAV-hSyn-GCaMP8 in the striatum with an optic fiber implanted in either the mOFC or lOFC. We are testing mice following treatment with 0, 3, or 6 mg/kg RU24969 in the DAT, and the OFT. Given the role of lOFC orbitostriatal projections in punishment-driven learning, we expect to see a reduction in activity correlate with an increase in perseverative errors. Conversely, we predict activity of mOFC orbitostriatals will be negatively correlated with perseverative errors. We hope that a further understanding of the contributions of these unique circuits will allow for more targeted clinical interventions.

Disclosures: P. Fenton: None. **A.M. Libster:** None. **S.C. Dulawa:** None.

Poster

148. Stress, Depression, and Other Psychiatric Disorders

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 148.09

Topic: G.08. Other Psychiatric Disorders

Support: MOST 109–2420-H-004–021

Title: Striatal CK2 mediated DARPP-32 phosphorylation associates with impulsive action measured by a differential reinforcement of low-rate response task in rats

Authors: S.-F. CHEN[1,2], L.-C. CHAO[1], W.-C. HSU[1], X.-Y. LU[1], C.-Y. WANG[2], S.-K. CHEN[2,3], C.-C. CHAO[2,3], *R.-M. LIAO[1,2,3];
[1]Dept. of Psychology, [2]Inst. of Neurosci., [3]Res. Ctr. for Mind, Brain, and Learning, Natl. Cheng-Chi Univ., Taipei, Taiwan

Abstract: Impulsive traits play a prominent role in addictive behavior including drug addiction; conversely, substance use may have a state effect on impulsivity. It has been repeatedly shown that psychoactive drugs induce impulsive behavior. In terms of neural signaling, DARPP-32 is one of the substrate proteins of protein kinase CK2 (a serine/threonine-protein kinase), which is important in mediating the cross-line between different neurotransmissions in the brain. Despite that CK2 and/or DARPP-32 signaling has been proposed to regulate genome expression landscape involved in drug abuse, whether this neural signaling is involved in impulsivity is poorly understood. In this study, a differential reinforcement of low rate (DRL) task is used to characterize individual differences of impulsive action in rats. A cohort of rats was trained to acquire a DRL 10s task over 14 daily sessions. High impulsive (HI) and low impulsive (LI) rats were screened by the mean response efficiency of the 14 days with quartiles. The results showed that the mean response efficiency of DRL with HI group was significantly lower than that of LI group, which impulsive trail-like effect was persistently confirmed by a subsequent DRL behavior retest. Biochemical assay using ELIAS revealed that CK2 enzyme activity in the striatum and hippocampus of HI group was significantly lower than that of LI group. The western blot analysis revealed that CK2 protein level of the striatum of HI group was significantly lower than that of LI. Moreover, the phospho-Ser97-DARPP-32 (CK2 phosphorylation site) in the prefrontal cortex, striatum, and hippocampus of HI group was significantly lower than those of LI group, whereas no between-group difference of phosphorylation on DARPP-32 (Thr34) residue was detected in any of targeted area. The mRNA levels of dopamine D1 receptor, glutamate NR1 receptor subunit, and brain-derived neurotrophic factor in the striatum were significantly higher in HI group than those of LI group. These results, together, implicate the trait of impulsive action of DRL behavior associated with the striatal CK2 mediated DARPP-32 signaling that integrates dopamine and glutamate neurotransmissions.

Disclosures: S. Chen: None. **L. Chao:** None. **W. Hsu:** None. **X. Lu:** None. **C. Wang:** None. **S. Chen:** None. **C. Chao:** None. **R. Liao:** None.

Poster

148. Stress, Depression, and Other Psychiatric Disorders

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 148.10

Topic: G.08. Other Psychiatric Disorders

Support: SRG/2019/000382, DST, Govt. of India

Title: Understanding the neural basis of human suicidal behaviour: focusing on neural circuits of survival behaviour and interoceptive awareness

Authors: *S. JHA, N. MJ;
SASTRA Deemed Univ., SASTRA Deemed Univ., Thanjavur, India

Abstract: Suicide is a leading cause of global mortality (www.who.int/teams/mental-health-and-substance-use/data-research/suicide-data). Suicidal behaviour (SB) is included in Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5), with proposed diagnostic criteria. The high rate of mortality due to SB necessitates effective prevention and treatment strategies. However, our current understanding of the neural basis of self-destructive behaviour is limited, which hinders the development of clinically effective suicide-prevention and treatment programs (Nishanth & Jha, 2022; Eur Arch Psychiatry Clin Neurosci. 272(3):531-533). The high prevalence of SB presents a counter-intuitive biological phenomenon in light of evolutionarily pervasive survival instinct, driving the struggle for biological existence in all life-forms. Here, we propose potential interactions between (i) neural basis of SB, (ii) survival circuits, and (iii) interoceptive networks to be underlying SB. Survival circuits (including hypothalamus, amygdala, and parabrachial nucleus, among other structures) in brain are proposed to regulate fundamental life-processes (energy and nutrition, fluid balance, thermoregulation, defence, and reproduction). Owing to their involvement in regulating essential biological processes, these circuits could also be associated with survival instincts. Aberrant functioning of these circuits might lead to weakened survival instincts and facilitate SB, which needs to be investigated through further research. Additionally, recent research has identified dysfunctional interoception as a physiological correlate of SB (Hielscher & Zopf, 2021; Behav Ther. 52(5):1035-54), which could also be related to survival behaviour. Importantly, brain regions implicated in SB, interoceptive awareness, and survival processes show a substantial overlap, suggesting an interplay between these processes. Further research to delineate the possible interrelations between interoceptive networks, survival circuits, and SB could provide valuable insights into the neural basis of suicidality, and also novel avenues for prevention and treatment of SB.

Disclosures: S. Jha: None. **N. Mj:** None.

Poster

148. Stress, Depression, and Other Psychiatric Disorders

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 148.11

Topic: G.08. Other Psychiatric Disorders

Title: Whole-brain structural and functional neuroimaging of individuals who attempted suicide and people who did not: a coordinate-based meta-analysis and seed-based connectivity study

Authors: *N. MEDA, A. MIOLA, G. CATTARINUSSI, F. SAMBATARO;
Univ. Degli Studi Di Padova, Univ. Degli Studi Di Padova, Padova, Italy

Abstract: Suicide is the cause of death of approximately 800'000 people a year. Despite the epidemiological and clinical relevance of this behavior, risk assessment tools strongly rely on clinician experience and subjective ratings. The importance of identifying objective findings that can aid the clinician and the individual asking for help better predict suicide risk cannot be overstated. One step in this direction could be examining if any neuroimaging findings can distinguish the people who attempted suicide from those who did not. We thus designed a systematic review and coordinate-based meta-analysis (CBMA) to evince if any neuroimaging features can aid in distinguishing individuals who attempted suicide from subjects who did not. Then, we used JuSpace to test if the significant brain clusters emerged from the CBMA correlated with receptor spatial localization maps based on PET scans. Lastly, we used data from the Human Connectome Project Young Adult database (151 healthy subjects, age range 22-36, 62 males) to evince the correlation between the brain clusters activity, or their functional connectivity (FC), with other brain areas and relevant psychometric scores.Out of 2660 publications screened, we meta-analysed 20 of them (for a total of 594 individuals with a history of SA and 823 patient controls). We found that a cluster of grey matter in the right Superior Temporal Gyrus (rSTG), a region implicated in emotion processing and goal-prediction, is functionally hyperactive in individuals who attempted suicide. Furthermore, we found that the cluster in the rSTG is significantly correlated ($R = 0.35$, $p = 0.003$) with the $5\text{-}HT_{1A}$ receptor spatial localization. Moreover, we show that the resting-state activity of the right STG presented a positive correlation with loneliness scores and that the functional connectivity of this region with other brain areas shows significant correlations with psychometric scores investigating loneliness, thwarted belongingness, and self-efficacy. Taking these pieces of evidence together, we show that: the rSTG might be functionally altered in people who attempted suicide; this region is enriched in $5\text{-}HT_{1A}$ receptors; its functional connectivity is associated with psychosocial variables that were reported to be critically relevant to identifying people who are at risk to act on their thoughts of death. High heterogeneity in the analytical techniques and weak power analysis of the single studies included in this CMBA currently limit the applicability of the finding, the replication of which should be prioritized.

Disclosures: N. Meda: None. **A. Miola:** None. **G. Cattarinussi:** None. **F. Sambataro:** None.

Poster

148. Stress, Depression, and Other Psychiatric Disorders

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 148.12

Topic: G.08. Other Psychiatric Disorders

Support: Canadian Institutes of Health Research (MOP-FDN-148418)

Title: Identifying eating disorder biomarkers in youth via video-based eye movement tracking

Authors: R. H. KIRKPATRICK[1], L. BOOIJ[3], H. C. RIEK[4], J. HUANG[5], I. PITIGOI[2], D. BRIEN[4], B. C. COE[6], B. J. WHITE[7], J. COUTURIER[8], S. KHALID-KHAN[5], *D. P. MUNOZ[1]; [1]Queens Univ., [2]Fac. of Hlth. Sci., Queen's Univ. Ctr. For Neurosci. Studies, Kingston, ON, Canada; [3]Concordia Univ., Montreal, QC, Canada; [4]Ctr. for Neurosci. Studies, [5]Queen's Univ., Kingston, ON, Canada; [7]Ctr. for Neurosci. Studies, [6]Queens Univ., Kingston, ON, Canada; [8]McMaster Univ., Hamilton, ON, Canada

Abstract: Eating disorders have one of the highest hospitalization costs compared to other psychiatric disorders and incidences have increased dramatically during the COVID-19 pandemic. There is an urgent need to increase our scientific understanding of these disorders and to increase early and accurate detection. Here, we combined clinical assessment with video-based eye tracking to study possible behavioural biomarkers in youth with eating disorders. To do that, we studied saccade, pupil and blink behaviours in youth with and without eating disorders. Female participants completed two eye tracking tasks and questionnaires assessing behavior, cognition and personality traits. We employed the interleaved pro-saccade (eye movements towards a stimulus) and anti-saccade (eye movements away from a stimulus) task. To date, 55 patients and 30 controls (M_{age}=20.71, SD_{age}=4.689) have been collected. Patients were divided into purgers (n=21, M_{age}=17.81, SD_{age}=3.776; those whose diagnosis involves purging such as bulimia nervosa and anorexia nervosa-binge/purge) and restricters (n=34, M_{age}=16.11, SD_{age}=3.134*;* those with a diagnosis without purging such as anorexia nervosa-restrictive). In prosaccade trials, compared to controls, restricters and purgers made more anticipatory saccades before stimulus appearance (F(2,82)=4.076, p=0.021) and had faster saccadic reaction times (F(2,82)=4.397, p=0.015). There were no significant differences in error rates or saccadic reaction time between the groups on anti-saccade trials. Restricters also blinked significantly less often than controls in both pro- and anti-saccade trials. Pupil constriction and dilation responses triggered in response to fixation and anticipated stimulus appearance, respectively, were exaggerated in both eating disorder groups compared to controls. Though preliminary, these results point towards the potential use of eye tracking to identify objective biomarkers of eating disorders in youth. Identifying these markers may allow clinicians to diagnose eating disorders faster and more impartially, potentially leading to earlier diagnosis and intervention.

Disclosures: R.H. Kirkpatrick: None. **L. Booij:** None. **H.C. Riek:** None. **J. Huang:** None. **I. Pitigoi:** None. **D. Brien:** None. **B.C. Coe:** None. **B.J. White:** None. **J. Couturier:** None. **S. Khalid-Khan:** None. **D.P. Munoz:** None.

Poster

148. Stress, Depression, and Other Psychiatric Disorders

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 148.13

Topic: G.08. Other Psychiatric Disorders

Title: Rs4570625 single nucleotide polymorphism as a protective factor against the development of depression in Mexican rural population

Authors: *M. HERNANDEZ MIXTECO[1], E. A. GARCIA MONTALVO[2], C. L. BALDERAS VAZQUEZ[3], J. F. CERNA CORTES[4], J. F. RODRIGUEZ LANDA[1], O. L. VALENZUELA LIMON[2], B. BERNAL MORALES[1];
[1]Neuropharm. Lab., Neuroethology Institute, Univ. Veracruzana, Xalapa, Mexico; [2]Chem. Sci. Faculty, Univ. Veracruzana, Orizaba, Mexico; [3]Pharmacobiologist Chemist School, Ctr. Universitario Interamericano, Cordoba, Mexico; [4]Natl. Sch. of Biol. Sciences, Natl. Polytechnic Inst., Mexico, Mexico

Abstract: Anxiety and depression impair quality of life and several environmental and/or genetic factors are involved in their development. The rs4570625 polymorphism consists of a change from guanine to thymine in the codifying gene for tryptophan hydroxylase 2 enzyme and is associated with a deficiency in brain serotonin synthesis and phenotypic expression of different emotional and affective disorders. However, these findings have not been explored in the Mexican population in vulnerable situation. The aim of this study was to analyze the score of standardized socio-affective scales comparing the genotypic distribution of the rs4570625 polymorphism in a sample of Mexican rural population (Ethics and Research Committee Approvals I071 and 001/2020, respectively). Ninety-nine volunteers participated (57±12 years old), 75 women and 24 men, all residents of Ixtaczoquitlan communities in Veracruz, Mexico. Sixty-one percent had diabetes mellitus, 23.2% arterial hypertension and 15% had both diseases. Conventional PCR technique followed by enzymatic restriction showed that 59% of the volunteers had GT genotype, 22% GG genotype and 19% TT genotype, which was in accordance with Hardy-Weinberg equilibrium (p=0.2737). The findings did not show significative differences between genotypes and depression scores [H=3.901; p=0.142], anxiety [H=0.707; p=0.702], and quality of life [H=0.444; p=0.801]. Interestingly, volunteers with the recessive TT genotype had normal mood, while those with the GG and GT genotypes had mild mood disturbance. The multivariate logistic regression showed that the recessive TT genotype could be a protector factor against the development of depression symptoms in volunteers with mild symptoms of anxiety and with a diagnosis of diabetes (OR=0.33, 95% CI= 0.099 -1.127, p= 0.077). Increasing the sample size may confirm this association and contribute to findings in populations with different genetic background, cultural, physical, and environmental characteristics. Although the lack of statistical differences in the symptomatology of depression, anxiety, and perception of quality of life in patients with chronic disorders, rs4570625 polymorphism is a latent element in affective disorders regulation in Mexican rural population.

Disclosures: **M. Hernandez Mixteco:** None. **E.A. Garcia Montalvo:** None. **C.L. Balderas Vazquez:** None. **J.F. Cerna Cortes:** None. **J.F. Rodriguez landa:** None. **O.L. Valenzuela Limon:** None. **B. Bernal Morales:** None.

Poster

148. Stress, Depression, and Other Psychiatric Disorders

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 148.14

Topic: G.08. Other Psychiatric Disorders

Title: Symptom Patterns of Postpartum Depression and Relevant Factors During the COVID-19 Pandemic in Japan: A Latent Profile Analysis

Authors: *K. HAGIWARA[1], H. LEI[1], C. CHEN[1], R. OKUBO[2], S. OKAWA[3,4], N. HIGUCHI[1], S. NAKAGAWA[1], T. TABUCHI[3];
[1]Div. of Neuropsychiatry, Dept. of Neurosci., Yamaguchi Univ. Grad. Sch. of Med., Ube, Japan; [2]Dept. of Clin. Epidemiology, Translational Med. Ctr., Natl. Ctr. of Neurol. and Psychiatry, Tokyo, Japan; [3]Cancer Control Ctr., Osaka Intl. Cancer Inst., Osaka, Japan; [4]Inst. for Global Hlth. Policy Research, Bureau of Intl. Hlth. Cooperation, Natl. Ctr. for Global Hlth. and Med., Tokyo, Japan

Abstract: Background: Postpartum depression has a significant impact on maternal health and child rearing, but the heterogeneity of symptoms and their association with personal characteristics and COVID-19 relevant factors remain poorly understood. This study aimed to investigate the symptom patterns of depression in postpartum Japanese mothers and identify factors that are common and unique to each symptom pattern.
Methods: We conducted a cross-sectional survey of postpartum women in October 2020 in Japan (n = 558). The Edinburgh Postpartum Depression Scale (EPDS) was used to measure postpartum depressive symptoms. We applied latent profile analysis to identify distinct symptom patterns of EPDS. To validate the derived patterns (or classes), we investigated the association between the derived patterns and personal characteristics including demographic information, personality traits, and childbirth and COVID-19 relevant factors.
Results: The best-fitting solution had three different symptom patterns, corresponding to different severities of depression. Pattern 1 had little depression (66.1% subjects, EPDS= 3.53±2.31), while Patterns 2 (26.7% subjects, EPDS=10.34±2.31) and 3 (7.2% subjects, EPDS=19.38±2.61) had moderate and high levels of depression. Compared to Pattern 1, subjects in Patterns 2 and 3 had a higher rate of pregnancy complications (e.g., gestational hypertension), lower family and partner support, higher feelings of loneliness, were more likely to have a psychiatric history and use hypnotics and anxiolytics, reported worse self-rated health and more COVID-19 infections in themselves or their family or colleagues, and had stronger fear towards COVID-19. Compared to Pattern 1, subjects in Pattern 2 had a higher rate of emergency C-sections, giving up hometown delivery, and higher neuroticism, while those in Patterns 3 had a higher rate of vaginal delivery, lower extraversion, a higher rate of smoking, and experienced

more severe economic hardship in the past six months.
Conclusions: To our knowledge, this is the first latent profile analysis that examined postpartum depression in Japanese subjects during the COVID-19 pandemic. We identified three different symptom patterns with each having their unique characteristics in terms of delivery mode, economic hardship, personality traits, psychiatric comorbidity, and COVID-19 relevant factors. The results may enhance our understanding of the etiology, prevention, and treatment of postpartum depression.

Disclosures: **K. Hagiwara:** None. **H. Lei:** None. **C. Chen:** None. **R. Okubo:** None. **S. Okawa:** None. **N. Higuchi:** None. **S. Nakagawa:** None. **T. Tabuchi:** None.

Poster

148. Stress, Depression, and Other Psychiatric Disorders

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 148.15

Topic: G.08. Other Psychiatric Disorders

Title: MDMA & OCD: a systematic review of the potential effects of 3,4-methylenedioxymethamphetamine-assisted therapy for PTSD on comorbid OCD

Authors: *U. R. CHATTERJEE;
Dept. of Neurosci., Univ. of Texas at Dallas, Richardson, TX

Abstract: Post-traumatic stress disorder (PTSD) and obsessive-compulsive disorder (OCD) are often comorbid psychiatric disorders within patients. Approximately 30% of patients diagnosed with PTSD are also diagnosed with OCD, which far supersedes the estimated 1% rate of OCD prevalence in the general population. First-line psychotherapies differ for both conditions, where PTSD is generally treated with cognitive-behavioral therapy (CBT) and OCD is treated with exposure & response prevention therapy (ERP). These psychotherapies fundamentally differ in their execution, with traditional CBT being contraindicated for OCD treatment. Especially in cases where patients' PTSD & OCD diagnoses present a dynamic functional relationship, the treatments for both conditions often result in both parallel and inverse results, such that PTSD treatment can often worsen OCD symptoms, and OCD treatment can also often worsen PTSD symptoms. Furthermore, patients with comorbid PTSD and OCD are shown to experience more severe symptomology of both illnesses than patients with either just PTSD or OCD. The contraindication of PTSD treatment on OCD symptomatology and overlapping symptom phenotypes suggest a possible overlap of neurobiological mechanisms between both diseases, where the mechanisms may have inverse or causal relationships.Thus, when studying the potential of 3,4-Methylenedioxymethamphetamine Assisted Therapy (MDMA-AT) for PTSD, a notable point of consideration is the potential challenge of comorbid OCD in PTSD patient populations. This meta-analysis poster reviews the current literature on the comorbid nature of dynamically-related PTSD & OCD diagnoses, potential theoretical and biological frameworks to describe the neurobiological overlap of these conditions, current challenges in the psychological

and pharmacological treatments of comorbid PTSD & OCD, and the potential pharmacological mechanisms of 3,4-Methylenedioxymethamphetamine that impact PTSD & OCD as individual and comorbid conditions. This poster also evaluates the current paradigm of MDMA-AT for PTSD as it relates to comorbid OCD and assesses its potentially contraindicative effects. Additionally, this poster provides several directions for further investigations into this topic across a wide range of relevant disciplines.

Disclosures: U.R. Chatterjee: None.

Poster

148. Stress, Depression, and Other Psychiatric Disorders

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 148.16

Topic: G.08. Other Psychiatric Disorders

Support: MOST Grant 109-2314-B-400-034-MY3
MOST Grant 110-2314-B-400 -027 -MY3

Title: L-4-fluorophenylglycine rescues behavioral and synaptic deficits induced by repeated ketamine exposure in mice

Authors: *H.-H. CHEN, C.-W. SUNG, G.-L. LU;
Ctr. for Neuropsychiatric Res., Natl. Hlth. Res. Inst., Zhunan, Taiwan

Abstract: Ketamine abuse is becoming a public health issue in many countries. Cognitive impairments and psychiatric symptoms are commonly observed in frequent ketamine users. L-4-fluorophenylglycine (L-4FPG), an inhibitor of neutral amino acid transporter ASCT1 and ASCT2, can increase extracellular levels of D-serine to regulate N-methyl-D-aspartate (NMDA) receptors. The present study assessed whether L-4FPG could rescue the behavioral deficits and synaptic dysfunction after repeated ketamine exposure. Male ICR mice received ketamine exposure (20 mg/kg, i.p., twice daily for 14 days) followed by L-4FPG (0.3 and 3 mg/kg, i.p.) treatment for 14 days. L-4FPG at the doses of 0.3 and 3 mg/kg could restore cognitive impairments in novel location/object recognition test, the deficits in sociability and social novelty in the three chamber test, PPI deficits in acoustic startle response, and the impaired hippocampal long-term potentiation (LTP) of field excitatory post-synaptic potentials (fEPSPs). However, only the higher dose of L-4FPG (3 mg/kg) could suppress the increased immobility time in forced swimming test and the enhancement of DOI-induced 5-HT_{2A} receptor mediated head-twitch response after repeated ketamine treatment. These findings suggest that modulation of ASCT might be a potential strategy to provide benefits for psychiatric and cognitive disorders after long-term heavy ketamine use.

Disclosures: H. Chen: None. **C. Sung:** None. **G. Lu:** None.

Poster

148. Stress, Depression, and Other Psychiatric Disorders

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 148.17

Topic: G.08. Other Psychiatric Disorders

Support: 5T15LM007093-30
5I01CX001937-02
1I01CX001937-01A2

Title: Using miR-124-3p Target Genes to Determine Brain Regions Affected in Borderline Personality Disorder Identify the Globus Pallidus and Reveal a Role in Suicidal Ideation Recovery

Authors: *M. S. ALOI[1], G. F. POBLETE[2], J. M. OLDHAM[2], M. A. PATRIQUIN[2], D. A. NIELSEN[3], T. KOSTEN[5], R. SALAS[4];
[1]Dept. of Psychiatry, [2]The Menninger Clin., Baylor Col. of Med., Houston, TX; [3]Psychiatry and Behavioral Sci., Baylor Col. of Med., Montgomery, TX; [4]Baylor Col. of Med., Houston, TX; [5]Michael E DeBakey VA Med. Ctr., Houston, TX

Abstract: Borderline personality disorder (BPD) is characterized by patterns of unstable affect, unstable interpersonal relationships, and chronic suicidal tendencies. Research on the genetics, epigenetics, and brain function of BPD is lacking. MicroRNA-124-3p (miR-124-3p) was recently identified in a Genome Wide Association Study as likely associated with BPD. Here, we identified the anatomical brain expression of genes likely modulated by miR-124-3p and compared morphometry in brain regions that co-express those genes the most in BPD inpatients vs. psychiatric controls matched for sex, age, and all possible psychiatric comorbidities. We isolated target genes likely modulated by miR-124-3p from TargetScan (v 8.0) by their preferentially conserved targeting (Aggregate P_{CT}). We applied Process-Genes-List (PGL) to identify regions of interest associated with co-expression of miR-124-3p target genes. We compared the volume of the top region of interest co-expressing those genes between BPD inpatients (n=111, 46% female) and psychiatric controls (n=111, 54% female) at The Menninger Clinic in Houston, Texas. We then correlated personality measures, suicidal ideation intensity, and recovery from suicidal ideation with volumetrics. Gene targets of miR-124-3p were significantly co-expressed in the left Globus Pallidus (GP), which was significantly smaller in BPD than in psychiatric controls (Wilcoxon rank-sum test $p < 0.0001$). Smaller GP volume was negatively correlated with agreeableness and with recovery from suicidal ideation post-treatment. In addition, GP volume decreased with age in BPD but not in psychiatric controls In BPD, GP volume may be reduced through miR-124-3p regulation and suppression of its target genes. In conclusion, we believe miR-124-3p epigenetic modulation in BPD may be a compensatory mechanism allowing BPD patients to have better treatment outcomes, especially during aging, explaining the fact that BPD patients tend to improve with age.

Disclosures: M.S. Aloi: None. **G.F. Poblete:** None. **J.M. Oldham:** None. **M.A. Patriquin:** None. **D.A. Nielsen:** None. **T. Kosten:** None. **R. Salas:** None.

Poster

148. Stress, Depression, and Other Psychiatric Disorders

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 148.18

Topic: G.08. Other Psychiatric Disorders

Support: NRF-2012R1A3A1050385
JSPS KAKENHI 16K15565 JP16H06276 [AdAMS],
JSPS KAKENHI 17K08612
Suzuken Memorial Foundation

Title: Differential effects of sub-anesthetic dose of ketamine on spontaneous excitatory postsynaptic currents in GluN2D knock-out mice

Authors: *D. HAN[1], I. HONG[1], J. CHOI[1], P. PARK[1], J.-Y. BAEK[1], H. PARK[1,2], S. IDE[2], K. IKEDA[2,3], M. MISHINA[3], B.-K. KAANG[1];
[1]Seoul Natl. Univ., Seoul Natl. Univ., Seoul, Korea, Republic of; [2]Tokyo Metropolitan Inst. of Med. Sci., Tokyo, Japan; [3]Ritsumeikan Univ., Shiga, Japan

Abstract: There has been growing interest in the long-lasting antidepressant effects of ketamine which is well known as an antagonist of the N-methyl-D-aspartate receptor (NMDAR). However, sub-anesthetic dose of ketamine exerts side effects including hyperlocomotion, necessitating a further understanding of its working mechanism. Previous research pointed out GluN2D-containing NMDARs as the molecular mediator of ketamine-induced hyperlocomotion in rodents. Another line of research suggested that an increased synaptic transmission in the medial prefrontal cortex (mPFC) is a potential physiological mechanism through which ketamine triggers hyperlocomotion. Therefore, we examined the potential role of GluN2D-containing NMDARs in the ketamine-induced increase in the synaptic transmission in mPFC. Ketamine (25 mg/kg) administration increased the frequency of spontaneous excitatory postsynaptic currents (sEPSC) in wildtype mice, which effect was absent in GluN2D knock-out mice. Injection of the same dose of ketamine did not change the paired-pulse ratio and the amplitude of sEPSC in both of the genotypes. This study adds evidence to the perspective that GluN2D-containing NMDARs are involved in the ketamine-induced increase in the number of excitatory synapses and hyperlocomotion.

Disclosures: D. Han: None. **I. Hong:** None. **J. Choi:** None. **P. Park:** None. **J. Baek:** None. **H. Park:** None. **S. Ide:** None. **K. Ikeda:** None. **M. Mishina:** None. **B. Kaang:** None.

Poster

148. Stress, Depression, and Other Psychiatric Disorders

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 148.19

Topic: G.08. Other Psychiatric Disorders

Support: NRF-2021R1C1C2011217

Title: Chlorpromazine Causes Xerostomia Through Inhibition of Intracellular Calcium Signaling.

Authors: *Y.-J. KIM[1], S. KIM[1], H.-K. PARK[2], S.-Y. CHOI[1];
[1]Physiol. And Neurosci., [2]Oral Med. And Oral Diagnosis, Seoul Natl. Univ. Sch. of Dent., Seoul, Korea, Republic of

Abstract: Saliva plays various roles in maintaining a healthy oral environment. Chlorpromazine, a xerostomia-inducing drug, is an antipsychotic drug widely used to treat schizophrenia. It mainly acts as a dopamine D2 receptor inhibitor in the brain. However, the exact molecular mechanism of chlorpromazine inhibiting secretory function in the salivary glands is still unknown. We determined whether chlorpromazine affects predominantly G-protein-coupled receptor (GPCR)-mediated Ca^{2+} signaling in the salivary glands. It was confirmed that chlorpromazine decreased salivation by muscarinic signaling in a concentration-dependent manner in a mouse model. In addition, in human salivary gland cells, this drug inhibited the increase of intracellular calcium by muscarinic and histamine signaling. Ca^{2+} release from the endoplasmic reticulum (ER) and the influx of extracellular Ca^{2+} through store-operated Ca^{2+} entry (SOCE) were involved in these inhibitory effects. These findings indicate that in the salivary glands, chlorpromazine induces xerostomia inhibiting intracellular calcium signaling through various sites of action, including ER and SOCE.

Disclosures: Y. Kim: None. **S. Kim:** None. **H. Park:** None. **S. Choi:** None.

Poster

148. Stress, Depression, and Other Psychiatric Disorders

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 148.20

Topic: G.08. Other Psychiatric Disorders

Support: CIHR FDN148374

Title: Alterations in cell-type specific chromatin accessibility in individuals with major depressive disorder: delving into gene-regulatory mechanisms.

Authors: *A. CHAWLA[1], M. SUDERMAN[3], M. MAITRA[1], W. ZHANG[1], D. CAKMAKCI[2], M. DAVOLI[4], J. YANG[4], Y. LI[1], C. NAGY[1], G. TURECKI[1];
[1]McGill Univ. Integrated Program in Neurosci., [2]Computer Sci., McGill Univ., Verdun, QC,

Canada; [3]MRC Integrative Epidemiology Unit, Univ. of Bristol, Bristol, United Kingdom; [4]Neurosci., Douglas Mental Hlth. Inst., Verdun, QC, Canada

Abstract: For psychiatric disorders, including major depressive disorder (MDD), the genetic risk variants identified by Genome-Wide Association Studies (GWAS) tend to be enriched in the non-coding regions of the genome [1]. The manner in which these risk variants associate with the non-coding regions, such as enhancers, to regulate gene expression changes remains unclear. The active regulatory regions are in an accessible chromatin conformation which allows transcription factor binding and long-distance interactions for precise gene regulation in a cell-type-specific manner. Therefore, examining these changes with cell-type specificity can pinpoint potential molecular mechanisms underlying MDD. We used single-nucleus Assay for Transposase-Accessible Chromatin sequencing (snATAC-seq) [2] to profile chromatin accessibility in the dorsolateral prefrontal cortex of 44 individuals who had a history of major depression and died by suicide, and 40 sex- and age-matched healthy controls. We multiplexed male and female nuclei and used a novel approach for the in-silico splitting of these combined libraries at single-cell resolution. We used ArchR [3] to divide the genome into 500bp bins followed by dimensionality reduction and graph-based unsupervised clustering. Clusters were annotated to brain cell types by their promoter accessibility at cell-type-specific marker genes. Further, snRNA-seq from the same subjects [4] was integrated with snATAC-seq to impute gene-expression and identify potential regulatory markers of the coding genes. We captured more than 200 thousand nuclei and classified them into neuronal and glial subtypes having highly specific cis- and trans-regulatory profiles. Differential open chromatin regions between MDD and controls were majorly found in the deep-layer excitatory neurons and microglia. Moreover, chromatin accessibility changes with sex differences were mainly concentrated in the cell types of oligodendrocytic lineage. Further, we identified key transcription factors and biological pathways associated with MDD. Using linkage-disequilibrium score regression (LDSC), we found an enrichment of GWAS-associated MDD SNPs in specific cell types and dysregulated regions. Finally, overlapping prioritized risk variants with differentially accessible regions linked variants to potential risk genes. Thus, our study integrated multi-omics features to elucidate biological changes associated with MDD in a sex-specific manner with cell-type specificity.
[1.]Ormel J. Trans Psych. 9, 114 (2019) [2.]Buenrostro, J. Nat Met. 10, 1213-1218 (2013) [3.] Granja MJ, Nat Gen. 53, 403-411 (2021)[.] [4.]Nagy, C. Nat Neuro. 23(6):771-781 (2020)

Disclosures: **A. Chawla:** None. **M. Suderman:** None. **M. Maitra:** None. **W. Zhang:** None. **D. Cakmakci:** None. **M. Davoli:** None. **J. Yang:** None. **Y. Li:** None. **C. Nagy:** None. **G. Turecki:** None.

Poster

148. Stress, Depression, and Other Psychiatric Disorders

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 148.21

Topic: G.08. Other Psychiatric Disorders

Support: 19K17088
22K15786

Title: Decreased idea fluency in patients with anorexia nervosa

Authors: *M. SUNADA[1], Y. SETA[1], T. NODA[1], M. KAWABATA[1], K. MORIMOTO[1], K. TOSE[1], R. MISHIMA[2], H. KOZUKI[1], T. UWATOKO[1], T. MURAI[1], M. ISOBE[1];
[1]Kyoto Univ., Kyoto-city, Japan; [2]Kyoto Katsura Hosp., Kyoto-city, Japan

Abstract: Anorexia nervosa are characterized by cognitive deficits represented by body image distortions and eating behavioral abnormalities. It has been pointed out that it is difficult to change behavior and patients repeat the same behavior when abnormal eating behavior becomes a habit. We hypothesized that one of the reasons for this is that patients with anorexia nervosa may not be able to come up with new behavioral options due to reduced the idea fluency. The purpose of this study is to compare the idea fluency of normal subjects and anorexia nervosa patients using the TCT creativity test. Anorexia nervosa patients attending the Department of Psychiatry, Kyoto University Hospital, and age and gender matched healthy subjects participated in the study. The subjects were asked to think of uses for empty cans and saran wrap cores, and were scored on how fluently they could think of various uses. In accordance with previous reports, each answer was classified into four genres based on the characteristics of the use: “Task-dependence", which is for responses that are entirely influenced by the task-setting. In other words, this is the simplest way to think. “Task-modification", which is for responses that are produced more flexibility than “Task-dependence", but still influenced by the task-setting. "Homomorphosis", which is for responses that are made by attending to only a part of the task-setting and neglecting the rest. "Heteromorphosis”, which is for responses that are quite free from the task-setting. In addition to the number of responses for each genre, we examined the total number of uses that came to mind and the number of times the genre was switched as items that reflect fluency. The number of answers categorized into “Task-dependence", the total number of uses that came to mind, and the number of times the genre was switched were significantly lower in patients with anorexia nervosa. In addition, we investigated correlations between idea fluency and psychological measures that might be related to it. We found a correlation between the IRI and "Task-dependence”. The results so far suggest that anorexia nervosa patients may have less idea fluency in their thinking, that may cause continuation of their abnormal eating behaviors.

Disclosures: M. Sunada: None. **Y. Seta:** None. **T. Noda:** None. **M. Kawabata:** None. **K. Morimoto:** None. **K. Tose:** None. **R. Mishima:** None. **H. Kozuki:** None. **T. Uwatoko:** None. **T. Murai:** None. **M. Isobe:** None.

Poster

148. Stress, Depression, and Other Psychiatric Disorders

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 148.22

Topic: G.08. Other Psychiatric Disorders

Support: Klarman Family Foundation Eating Disorders Research Grants Program (Grant ID 4770)

Title: A subpopulation of central extended amygdala neurons regulates the development of activity-based anorexia (ABA)

Authors: *W. I. SCHNAPP, J. KIM, S. TIMILSENA, A. NIGAM, H. CAI;
Neurosci., Univ. of Arizona, Tucson, AZ

Abstract: Anorexia Nervosa (AN) is a prevalent eating disorder seen primarily in females that significantly disrupts life and health, to the point of reaching fatality in extreme cases. AN is characterized by self-starvation, fear of gaining weight, and excessive exercise, but also is often co-diagnosed with psychiatric and emotional disorders, such as depression, anxiety and obsessive compulsive disorder. The mechanisms underlying the development of AN and associated emotional conditions remain ambiguous. We aim to identify the neural circuits that regulate hyperactivity and disrupted eating behavior similar to what is seen in AN while focusing on the amygdala, a part of the brain with established roles in regulating emotional behaviors, including fear and anxiety. Recent studies demonstrate that various subpopulations of neurons in the amygdala regulate eating behavior as well. In this study, we assessed the involvement of neurons expressing protein kinase C-δ^+ (PKC-δ^+) in two regions of the central extended amygdala (CEA)—the central amygdaloid nucleus (CeA) and the oval region of the bed nucleus of the stria terminalis (ovBNST)—in the development of activity-based anorexia (ABA). ABA is a common animal model that characterizes the excessive exercise and self-starvation aspects of AN within stressful conditions, and leads to disordered homeostatic mechanisms needed for survival. Our results demonstrate that mice do not develop ABA when PKC-δ^+ neurons are exclusively eliminated in *both* of these regions of the CEA. Analysis of the mouse behavior indicates that there was a significant change in energy intake and output in mice with $CeA^{PKC\text{-}\delta}$ and $ovBNST^{PKC\text{-}\delta}$ neuron ablation compared to WT mice, suggesting these neurons function together to regulate energy balance in the context of ABA. Additionally, we identified that dual ablation of these neurons abolishes sexual divergence typically seen in WT mice undergoing ABA. These results provide insight into neural circuits that coexist to modulate stress-induced alterations in energy intake (eating behavior) and output (running wheel activity), consequential energy imbalances, and even sexual dimorphisms. Overall, this work contributes to better understanding relevant factors in the neurobiological and physiological basis of AN.

Disclosures: W.I. Schnapp: None. **J. Kim:** None. **S. Timilsena:** None. **A. Nigam:** None. **H. Cai:** None.

Poster

148. Stress, Depression, and Other Psychiatric Disorders

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 148.23

Topic: G.08. Other Psychiatric Disorders

Support: NIH Grant P50DA037844

Title: Sex differences in delay discounting measured with a sequential patch depletion procedure in a large cohort of heterogeneous stock rats

Authors: *K. ISHIWARI[1], F. AKTAR[1], H. M. BOOL[1], C. R. BRUNO[1], A. M. GEORGE[2], A. KHALIL[2], F. KWARTENG[1], C. D. MARTIN[1], D. RAMSOOMAIR[1], L. J. SHERWOOD[2], W. SMITH-PETERS[1], M. C. TURK[1], L. C. SOLBERG WOODS[3], O. POLESSKAYA[4], A. A. PALMER[4], J. B. RICHARDS[1], D. M. DIETZ[1];
[1]Pharmacol. and Toxicology, [2]Clin. and Res. Inst. on Addictions, Univ. at Buffalo, Buffalo, NY; [3]Mol. Med., Wake Forest Univ., Winston-Salem, NC; [4]Psychiatry, Univ. of California San Diego, San Diego, CA

Abstract: Delay discounting is linked to multiple psychiatric disorders including drug abuse, but past studies examining sex differences in delay discounting have yielded mixed results in both rodents and humans. In typical delay discounting studies in rats, a simultaneous choice is given between a small, immediate reward and a large, delayed reward. However, such simultaneous choices may not occur often in nature, where animals more frequently encounter sequential choice problems. For example, in patch foraging, an animal consumes resources in a patch, and as the patch gets depleted the animal chooses between staying in the depleting patch and traveling to a new patch, which imposes a delay. Here, we examined sex differences in delay discounting measured with a sequential choice procedure simulating patch foraging in a large cohort of genetically diverse heterogeneous stock (HS) rats. Water-restricted 947 male and 948 female HS rats alternated drinking water at two feeders (patches) in an operant chamber. When remaining at the same feeder, rats received successively smaller amounts of water (reduced by 20 %) every 4 s with the initial amount of 150 µl. Switching to the other feeder would reset the amount to 150 µl but result in a delay (0, 6, 12, 18, or 24 s) to the activation of the new feeder. The indifference point was defined as the amount of water available in the depleting patch right before the rat switched patches, and the discount curve was obtained by plotting the indifference point as a function of delay. We found that female HS rats discounted delayed rewards more steeply than males, while males earned more water per unit time than females. In addition to delay discounting, we observed another distinct phenotype, a propensity to switch feeders with the 0-s delay, which was not correlated with discounting in either sex. When the rats were divided into 4 groups based on median splits on these two phenotypes, and water consumption rates of the 4 groups were compared to see which group performed most optimally, males and females displayed different patterns of results. In males, rats that were high in both discounting and switching earned more water per unit time than any of the other three groups. In contrast, in females, there was no difference in water consumption rate between high and low discounters in either high switchers or low switchers, and high switchers earned more water than low switchers, regardless of whether they were high or low discounters. Our results are consistent with some past studies in rodents that showed greater delay discounting in females. They also suggest that the best strategies for optimizing resource intake in the foraging context might differ between the sexes.

Disclosures: K. Ishiwari: None. **F. Aktar:** None. **H.M. Bool:** None. **C.R. Bruno:** None. **A.M. George:** None. **A. Khalil:** None. **F. Kwarteng:** None. **C.D. Martin:** None. **D. Ramsoomair:**

None. **L.J. Sherwood:** None. **W. Smith-Peters:** None. **M.C. Turk:** None. **L.C. Solberg Woods:** None. **O. Polesskaya:** None. **A.A. Palmer:** None. **J.B. Richards:** None. **D.M. Dietz:** None.

Poster

148. Stress, Depression, and Other Psychiatric Disorders

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 148.24

Topic: G.08. Other Psychiatric Disorders

Title: The role of m6A RNA methylation in sex-influenced molecular changes in depression

Authors: *H. MITSUHASHI[1], Z. AOUABHED[2], C. NAGY[1,2], G. TURECKI[1,2];
[1]McGill Univ., Montreal, QC, Canada; [2]Douglas Mental Hlth. Univ. Inst., Montreal, QC, Canada

Abstract: Introduction: Females are twice as likely to be diagnosed with Major Depressive Disorder (MDD) compared to males. This is a striking example of sex differences in MDD, and mounting evidence suggests that it may be driven by sex-specific molecular mechanisms. Epigenetic mechanisms, which are altered in response to environmental factors, are known to be involved in the pathophysiology of MDD; however, little is known about the impact of the epitranscriptome. In recent years, RNA modifications have emerged as a dynamic and crucial mechanism in the post-transcriptional regulation of gene expression. Emerging evidence suggests that N6-methyladenosine (m6A) plays an important role in the brain, including neurodifferentiation, neurogenesis, and memory and learning. Moreover, recent studies have linked m6A to molecular and behavioral responses to stress, making it an important candidate regulator of stress-related psychiatric disorders, including MDD. This study aims to describe the landscape of m6A in the human brain and to identify changes that may occur in the context of MDD.**Methods:** The ventromedial prefrontal cortex was obtained from male and female MDD and healthy control subjects. m6A-seq were performed to investigate m6A at transcripts levels and the impact of m6A on gene expression.**Results:** Using our optimized protocol, we identified ~20,000 m6A peaks in the human brain, and these peaks were enriched in the known m6A consensus motif "GGAC" and 3'UTR and coding region as suggested by previous studies. Gene ontology of m6A tagged genes revealed that these genes are related to neuronal and synaptic regulation confirming that m6A plays a vital role in general brain function. Our differential methylation analysis shows a distinct m6A profile in MDD and control, with a little overlap between males and females. These differentially methylated genes were enriched for synaptic function in both males and females with MDD. However, only a few differentially regulated genes and methylated genes overlapped, suggesting that m6A may not have a significant impact on gene expression or stability of the target transcript. **Conclusion:** Our results highlight a significant role of m6A in MDD, possibly by adjusting the function of synaptic-related gens. Further analysis will help us understand the role of m6A in stress-related psychiatric disorders and will serve as an example of sex-specific analysis in MDD.

Disclosures: **H. Mitsuhashi:** None. **Z. Aouabhed:** None. **C. Nagy:** None. **G. Turecki:** None.

Poster

148. Stress, Depression, and Other Psychiatric Disorders

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 148.25

Topic: G.08. Other Psychiatric Disorders

Support: CIHR Fellowship
SickKids Restracomp Fellowship

Title: Habenula Deep Brain Stimulation for reducing symptoms of autism in the Fmr1-KO transgenic model of Fragile X Syndrome and Autism Spectrum Disorder

Authors: *F. VENETUCCI GOUVEIA[1], K. ZHANG[2], G. M. IBRAHIM[3];
[1]Neurosciences and Mental Hlth., [2]Neurosci. and Mental Hlth., The Hosp. For Sick Children, Toronto, ON, Canada; [3]The Hosp. for Sick Children, Toronto, ON, Canada

Abstract: Introduction: Fragile X syndrome (FXS) is the most frequent cause of inherited autism spectrum disorder,and is caused by mutations on the Fmr1 gene, resulting alterations in the neurocircuitry involved in the control of emotions, cognition, and neurotransmitter release. The habenula (Hb) is of particular interest as it is responsiblefor modulating the reward value of social interactions, and for the sensory integration necessary for flexible behavioural adjustments. The Hb is a relatively new target for deep brain stimulation (DBS), a therapy that can modulate dysfunctional neural circuitry through the delivery of intracranial electrical stimulation. In order to facilitate the development of novel neuromodulation therapies, translational studies are necessary for studying effects and mechanisms of action. The Fmr1 knockout (Fmr1-KO) mice are a well established mouse model of FXS showing comparable behavioural deficits and brain structural and functional differences, as seen in patients with this syndrome. **Objective:** This study aimed to investigate Hb-DBS as a potential therapy for reducing behavioural deficitsin the Fmr1-KO model. **Methods:** 9 weeks-old male Fmr1-KO mice were randomly assigned to receive active, sham or control Hb-DBS. All procedures were performed after approval from the Animal Care Committee. Stimulation sessions were held for 3 hours/day for 6 days. Stimulation parameters were individually titrated, as performed in the clinic. The Active-Hb-DBS group was connected to the stimulator and received active stimulation, the Sham-Hb-DBS group was connected to the stimulator but receive no stimulation, and the Control-Hb-DBS group were not connected to the pulse generator but kept under the same conditions as the other groups. Following treatment animals were tested for: I) sociability (i.e 3 chambered social test), II) repetitive behaviour (i.e marble burying test), III) anxiety-like behaviour (i.e open field test), IV) sensory deficits (i.e. tactile discrimination and hot plate tests). Linear models were used for statistical analysis (R studio) and the significance level was set as $p<0.05$. **Results:** In comparison with control groups, Active-Hb-DBS resulted in: i) Increased time spent in the social chamber, II) Reduced number of buried marbles, III) Increased entries in

the centre of the open field; IV) increased time spent on the smooth area, and reduced latency to reaction in the hot plate test. **Conclusion:** Active-Hb-DBS resulted in behavioural improvements in all aspects investigated, with treated animals showing reduced anxiety-like and repetitive behaviours, increased sociability and improved sensory perception.

Disclosures: F. Venetucci Gouveia: None. **K. Zhang:** None. **G.M. Ibrahim:** None.

Poster

148. Stress, Depression, and Other Psychiatric Disorders

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 148.26

Topic: G.08. Other Psychiatric Disorders

Support: H2020-EU Grant 847826, Brain Involvement iN Dystrophinopathies (BIND) project
Ministère de l'Enseignement Supérieur et de la Recherche (France)
Association Monégasque contre les Myopathies (AMM, Monaco)
Centre National de la Recherche Scientifique (CNRS, France)
Université Paris-Saclay (France)

Title: Emotional and cognitive profiling of mdx52 and mdx^{5cv} mouse models of Duchenne muscular dystrophy

Authors: *M. D. MITSOGIANNIS[1], A. SAOUDI[2,3], F. ZARROUKI[2], C. FERGUS[4], E. STOJEK[1], S. TALAVERA[1], V. KELLY[4], A. GOYENVALLE[3], F. MONTANARO[5], F. MUNTONI[5], E. SOKOLOWSKA[6], C. VAILLEND[2];
[1]Transpharmation Ireland Ltd., Dublin, Ireland; [2]Univ. Paris-Saclay, CNRS, Inst. des Neurosciences Paris Saclay, Gif-sur-Yvette, France; [3]Univ. Paris-Saclay, UVSQ, Inserm, END-ICAP, Versailles, France; [4]Sch. of Biochem. & Immunol., Trinity Col., Dublin, Ireland; [5]Great Ormond Street Inst. of Child Health, Dubowitz Neuromuscular Ctr., Univ. Col. London, London, United Kingdom; [6]Transpharmation Poland Sp. z o.o., Olsztyn, Poland

Abstract: In Duchenne muscular dystrophy (DMD) dystrophin loss disrupts both muscle and cognitive-affective functions. To investigate how specific *DMD* mutations, impacting different dystrophin isoforms, contribute to neurobehavioural comorbidities in DMD, we examined emotional responses and cognitive performance in *mdx52* mice, lacking Dp427 & Dp140 brain dystrophins due to a distal exon 52 deletion, and *mdx^{5cv}* mice, in which a proximal exon 10 mutation impairs Dp427 expression only.
A first group of hemizygous *mdx52* or *mdx^{5cv}* male mice and wild-type littermates (WT) underwent the elevated zero maze (EZM), unconditioned fear response (UFR), and inverted screen grip tests at adolescent and adult stages. In the EZM, *mdx52* and *mdx^{5cv}* mice displayed higher anxiety levels than WT at all ages; moreover, young *mdx52* mice showed hyperanxious responses compared to *mdx^{5cv}* mutants. In the UFR assay, young and adult *mdx52* and *mdx^{5cv}*

mice presented significantly higher restraint-induced freezing compared to WT (>75% versus <20% of test time), but combined Dp427-Dp140 loss did not worsen fear responses compared to Dp427 loss alone.
To investigate cognitive functions, separate cohorts of *mdx52*, *mdx*^{5cv} and WT mice were subjected to either a fear conditioning (FC), a novel object recognition (NOR), or a T-maze delayed alternation (TDA) task. FC acquisition and retention were significantly impaired in *mdx52* and *mdx*^{5cv} mice compared to WT, whereas no significant differences across genotypes were observed in non-spatial (NOR) or spatial (TDA) recognition assays. Overall, both mutant and WT mice robustly retained acquired memories at short delays (NOR: 10-30 min, TDA: 1-6 h), while *mdx*^{5cv} mice showed a marginal recognition memory deficit at 24 h delay.
Findings of marked fear/anxiety behaviours in *mdx52* and *mdx*^{5cv} mice resemble those similarly obtained in another well-characterised *mdx* mutant mouse lacking Dp427 (*mdx23*). This indicates that loss of brain dystrophins is linked to enhanced emotional reactivity and impaired amygdala-dependent associative learning for both proximal and distal *Dmd* mutations. The higher anxiety observed in young *mdx52* mice versus *mdx*^{5cv} mice suggests that Dp140 loss aggravates emotional disturbances. Phenotypic commonalities observed across DMD mouse models point to emotional responses and fear learning as ideal readouts in assessing CNS-targeted therapies for DMD.

Disclosures: **M.D. Mitsogiannis:** A. Employment/Salary (full or part-time):; Transpharmation Ireland Ltd... **A. Saoudi:** None. **F. Zarrouki:** None. **C. Fergus:** None. **E. Stojek:** A. Employment/Salary (full or part-time):; Transpharmation Ireland Ltd. **S. Talavera:** A. Employment/Salary (full or part-time):; Transpharmation Ireland Ltd.. **V. Kelly:** None. **A. Goyenvalle:** None. **F. Montanaro:** None. **F. Muntoni:** None. **E. Sokolowska:** A. Employment/Salary (full or part-time):; Transpharmation Poland Sp. z o.o.. **C. Vaillend:** None.

Poster

148. Stress, Depression, and Other Psychiatric Disorders

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 148.27

Topic: G.08. Other Psychiatric Disorders

Support: MOST, Taiwan Grant 110-2321-B-A49A-502
MOST, Taiwan Grant 110-2628-B-A49A-509
MOST, Taiwan Grant 110-2634-F-075-001
MOST, Taiwan Grant 110-2634-F-A49-005
Mt. Jade Young Scholarship Award from Ministry of Education, Taiwan
National Yang Ming Chiao Tung University and the Ministry of Education (Aim for the Top University Plan), Taipei, Taiwan

Title: Differentiating primary insomnia from good sleeper based on electroencephalographic spectral biomarkers using machine learning approach

Authors: *W.-Y. HUANG[1], S.-J. TSAI[3], A. YANG[1,2,4];
[1]Inst. of Brain Sci., [2]Digital Med. and Smart Healthcare Res. Ctr., Natl. Yang Ming Chiao Tung Univ., Taipei, Taiwan; [3]Dept. of Psychiatry, [4]Dept. of Med. Res., Taipei Veterans Gen. Hosp., Taipei, Taiwan

Abstract: The diagnosis of primary insomnia (PI) is based on subjective reporting during clinical interviews or on responses to self-report questionnaires. The findings of previous polysomnographic and electroencephalographic (EEG) studies were inconsistent and the detailed spectral features to discriminate PI in different sleep stages and recording electrodes were also unclear. We aimed to construct machine learning models to differentiate PI from good sleepers accurately via power spectral features in individual sleep stage and EEG channel and examine the disease-related impacts on specific frequency. A total of 93 participants were included with 40 patients with PI and 53 good sleepers. For each channel, we extracted EEG epochs from same sleep stage and built up a stage-specific dataset. There were 5 stage-specific datasets (wake, REM, NREM1, NREM2 and NREM3) in each channel (F3, F4, C3, C4, O1 and O2). Normalized power spectra of epochs in same sleep stage with frequencies ranging from 0.03 to 50 Hz were used as features. Each dataset was divided into 80% set for training on online commercial AI platform (AI-PaaS) with hold-out cross-validation. Various machine learning models were used as ensemble learning. The remaining 20% data was used for testing. The results of accuracy showed that the best model developed for classification of PI was in NREM3 at F3 channel (92.8%) by Gradient boosting classifier. Models from NREM3 had higher classifying accuracies at all EEG channels which suggested that insomnia affects NREM3 more than other stages. Furthermore, F3 had the best performance of classifying insomnia in most of sleep stages except that the best performance of EEG channel in REM was F4. Meanwhile, the Xgboost classifiers had better performances compared with other models in our ensemble trials. For the model explainability, EEG frequencies around 30 Hz had the most dominantly discriminative ability, others important frequency features were all in the beta band. Our findings indicate that spectral features of specific sleep stage can be used to accurately categorize PI across all EEG channels and insomnia affects largely on beta oscillation across entire night. These findings have advanced the understanding of insomnia in relation to sleep electrophysiological changes and can be further investigated as biomarkers for objective evaluation of PI.

Disclosures: **W. Huang:** None. **S. Tsai:** None. **A. Yang:** None.

Poster

148. Stress, Depression, and Other Psychiatric Disorders

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 148.28

Topic: F.03. Stress and the Brain

Support: JSPS KAKENHI Grant Number 21H03785
JSPS KAKENHI Grant Number 21K12797

Title: Changes in EEG functional connectivity following an online mindfulness meditation training course

Authors: *N. HASHIMOTO, S. SHIMADA;
Meiji Univ., Kawasaki, Japan

Abstract: Mindfulness is the awareness that comes from deliberately paying attention to one's body and mind without value judgments. As the spread of the novel coronavirus infection restricts the freedom of daily life and demands a better way to deal with stress, the practice of mindfulness meditation can be one of the ways to lead a healthy life. Herein, we developed a four-week online meditation training course for practicing mindfulness meditation. The training consisted of weekly online meetings and daily meditation practice. The meetings consisted of a review of the previous week and a lecture on the next week's content. Participants were able to conduct their daily meditation using the audio instructions of the online application on their smartphones. To test the effectiveness of this training course, 61 participants (aged 19.9 ± 1.66 years, mean ± SD) were divided into two groups: a meditation group (N = 31) and a control group (N = 30). The meditation group participated in the online meditation training course, while the control group participated in an online training course where they listened to classical music instead of meditating. All participants completed mindfulness and psychological scales at baseline and at 1, 2, 3, 4, and 16 weeks. In addition, 36 of the participants completed 10-minute resting-state EEG measurements at baseline and at 4 and 16 weeks. In the questionnaire, one-way repeated measures ANOVA in the meditation group showed significant main effects on the FFMQ (non-reaction, non-judgement), FMI and BDI-II (FFMQ (non-reaction): $F(3.46, 93.52) = 5.012$, $p = .002$; FFMQ (non-judgement): $F(2.97, 80.17) = 8.827$, $p < .001$, FMI: $F(5, 135) = 8.515$, $p < .001$; BDI-II: $F(3.33, 89.88) = 16.55$, $p < .001$). The meditation group showed a significant increase in the score of mindfulness skills (FFMQ, FMI) and a significant decrease in the score of depressive tendency (BDI-II). In the functional connectivity analysis of resting EEG data, one-way repeated measures ANOVA in the meditation group showed significant main effects on the functional connectivity in β1 rhythm (13-18 Hz) between the right medial prefrontal cortex and right superior parietal lobule ($F(1.42, 21.27) = 5.685$, $p = .018$). We found significantly enhanced functional connectivity at 4 weeks compared to that at baseline in the meditation group. The results of the questionnaire and connectivity analysis suggest that the online meditation training course developed in this study is effective in increasing the degree of mindfulness and reducing depressive mood, leading to resting-state functional connectivity changes.

Disclosures: **N. Hashimoto:** None. **S. Shimada:** None.

Poster

149. Addictive Substances and Memory Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 149.01

Topic: G.09. Drugs of Abuse and Addiction

Support: DA042102

Title: Cocaine seeking is mediated by prelimbic neuronal ensembles after behavioral acquisition in male and female rats.

Authors: *B. W. SORTMAN, S. RAKELA, B. CERCI, B. L. WARREN;
Pharmacodynamics, Univ. of Florida, Gainesville, FL

Abstract: Fos-expressing neuronal ensembles are sparsely distributed subsets of neurons that mediate a learned behavioral response. Fos-expressing neuronal ensembles in the infralimbic cortex (IL) are necessary for acquisition and maintenance of operant food- and drug-seeking behaviors. However, the role of prelimbic (PL) neuronal ensembles in the initiation of cocaine-seeking behavior is unknown. Therefore, we sought to elucidate the role of PL neuronal ensembles in initial cocaine seeking. We hypothesize that neuronal ensembles controlling cocaine-seeking form rapidly in the PL during cocaine self-administration. To test this hypothesis, we injected a cocktail of two viruses, a Cre-dependent inhibitory designer receptor exclusively activated by designer drugs (DREADDs), and a Fos-driven CreER^{T2} molecule into the PL. We then trained rats to lever press for intravenous infusions of cocaine (0.75mg/kg) until individual rats met our acquisition criteria of ≥ 30 active lever presses and ≥ 70% of total lever responses on the active lever. We then microinfused 4-OH-tamoxifen in the PL to drive recombination within Fos-expressing neurons, resulting in DREADD expression in Fos-expressing neuronal ensembles associated with initial cocaine-seeking behavior. Two weeks later, we injected rats with either vehicle or compound 21(C21) and measured their lever pressing in a non-reinforced cocaine seeking test. Rats in the C21 group decreased active lever pressing on test day, suggesting that Fos expressing ensembles in the PL rapidly form to mediate cocaine-seeking behavior. This viral approach allows us to perform targeted recombination in Fos-expressing neuronal ensembles in rats, opening the possibility for robust behavioral models not available in mouse models.

Disclosures: B.W. Sortman: None. **S. Rakela:** None. **B. Cerci:** None. **B.L. Warren:** None.

Poster

149. Addictive Substances and Memory Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 149.02

Topic: G.09. Drugs of Abuse and Addiction

Support: National Research Foundation of Korea (2020R1A2C2102134)
National Research Foundation of Korea (2020R1A2C2014830)
National Research Foundation of Korea (2021M3E5D2A01023887)

Title: Stimulation of parabrachial CGRP neurons extinguishes addictive-like behavior

Authors: *G. PYEON, J.-S. CHOI, Y. JO;
Sch. of Psychology, Korea Univ., Seoul, Korea, Republic of

Abstract: To extinguish unwanted, but addictive behavior, various types of punishment such as electric shocks or physical discipline have been used across cultures. Among these methods, electrical shocks produce the strongest effects on behavioral correction, but they could come with a considerable risk of harm. Recently, it has been shown that calcitonin gene-related peptide in the parabrachial nucleus ($CGRP^{PBN}$) provides affective pain signals and generates general alarm signals. Here we investigated whether stimulation of $CGRP^{PBN}$ neurons can mimic electrical shock and able to suppress addictive-like behavior. To address this idea, we first genetically expressed channelrhodopsin-2 (ChR2) in midbrain dopamine neurons and $CGRP^{PBN}$ neurons of DAT-cre::Calca-cre mice. To form addictive-like behavior, the mice were first trained to press a lever to receive a brief optical stimulation of dopamine cells (1s, 20Hz) until they reached the asymptotic level (more than 400 lever presses per hour). Then, they received optical stimulation into the $CGRP^{PBN}$ (3s, 30Hz) instead of the stimulation of dopamine cells when they pressed the lever. Upon activation of $CGRP^{PBN}$ neurons, the mice exhibited brief freezing responses, and their lever-pressing behavior was significantly reduced compared to the control animals without ChR2 expression in $CGRP^{PBN}$ neurons. This also had an impact on long-term memory in which the suppression effect on addictive-like behavior remained even 10 days after the last stimulation of $CGRP^{PBN}$. Moreover, combined stimulation of $CGRP^{PBN}$ neuron terminals with combinations of two among multiple downstream targets (central amygdala, substantia innominata, and ventroposteromedial thalamus) was able to suppress addictive-like behavior compared to the control group. We then investigated whether the inactivation of $CGRP^{PBN}$ can abolish alarm signals in the brain even in the presence of an electrical footshock. $CGRP^{PBN}$ was inactivated by tetanus toxin which blocked the release of neurotransmitters. The mice underwent the same procedure to elicit lever-pressing behavior, and then instead of activating $CGRP^{PBN}$ when they press the lever, a footshock was delivered (1s, 0.3mA). Usually when the animals received a footshock, they learned to avoid and did not press the lever almost immediately. However, the mice with inactivated $CGRP^{PBN}$ pressed the lever more than the control animals. Collectively, these results show that stimulation of $CGRP^{PBN}$ generates alarm signals in the brain and able to extinguish addictive-like behaviors. Moreover, stimulation of $CGRP^{PBN}$ mimics electric shock in behavioral correction but does not elicit physical pain or fear responses.

Disclosures: G. Pyeon: None. **J. Choi:** None. **Y. Jo:** None.

Poster

149. Addictive Substances and Memory Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 149.03

Topic: G.09. Drugs of Abuse and Addiction

Support: National Institute on Drug Abuse grants R01 DA025646
F31 DA045430
State of Washington Initiative Measure No. 173

Title: Optogenetic inhibition of the dorsal hippocampus CA3 region during early-stage cocaine-memory reconsolidation disrupts subsequent context-induced cocaine seeking

Authors: *S. QI[1], S. TAN[1], R. WANG[1], J. A. HIGGINBOTHAM[1], J. L. RITCHIE[1], C. K. IBARRA[1], A. A. ARGUELLO[1], R. J. CHRISTIAN[1], R. A. FUCHS[1,2];
[1]Dept. of Integrative Physiol. and Neurosci., Washington State Univ. Col. of Vet. Med., Pullman, WA; [2]Alcohol and Drug Abuse Res. Program, Washington State Univ., Pullman, WA

Abstract: Interference with memory reconsolidation weakens cocaine-associated memories and reduces cocaine seeking-behaviors in preclinical models of drug relapse. The dorsal hippocampus (DH) is a brain region that plays a critical role in context-cocaine memory reconsolidation. Inhibition of protein synthesis in the DH fails to alter memory reconsolidation, but neural conductance in the DH is necessary for protein synthesis-dependent memory reconsolidation in the basolateral amygdala. Therefore, the functional contribution of the DH is likely limited to the early stages of cocaine-memory reconsolidation. To test this hypothesis, we examined the time-dependent role of the cornu ammonis 3 DH subregion (dCA3) in cocaine-memory reconsolidation by utilizing the temporal and spatial specificity of optogenetics. Rats received bilateral intra-DH infusions of AAV5-hSyn-eNpHR3.0-eYFP-WPRE-PA (or AAV5-hSyn-eYFP), indwelling optic fiber implants aimed at the dCA3 and jugular catheter implants. Rats received cocaine self-administration and extinction training in different contexts. Then the rats were introduced to the cocaine-paired context for memory reactivation. After memory reactivation, rats in each group then received laser-light stimulation (532nM) or no laser light stimulation immediately after or 1-hour after the memory retrieval session or home cage stay. We found that optogenetic dCA3 inhibition during the early-stage, but not late-stage of memory reconsolidation, reduced context-cocaine memory strength ($p = 0.02$). DH engagement was dependent on context-cocaine memory retrieval, and the effects of optogenetic inhibition did not reflect nonspecific effects of virus expression or light exposure on cell health. We also found that reduced cocaine memory strength, which was induced by early-stage optogenetic inhibition, was associated with decreased c-Fos expression in the stratum lucidum (SL) layer. Together, these findings suggest that the critical contribution of the dCA3 is limited to early-stage memory reconsolidation, supporting the idea that the DH may support the maintenance of labile context-cocaine memories prior to their re-stabilization in long-term memory stores, and the dCA3 SL neurons are necessary for facilitating the labile memories processed in the DH.

Disclosures: S. Qi: None. **S. Tan:** None. **R. Wang:** None. **J.A. Higginbotham:** None. **J.L. Ritchie:** None. **C.K. Ibarra:** None. **A.A. Arguello:** None. **R.J. Christian:** None. **R.A. Fuchs:** None.

Poster

149. Addictive Substances and Memory Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 149.04

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH/NIDA R01DA039146 (GTC)
IRPs of NIDA and NIAAA (KCR)

Title: Impact of extended access to stimulant self-administration on recognition memory in rats

Authors: *R. SEAMAN, Jr[1,2], A. SULIMA[3], K. RICE[3], G. COLLINS[1,2];
[1]UT Hlth. Sci. Ctr. at San Antonio, San Antonio, TX; [2]South Texas Veterans Hlth. Care Syst., San Antonio, TX; [3]NIDA/NIAAA Intramural Res. Programs, Bethesda, MD

Abstract: Tens of millions of people suffer from a stimulant use disorder, worldwide. Given the chronicity of this disorder, it is crucial to gain a better understanding of the toxicity associated with prolonged drug use. Regarding stimulants, monoamine releasers (e.g., methamphetamine) rather than monoamine uptake inhibitors (e.g., cocaine) are typically associated with neuroinflammatory and neurodegenerative effects that are thought to underlie cognitive dysfunction. Interestingly, recent data suggest that a synthetic cathinone, MDPV (a monoamine uptake inhibitor), has neurotoxic effects; however, the cognitive and neurochemical consequences of MDPV self-administration remain largely unexplored. Furthermore, despite the prevalence of caffeine in MDPV-containing drug mixtures, little is known regarding the toxic effects produced by of co-use of these two stimulants. The current study aims to investigate the degree to which self-administered MDPV and a mixture of MDPV+caffeine can produce deficits in recognition memory relative to methamphetamine and cocaine. Male Sprague-Dawley rats (n=8/group) were allowed 90-min or 12-h access to grain pellets on one lever and infusions of either MDPV (0.032 mg/kg), MDPV+caffeine (0.032 mg/kg+0.11mg/kg, respectively), methamphetamine (0.1 mg/kg), cocaine (0.32 mg/kg), or saline on the other lever for 5 days per week, for 6 weeks. Novel object recognition was evaluated prior to any drug self-administration history, 3 and 6 weeks after rats had begun self-administering, and once more following a 3-week drug-free period. Rats that had 12-h access to MDPV, MDPV+caffeine, or methamphetamine exhibited time-dependent deficits in the novel object recognition assay relative to rats given access to saline. No deficits were observed in rats that self-administered cocaine in 12-h sessions. Rats provided 90-min access to a mixture of MDPV+caffeine also exhibited deficits in recognition memory, whereas 90-min access to other reinforcers did not result in recognition memory deficits. These data suggest that unlike cocaine, the prototypical monoamine uptake inhibitor, MDPV is capable of producing memory deficits often associated with neuroinflammation and/or neurodegeneration. These data also demonstrate that mixtures of MDPV+caffeine produce deficits in recognition memory following both 90-min and 12-h access, despite lower levels of MDPV intake, suggesting that caffeine might be enhancing toxicity produced by MDPV. Future studies will evaluate markers of neuroinflammation in these rats and explore pharmacological avenues to mitigate stimulant-induced cognitive deficits.

Disclosures: **R. Seaman:** None. **A. Sulima:** None. **K. Rice:** None. **G. Collins:** None.

Poster

149. Addictive Substances and Memory Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 149.05

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH Grant R01DA042499

Title: Differential role of SK2 calcium-gated potassium channels in encoding and retrieval of morphine conditioned place preference memory.

Authors: *K. IBRAHIM, D. BUREK, O. IDOWU, A. ZEC, S. WILLIAMS, N. MASSALY, J. MORON-CONCEPCION;
Washington Univ., St. Louis, MO

Abstract: Drugs of abuse such as opioids target learning and memory circuitry to form a long-lasting association between the drug and the context that they are taken in, which results in cravings and addiction relapse. We have previously shown that context-specific morphine administration is associated with an increased basal synaptic transmission but disrupted long-term potentiation (LTP) in the dorsal hippocampus (dHPC) (Portugal et al., 2014; Xia et al., 2011). An impaired hippocampal LTP may contribute to relapse by making it difficult to unlearn associations that drive cravings. We found that morphine-induced context-dependent sensitization not only had impaired LTP but also an enhanced SK2 channel-mediated negative feedback on NMDA receptors (Fakira et al., 2014). These calcium-gated potassium SK2 channels have been reported to be critically involved in contextual learning by controlling membrane excitability and synaptic plasticity (Hammond et al., 2006). However, the role of SK2 channels in modulating morphine-seeking behavior has not been investigated. To assess this, we use a drug-paired memory-based paradigm, conditioned place preference (CPP), and intracranially infused either SK2 channel blocker (Lei-Dab7) or activator (NS309) into the dHPC of C57/BL6 male mice. Our initial findings showed no change in SK2 gene expression or protein levels in the HPC post-morphine CPP (MorCPP) test with polymerase chain reaction and western blots, respectively. However, blocking the SK2 channel with Lei-Dab7 prior to the post-conditioning test attenuates the retrieval of MorCPP memory in a dose-dependent manner. Interestingly, blocking the SK2 channel before morphine conditioning trials strengthens the preference for the morphine-paired compartment. These findings suggest the potential differential role that SK2 channels play during the encoding and retrieval of MorCPP. Currently, we are assessing the effects of activating the SK2 channel with NS309 on the encoding and retrieval of MorCPP. We will also investigate the effects of morphine on dHPC and how SK2 blocker could alter it using *in-vivo* electrophysiology techniques. Overall, we aim to elucidate the mechanism by which the calcium-gated potassium SK2 channel mediates hippocampal plasticity underlying drug-paired contextual memory formation.

Disclosures: K. Ibrahim: None. **D. Burek:** None. **O. Idowu:** None. **A. Zec:** None. **S. Williams:** None. **N. Massaly:** None. **J. Moron-Concepcion:** None.

Poster

149. Addictive Substances and Memory Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 149.06

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH NIDA 2 R01 DA025646
Washington State I-171 research funds administered through the WSU ADARP
Poncin Research Fellowship

Title: Dorsal raphe and prelimbic cortex are differently involved in cocaine-memory reconsolidation

Authors: *J. L. RITCHIE, R. J. CHRISTIAN, S. QI, J. M. C. GALLIOU, M. J. GREENWOOD, R. A. FUCHS;
Integrative Physiol. and Neurosci., Washington State Univ., Pullman, WA

Abstract: Retrieval of cocaine-associated memories elicits drug craving and relapse but can also lead to the destabilization of these memories. Destabilized cocaine memories must be reconsolidated into long-term memory stores to be maintained over time. Furthermore, therapeutic interference with reconsolidation can reduce stimulus control over cocaine-seeking behavior. Corticotropin-releasing factor (CRF) signaling in the basolateral amygdala (BLA) regulates cocaine-memory reconsolidation, but the critical source of CRF is not known. To identify candidate CRF neuronal populations, we combined retrograde tracing, fluorescence immunohistochemistry, and an instrumental model of cocaine relapse. Male and female Sprague Dawley rats received bilateral retrograde tracer, Retrobreads^{TM} (RB), infusions into the BLA and were trained to self-administer cocaine (10 days) in a distinct context to establish context-cocaine memories. After extinction training in a separate context (7 days), they were re-exposed to the cocaine-paired context (15 minutes) to retrieve cocaine-associated memories and initiate reconsolidation (controls remained in their home cages). Brain tissue was collected 2 hours later to assess c-Fos expression (index of neuronal activation) during reconsolidation. RB labeling, CRF immunolabeling (IR), and c-Fos IR were visualized using confocal microscopy. Based on RB and CRF-IR colocalization, we quantified c-Fos IR in BLA-projecting CRF cell populations in five brain regions: the anterior cingulate cortex (AC), prelimbic cortex (PrL), infralimbic cortex (IL), insular cortex (IC), and dorsal raphe nucleus (DRN). A memory-reactivation-dependent increase in c-Fos IR in BLA-projecting CRF neurons was observed in the AC, PrL, and DRN only. We have shown that tetrodotoxin-induced inactivation of the AC fails to impair reconsolidation (Ramirez et al. 2009). Therefore, we then examined whether neuronal activity in the PrL or DRN is necessary for cocaine-memory reconsolidation using local administration of baclofen/muscimol (B/M, GABA agonists) or vehicle immediately after cocaine-memory reactivation. B/M-induced DRN inactivation, but not PrL inactivation, during reconsolidation attenuated cocaine-memory strength (as indexed by cocaine-seeking behavior), relative to vehicle. This suggests that the DRN contributes to cocaine-memory reconsolidation, possibly through CRF projections to the BLA. Ongoing projects examine this hypothesis using CRF-neuron selective pathway manipulations.

Disclosures: **J.L. Ritchie:** None. **R.J. Christian:** None. **S. Qi:** None. **J.M.C. Galliou:** None. **M.J. Greenwood:** None. **R.A. Fuchs:** None.

Poster

149. Addictive Substances and Memory Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 149.07

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH Grant GM136467

Title: Role of environmental conditioning in the cross-sensitization between RU 24969 and cocaine in juvenile rats

Authors: *L. COTTER, D. J. GONZALEZ, J. A. M. ROBINSON, C. A. CRAWFORD, S. A. MCDOUGALL;
Dept. of Psychology, California State Univ., San Bernardino, CA

Abstract: Recently, we found that cocaine and the nonselective 5-$HT_{1A/1B}$ receptor agonist RU 24969 show reciprocal cross-sensitization using a multi-trial procedure in preweanling rats. Interestingly, when a one-trial pretreatment regimen was used, cross-sensitization was only apparent when preweanling rats were pretreated with RU 24969 and tested with cocaine, but not the reverse. Since one-trial sensitization is known to be more context dependent than multi-trial procedures, it is possible that the discrepancies in cocaine/RU 24969 cross-sensitization may be explained by differences in associative learning. Thus, in the present study, we assessed the role of environmental cues by altering the drug pretreatment context. Specifically, on the pretreatment day [i.e., postnatal day (PD) 20], preweanling rats were injected with saline, cocaine (30 mg/kg), or RU 24969 (5 mg/kg) and immediately placed in one of the three pretreatment compartments (locomotor activity chamber, operant chamber, or home cage) for 45 min. Thirty min after being returned to the home cage, rats given cocaine or RU 24969 were given an injection of saline. Rats that had received saline initially were divided into three groups and received a saline, cocaine, or RU 24969 injection. Two days later (i.e., PD 22), rats that received cocaine during pretreatment were challenged with RU 24969 (5 mg/kg) and rats that received RU 24969 were challenged with cocaine (20 mg/kg). Rats that had previously received two saline injections received either cocaine or RU 24969. All rats were placed in the locomotor activity chamber immediately after injection for a 120 min testing session. Thus, rats in this cross-sensitization experiment were either pretreated in the same activity chamber as they were tested (associative group), pretreated in their home cage and tested in activity chamber (non-associative familiar group) or pretreated in operant chamber and tested in activity chamber (non-associative novel group). Similar to our earlier finding, cross-sensitization was only seen in rats pretreated with RU 24969 and challenged with cocaine and not the reverse. This cross-sensitization between RU 24969 and cocaine was seen in both the associative and non-associative novel groups but not in the group that received their drug in the home cage.

Unexpectedly, we also found rats pretreated with cocaine showed a decreased response to a RU 24969 challenge that was most apparent in the non-associative familiar group. In summary, these results indicate that context is important in the cross sensitization of cocaine and RU 24969, but it is not clear if associative learning is mediating the effect of these environmental cues.

Disclosures: L. Cotter: None. **D.J. Gonzalez:** None. **J.A.M. Robinson:** None. **C.A. Crawford:** None. **S.A. McDougall:** None.

Poster

149. Addictive Substances and Memory Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 149.08

Topic: G.09. Drugs of Abuse and Addiction

Support: This project was supported by the Intramural Research Program of the National Institute on Drug Abuse (NIDA), NIH, and DHHS (grant #-DA000552 (2021)).

Title: Compulsive methamphetamine taking behavior in the presence of punishment is accompanied by specific transcriptional changes in the rat hippocampus.

Authors: *S. JAYANTHI, C. C. MUNOZ, B. LADENHEIM, M. T. MCCOY, J. L. CADET; NIDA-IRP, NIDA-IRP, Baltimore, MD

Abstract: Methamphetamine use disorder (MUD) is a major public health problem worldwide. To develop promising treatment strategies against MUD, it is important to elucidate the basic molecular mechanisms that might subsume this neuropsychiatric diathesis. This approach necessitates the development of animal models that replicate human conditions. To mimic MUD in rodents, we have been using a preclinical model in which rats are trained to self-administer methamphetamine for a period of 21 days. After the rats had escalated their drug intake, lever presses for methamphetamine are punished by mild foot-shocks for 8 days (0.18-0.36 mA). Animals that were self-administering saline were also yoked to methamphetamine rats to receive shocks coincident with the administration of shocks to methamphetamine rats. In the present study, we measured genome-wide transcriptional changes using Illumina HiSeq2500 station at the end of the behavioral experiments. The hippocampus was used in the molecular studies because that structure plays important roles in learning and memory formation. All methamphetamine-trained rats escalated their intake during self-administration. Foot-shocks led to the segregation of methamphetamine rats into two phenotypes: one group that continued to compulsively press the lever for methamphetamine (shock- resistant) and another group that progressively decreased their methamphetamine intake (shock-sensitive). RNA-Seq data revealed that, in comparison to control rats, saline yoked-shock, and shock-sensitive rats, shock-resistant rats showed up-regulation of 51, 54, and 35 genes but down-regulation of 60, 113, and 54 genes. Ingenuity Pathway Analysis identified voltage-gated potassium channel, T-cell receptor, and ERK signaling as important functional networks affected in the shock-resistant

animals. These observations support the notion that this model might help us to develop pharmacological approaches against MUD using a more representative animal model of substance used disorder. Acknowledgement: This work is supported by DHHS/NIH/NIDA/IRP.

Disclosures: S. Jayanthi: None. **C.C. Munoz:** None. **B. Ladenheim:** None. **M.T. McCoy:** None. **J.L. Cadet:** None.

Poster

149. Addictive Substances and Memory Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 149.09

Topic: G.09. Drugs of Abuse and Addiction

Support: MOST grants 109-2423-H-006-002-MY2
MOST grants 111-2423-H-006-001-

Title: Ketamine affects reconsolidation and stress-induced reinstatement of methamphetamine-induced conditioned place preference

Authors: *Y.-H. LIAO[1,2], L. YU[1];
[1]Dept. of Physiol., Natl. Cheng Kung Univ. Col. of Med., Tainan, Taiwan; [2]Div. of Cardiol., Ditmanson Med. Fndn. Chia-Yi Christian Hosp., Chiayi City, Taiwan

Abstract: Methamphetamine (MA) and ketamine (KE) emerge as the most popular poly-drug of choice in local area. Recently, KE has been reported for its efficacy in reducing problematic alcohol use and drug addiction by disrupting reconsolidation of memory associated with those addictive drugs-related cues. This study was undertaken to first assess the modulating effects of KE on the reconsolidation of MA-induced conditioned place preference (CPP) using short (3 min) and long (30 min) reactivation intervals. And KE was then assessed for its effects on stress- and MA challenge-elicited MA CPP reinstatement. Mice received 4-day conditionings to establish their MA CPP. To assess the plausible reconsolidation-modulating effect of KE, mice underwent MA CPP reactivation using 3-min or 30-min reactivation intervals. These animals were further subdivided into two groups, with one half receiving a single saline injection and the remaining half KE injection immediately after the reactivation. We hereby report that KE treatment immediately after a 3-min, but not 30-min, reactivation seems to effectively disrupt reconsolidation of MA CPP. Moreover, cementing KE treatment and short reactivation seems to significantly modulate the expression of medial prefrontal cortical and amygdaloid mGluR5 and VTA β1 adrenergic receptor. Finally, such KE treatment also prevents stress-elicited MA CPP reinstatement. These results, taken together, prompt us to conclude that KE merits consideration for its use on facilitating MA use-related memory extinction and preventing stress-elicited MA memory reinstatement.

Disclosures: Y. Liao: None. **L. Yu:** None.

Poster

149. Addictive Substances and Memory Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 149.10

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH Grant UH3 NS096833
NIH Grant R01 DA049544

Title: Corticotrophin Releasing Factor Receptor 2 and Nonmuscle Myosin II-mediated methamphetamine-associated memories

Authors: *M. HAFENBREIDEL, S. B. BRIGGS, M. ARZA, S. REED, S. BONTHU, A. TILLER, C. FISHER, A. HALL, L. LIN, S. KHAN, M. CAMERON, G. RUMBAUGH, C. MILLER;
Scripps Res., UF Scripps Biomed. Res., Jupiter, FL

Abstract: Substance use disorders (SUD) are perpetuated by associative memories that induce motivation to seek drug. We previously reported that inhibition of the actin motor ATPase nonmuscle myosin II (NMII) with the inhibitor blebbistatin (blebb), results in actin depolymerization in the basolateral amygdala (BLA) and a retrieval-independent disruption of methamphetamine (METH)-associated memories and METH seeking. The effect is selective, as it is not effective in other brain regions (e.g. dorsal hippocampus (dPHC), nucleus accumbens (NAc)), nor does it interfere with other associative stimuli, including cocaine (COC). To investigate the source(s) of this selectivity, we used RNA-seq following conditioned place preference (CPP) conditioning to determine transcriptional differences between METH- and COC-associated memories. One gene selectively upregulated in METH-treated mice in BLA, but not dHPC or NAc, was *crhr2*, which encodes Corticotrophin Releasing Factor receptor 2 (CRF2). Besides its role in the stress response, its ligand, CRF, is released in BLA following COC or METH administration, and CRF receptor 1, but not CRF2, is involved in COC-associated memory. Interestingly, CRF2 has been linked to NMII regulation outside the CNS, but its role and potential interaction with NMII in METH-associated memories was unknown. To test for this interaction, we first established the impact of CRF2 inhibition after METH CPP conditioning. Mice received intra-BLA infusions of vehicle or the CRF2 antagonist Astressin-2B (AS2B) after the final METH conditioning session. CRF2 inhibition was not sufficient to disrupt the memory, as both groups expressed a METH CPP when tested 48hr later. Moreover, unlike AS2B, NMII inhibition with blebb (IP) shortly after the last METH conditioning session disrupted METH CPP expression. Taken together, these results enabled examination of the interaction between CRF2 and NMII. For this, mice received intra-BLA infusions of vehicle or AS2B after the last conditioning session, followed by blebb (IP) shortly after. METH CPP was disrupted in mice treated with vehicle and blebb, replicating our previous results. However, METH-associated memory was protected in mice that received AS2B and blebb. These results suggest that CRF2 is required in combination with NMII activity in BLA to render METH-

associated memories selectively vulnerable to NMII inhibition. Currently, we are overexpressing CRF2 in the BLA in order to determine if this will render a COC-associated memory susceptible to disruption by NMII inhibition. CRF2 may represent a general target for destabilizing memory via (yet to be identified) downstream effects on NMII.

Disclosures: **M. Hafenbreidel:** None. **S.B. Briggs:** None. **M. Arza:** None. **S. Reed:** None. **S. Bonthu:** None. **A. Tiller:** None. **C. Fisher:** None. **A. Hall:** None. **L. Lin:** None. **S. Khan:** None. **M. Cameron:** None. **G. Rumbaugh:** None. **C. Miller:** None.

Poster

149. Addictive Substances and Memory Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 149.11

Topic: G.09. Drugs of Abuse and Addiction

Support: NIDA R01DA045499
NCCIH R21AT010404
NIDA P30DA013429

Title: Subchronic mitragynine causes sex-dependent changes in brain cytokine levels in rats with minimal cognitive and locomotor effects

Authors: *R. L. BURROUGHS[1], K. POWELL[1], T. K. EISENSTEIN[2], J. B. MEISSLER[2], D. FARKA[2], S. M. RAWLS[2], L. E. BAKER[1];
[1]Psychology, Western Michigan Univ., Kalamazoo, MI; [2]Ctr. for Substance Abuse Research, Dept. of Neural Sci., Lewis Katz Sch. of Medicine, Temple Univ., Philadelphia, PA

Abstract: *Mitragyna speciosa* (Kratom) is a medicinal plant indigenous to Southeast Asia and Africa with a long history of use for a variety of ailments, including diarrhea, pain relief, cough suppression, and amelioration of opiate withdrawal symptoms. Despite its status as an herbal remedy, Kratom is banned in some countries due to a myriad of negative health risks. Preclinical psychopharmacology studies of mitragynine (MG), the main alkaloid of Kratom, indicate it has opioid-like effects, with lower potency than morphine. Lower doses reportedly produce psychostimulant-like effects. Few studies have evaluated the neurobehavioral effects of repeated MG exposure. The current study utilized a repeated measures design to evaluate the effects of repeated MG (0, 1, 10 mg/kg) exposure on locomotor activity and on the acquisition of a spatial memory task in Wistar-Han rats (24 M, 24 F, N=8 per group). For the locomotor activity assay, rats were injected every other day for five days and activity was recorded in an open field for 1 h immediately before and 1 h immediately after injections. Activity measures assessed included total distance, stereotypy, and time in center. The same rats were assessed one week later for spatial memory acquisition in an eight-arm radial maze (RAM) while injections continued daily after each learning trial for eight days. Maze acquisition was assessed by latency to complete each trial, total arm entries, and repeat arm entries. One day after the last injection, rats were

euthanized and brains were harvested and stored at -80 º C for analysis. The amygdala, hippocampus, periaqueductal gray (PAG), and prefrontal cortex (PFC) were dissected and assessed by Luminex (IL-1β, IL-6, IL-10, IL-17A, CCL2/MCP-1, CCL5/RANTES) or ELISA (CXCL12/SDF-1α) to determine tissue cytokine/chemokine levels. Both MG doses produced stronger psychomotor stimulant effects in females compared to males, though neither dose produced locomotor sensitization in either sex. RAM acquisition was unaffected by mitragynine treatment in either sex. In male brains, most cytokines were significantly reduced in the amygdala, hippocampus, and PAG after repeated exposure to 10 mg/kg MG, and 1 mg/kg produced significant reductions in all cytokine levels in the amygdala. In female brains, similar results were obtained in the amygdala. However, hippocampal cytokine levels were elevated by 1 mg/kg MG in females. Interestingly, cytokine levels in the PFC were not impacted in male or female rats. In summary, despite nonsignificant effects in behavioral assessments of activity and spatial memory, brief intermittent MG exposure caused region- and sex-dependent changes in brain cytokine levels.

Disclosures: R.L. Burroughs: None. **K. Powell:** None. **T.K. Eisenstein:** None. **J.B. Meissler:** None. **D. Farka:** None. **S.M. Rawls:** None. **L.E. Baker:** None.

Poster

149. Addictive Substances and Memory Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 149.12

Topic: G.09. Drugs of Abuse and Addiction

Title: Escalating morphine and naloxone-precipitated withdrawal effects on conditioned fear learning in Sprague Dawley rats; a fear-potentiated startle (FPS) study.

Authors: *G. LEVASSEUR, T. CILLEY, Jr., M. RISER, J. NANNOSHI, S. PERRINE, S. NORRHOLM;
Psychiatry & Behavioral Neurosciences, Wayne State Univ., Detroit, MI

Abstract: Opioid use disorder (OUD) is highly comorbid with stress. National surveys have shown that up to 33% of patients with OUD met the criteria for posttraumatic stress disorder (PTSD) diagnosis vs. only 7% of the population. Great effort has been made to investigate the effects of extreme stress on the risk of opioid use. Fewer investigations have explored the opposite: how opioid use affects threat perception and reactions to extreme stress. Opioids can produce profound changes in associative learning mechanisms, leading to dependence and altered fear learning following stress exposure. Fear conditioning and its sequelae are laboratory models of the associative learning processes that appear to underlie PTSD development and symptomatology. In this study, we used 47 male Sprague Dawley rats to: 1) develop a replicable FPS paradigm that allowed for the study of fear learning outcomes (n=32) and 2) determine the effect of morphine withdrawal on FPS learning outcomes, including fear expression, extinction

learning, extinction recall, and subsequent reinstatement (morphine: n=7, saline: n=8). Escalating doses of morphine were administered twice daily for 10 days (5 mg/kg + 5 mg/kg/day) to a final morphine dose of 50 mg/kg. Morphine injections were vehicle controlled by a saline group. All animals received a single naloxone injection (1.5 mg/kg) after the last dose of morphine and prior to fear conditioning. RESULTS: (all F tests listed are 2way ANOVA) 1) For development of FPS parameters, we found a main effect of fear conditioning trial type ($F(4, 116) = 83.3$, $P<0.0001$). Tukey's multiple comparisons showed significant increase in startle in the presence of the conditioned stimulus (CS) as compared to noise alone ($p<0.0001$), a significant within-session decrease in FPS during extinction ($P<0.0001$), and no significant difference in FPS between extinction end vs. extinction retention test. 2) Morphine withdrawal experiments showed robust fear expression in both morphine and saline groups ($F(2, 14) = 34.7$; $p<0.0001$). The extinction retention test revealed both morphine and saline groups reliably extinguished response to the CS, showing no main effect of trial type ($F(2, 14) = 2.29$, $p=0.14$) and no main effect of drug ($F(1, 7) = 4.16$, $p=0.08$). Interestingly, a test of fear reinstatement revealed a robust return of fear in the saline group that was blocked in the morphine group ($F(2,12) = 14.7$, $p=0.0006$). These findings and future investigations may be helpful for identifying neurobiological changes relevant to both chronic opioid administration and later exposure to extreme stress, and may ultimately clinically inform our understanding of OUD and traumatic stress comorbidity.

Disclosures: G. LeVasseur: None. **T. Cilley:** None. **M. Riser:** None. **J. Nannoshi:** None. **S. Perrine:** None. **S. Norrholm:** None.

Poster

149. Addictive Substances and Memory Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 149.13

Topic: G.09. Drugs of Abuse and Addiction

Support: National Institute on Drug Abuse, Intramural Research Program, NIH

Title: Identification of S6 and calcineurin proteins as markers of activated PFC to NAc synapses using flow cytometry of synaptoneurosomes (FCS)

Authors: *F. J. RUBIO[1], D. OLIVARES[2], C. DUNN[4], S. ZHANG[3], E. M. HILAIRE[1], A. HENRY[1], C. A. MEJIAS-APONTE[3], C. J. NOGUERAS-ORTIZ[5], P. V. SELVAM[1], F. C. CRUZ[6], M. F. MORALES[3], B. T. HOPE[1];
[1]BNRB, [2]NIH, Natl. Inst. On Drug Abuse, [3]INRB, NIH, NIDA IRP, Baltimore, MD; [5]Lab. of Clin. Investigation, [4]NIH, NIA IRP, Baltimore, MD; [6]Univ. Federal de Sao Paulo, Univ. Federal de Sao Paulo, Sao Paulo, Brazil

Abstract: Memories are encoded by long-lasting alterations (engrams) within specific patterns of sparsely distributed cells and synapses activated during learning and memory recall. While

Fos has been used to identify activated ensemble neurons and the engrams within them, we have not had a similar marker for activated synapses that we can use to identify synaptic engrams. Neuroadaptations within glutamatergic terminals from the medial prefrontal cortex (mPFC) that synapse onto dendritic spines of medium spiny neurons in nucleus accumbens are thought to be important for learning in animal models of drug addiction. To identify candidate synaptic activity markers in these synapses, we developed a flow cytometry of synaptoneurosomes (FCS) procedure for assessing molecular alterations in selectively activated synapses. First, YFP-expressing AAV was injected into the mPFC and the expressed YFP protein was transported over 6-8 weeks to mPFC-specific presynaptic endings in the nucleus accumbens core (NAcc). On test day, we injected each rat intraperitoneally with 20 mg/kg cocaine and placed them in a novel environment to induce cellular and synaptic activation. We dissected the NAcc at 0, 5, 10, 30 and 60 min following the injection. We prepared synaptoneurosomes and confirmed their size and structure using electron microscopy and nanoparticle tracking analysis. We labeled the synaptoneurosomes with commercially available antibodies against candidate synaptic activation markers, including Arc, CaMKII, ribosomal protein S6, calcineurin and their phosphorylated proteins. We then used our FCS protocol to quantify these molecular elements selectively in PFC-NAc synaptoneurosomes labeled with YFP. We found increased S6 at 5-60 min and increased calcineurin at 5 and 10 min. Electron microscopy analysis confirmed increased S6 and calcineurin levels in synapses at 10 min. Finally, to demonstrate that S6 and calcineurin are synaptic 'activity' markers, we injected rats with the anesthetic chloral hydrate 10 min before the cocaine injections, which blocked cocaine+novelty-induced S6 and calcineurin increases in synaptoneurosomes. This indicates that FCS can be used with the endogenous synaptic activity markers S6 and calcineurin to characterize synaptic engrams in learned behaviors with single synapse resolution. Our FCS-based approach can be used to analyze up to 40 different proteins from 0.5-1 mg of tissue from individual rats or mice.

Disclosures: **F.J. Rubio:** None. **D. Olivares:** None. **C. Dunn:** None. **S. Zhang:** None. **E.M. Hilaire:** None. **A. Henry:** None. **C.A. Mejias-Aponte:** None. **C.J. Nogueras-Ortiz:** None. **P.V. Selvam:** None. **F.C. Cruz:** None. **M.F. Morales:** None. **B.T. Hope:** None.

Poster

149. Addictive Substances and Memory Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 149.14

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH Grant DA047981

Title: Investigating the role of GILZ at the interface of stress and cocaine-associated memory

Authors: *J. ROUNDS[1], E. A. KRAMÁR[2], M. A. WOOD[3];
[1]Univ. of California, Irvine, Irvine, CA; [2]Neurobio. and Behavior, Univerisity of California, Irvine, CA; [3]Neurobiol & Behavior, Univ. of California Irvine, Irvine, CA

Abstract: Repeated exposure to drugs of abuse can alter the structure and function of synaptic connections, giving rise to drug-associated memories that can persistently influence behavior. These drug-associated memories and their corresponding behaviors can be differentially recruited by environmental stress. However, there remains a paucity of knowledge in the mechanistic interactions between stressful stimuli and drug exposure underlying long-term behavioral adaptations. Here, we investigated the role of a stress-responsive candidate gene (glucocorticoid-induced leucine zipper, GILZ) in long term cocaine-associated memory processes within the nucleus accumbens (NAc) and ventral tegmental area (VTA) of mice. RT-qPCR revealed sex-specific GILZ expression patterns in both the NAc and VTA, where adult male and female mice exhibit differential expression of mRNA splice variants that code for distinct GILZ protein isoforms. These GILZ isoforms regulate transcription as well as the integration of key signaling cascades involved in plasticity, and their differential expression suggests potential sex differences in the reward-related actions of GILZ. To determine whether GILZ expression is necessary for the formation of cocaine-associated memory, males and females were infused with a site-specific siRNA (targeted to either the NAc or VTA) to knockdown all splice variants of GILZ prior to training in a cocaine-conditioned place preference (CPP) protocol. We found that VTA-GILZ knockdown significantly blunted cocaine-CPP acquisition in males but not females in a dose-dependent manner. In addition, we found that intra-NAc knockdown of GILZ attenuates long-term potentiation (LTP, a key measure of synaptic involvement in memory formation) in males. This impairment was replicated in GILZ-deficient hemizygous knockout male mice. Together, these data suggest a sex-specific role of GILZ in contributing to stable changes in neuronal function underlying reward-related memory processes.

Disclosures: J. Rounds: None. **E.A. Kramár:** None. **M.A. Wood:** None.

Poster

149. Addictive Substances and Memory Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 149.15

Topic: G.09. Drugs of Abuse and Addiction

Support: Discovery Grant from Natural Sciences and Engineering Research Council of Canada

Title: Memory modulation by heroin and heroin conditioned stimuli: relevance to addiction

Authors: T. J. FRANCIS[1], ***F. LERI**[2];
[1]Univ. of Guelph, Univ. of Guelph, Guelph, ON, Canada; [2]Univ. Guelph, Univ. Guelph, Guelph, ON, Canada

Abstract: Drugs of abuse and their conditioned stimuli can have significant faciliatory effects on memory consolidation, but the relevance of these observations to addictive behaviors has not

been addressed. That is, these behaviours typically involve active drug use and there is evidence in laboratory animals that self-administered and passively injected drugs can produce different neurobiological consequences in brain regions involved in memory formation. Furthermore, if memory facilitation is indeed a conditioned response to stimuli paired with self-administered and/or passively received drugs, it is important to establish whether this conditioned response is present during instances of drug-seeking observed in extinction conditions. Therefore, this study employed a yoked design in male Sprague-Dawley rats: one group was trained to intravenously self-administer 0.05 mg/kg/inf heroin paired with the activation of a light CS, while yoked rats received an equal number of infusions and light CS presentations independent of their lever responses. Self-administration training was followed by a period of extinction during which responses on the active lever had no consequences and, during a cue-induced reinstatement test, active lever responses resulted in the re-activation of the light-CS but no heroin delivery. The post-training effects of heroin (active and passive exposure), extinction and reinstatement sessions on memory consolidation were tested using the object location memory task. It was found that post-sample heroin enhanced object location memory in yoked, but not self-administration rats. However, the memory tests post extinction and reinstatement sessions indicated that both the context of heroin delivery and the CS paired with heroin infusion enhanced memory equally in both experimental groups. Taken together, these data in rats support the perspective that addictive behaviours could develop and be maintained by the cognitive consequences of drug exposure, and eventually of exposure to a variety of drug-paired stimuli.

Disclosures: **T.J. Francis:** None. **F. Leri:** None.

Poster

149. Addictive Substances and Memory Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 149.16

Topic: G.09. Drugs of Abuse and Addiction

Support: Discovery Grant from Natural Sciences and Engineering Research Council of Canada

Title: Corticotrophin releasing factor, central amygdala, and their role in memory modulation by opioid withdrawal

Authors: *N. BAIDOO[1], F. LERI[2];
[1]Univ. of Guelph, Guelph, ON, Canada; [2]Univ. Guelph, Univ. Guelph, Guelph, ON, Canada

Abstract: It has been recently demonstrated that opioid withdrawal facilitates memory consolidation. To further understand the neurobiology of this phenomenon, the current study focused on corticotrophin-releasing factor (CRF) and the central amygdala (CeA) because of their known involvement in opioid withdrawal and memory functions. Male Sprague-Dawley

rats were implanted with osmotic mini-pumps releasing 3.5 mg/kg/day heroin and withdrawal was precipitated by injections of 3 mg/kg naloxone (NLX) preceded either by systemic injection of 10 - 20 mg/kg antalarmin (CRF 1 receptor antagonist) or intra-CeA infusions of 0 - 2 ug antalarmin immediately after the sample phase of spontaneous object recognition task. It was found that both systemic and intra-CeA infusion of antalarmin blocked the memory-enhancing action of NLX-precipitated withdrawal. These experiments suggest the memory enhancing action of drug withdrawal could promote the permanence of addictive actions through a mechanism that involves neurotransmission of CRF in the CeA.

Disclosures: **N. Baidoo:** None. **F. Leri:** None.

Poster

149. Addictive Substances and Memory Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 149.17

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH Grant R00 DA04510 (NIDA)
NIH Grant U01 AA029971 (NIAAA)
Alkermes Pathways Research Award
Brain Research Foundation
Whitehall Foundation
Stanley Cohen Innovation Fund
NIH Training Grant 5T32MH064913-18 (MPI)

Title: Kappa opioid receptor blockade increases reinforcement learning rate by augmenting response to novelty

Authors: *Z. Z. FARAHBAKHSH, K. SONG, H. E. BRANTHWAITE, K. R. ERICKSON, S. MUKERJEE, S. O. NOLAN, C. A. SICILIANO;
Vanderbilt Brain Inst., Nashville, TN

Abstract: Kappa opioid receptors (KORs) are thought to function as a global negative valence system with augmented signaling highly implicated in the pathobiology of various psychiatric disorders, including depression and substance use disorders. Upregulation of the KOR system underlies dysphoria both in depression and during periods of abstinence in substance use disorders. The leading framework posits that KOR activation acts through negative reinforcement, driving maladaptive behaviors to alleviate or avoid the negative affective state. In support of this model, KOR antagonists have great therapeutic potential in treating the symptomatology characterizing these ailments. Preclinical effects of KOR antagonists have been widely reproduced, however predictions derived from this negative reinforcement model, and the role of the system in reinforcement learning, have not been directly assessed. To address this gap, we generated a series of *a priori* hypotheses based on the model and experimentally

assessed their validity. Since the KOR system is considered a critical driver of negative valence specifically, we hypothesized that antagonists of the system would have no effect on positive reinforcement learning and would decrease the rate of negative reinforcement learning. We then assessed this prediction by pairing systemic KOR antagonism with operant reinforcement learning tasks designed to assess behavior across both positive and negative reinforcement. We found that, contrary to our prediction, KOR blockade increased the rate of reinforcement learning independent of reinforcer valence. Learning was accelerated without altering the innate response to either the appetitive (sucrose) or aversive (footshock) stimuli, again against the hypotheses developed from the negative reinforcement model. Further experiments demonstrated that KOR blockade increased both novelty exploration and the intrinsic motivational value of novel stimuli - an effect that likely mediates the increased rate of reinforcement learning. These findings call for a reevaluation of the existing framework for understanding KOR involvement in fundamental behavioral processes as well as psychopathology. Based on our data and in line with previously demonstrated effects of KOR manipulation, we propose novelty processing as a falsifiable framework for conceptualizing KOR function and disfunction.

Disclosures: Z.Z. Farahbakhsh: None. **K. Song:** None. **H.E. Branthwaite:** None. **K.R. Erickson:** None. **S. Mukerjee:** None. **S.O. Nolan:** None. **C.A. Siciliano:** None.

Poster

149. Addictive Substances and Memory Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 149.18

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH Grant R00 DA04510 (NIDA)
U01 AA029971 (NIAAA)
Alkermes Pathways Research Award
Brain Research Foundation
Whitehall Foundation
Stanley Cohen Innovation Fund

Title: Dopamine signaling in the mouse medial prefrontal cortex tracks selective attention

Authors: *P. R. MELUGIN[1], S. O. NOLAN[3], Z. FARAHBAKHSH[4], C. F. FERRARA[1], C. SICILIANO[2];
[1]Pharmacol., Vanderbilt Univ., Nashville, TN; [2]Pharmacol., Vanderbilt Univ., NASHVILLE, TN; [3]Pharmacol., Vanderbilt Univ. Med. Ctr., Nashville, TN; [4]Vanderbilt Brain Inst., Nashville, TN

Abstract: Midbrain dopaminergic (DA) projections to the medial prefrontal cortex (mPFC) exert a powerful neuromodulatory influence over the mPFC and evidence has linked dysregulation of this pathway to an array of neuropsychiatric disorders. In accordance, mPFC DA transmission

has been implicated in a variety of behaviorally relevant processes including working memory, cognitive flexibility, and stress reactivity; however, relative to other brain regions whose activity is extensively modulated by midbrain DA systems, the role of mPFC DA transmission remains considerably less well understood. Until recently, investigations of mPFC DA have been prohibitively difficult and limited to either slow, direct measures of extracellular DA such as microdialysis, or fast but non-selective measures such as fast-scan cyclic voltammetry. Here, we utilized the fluorescent DA sensor dLight, which has high specificity for DA and sub-second temporal resolution, in conjunction with fiber photometry to parse mPFC DA dynamics in freely behaving mice. Contrary to prior work suggesting that mPFC DA release is preferentially evoked by stressful events, we demonstrate robust DA signal to novel (auditory tone), appetitive (sucrose), and aversive (footshock) stimuli. DA signal to novel stimuli diminished across sessions while the magnitude of responses to sucrose and footshock were proportional to lick bout size and shock intensity, respectively. Interestingly, while we observed no cue-evoked DA signal during an operant task in which animals learned to initiate a correct response for sucrose during a prolonged (30sec) cue presentation period, in a similar task wherein the cue indicating the correct operant response was only presented briefly (1sec) following a variable delay, we observed a cue-evoked increase in DA signal that was preceded by a pronounced decrease in signal during the delay period and that this decrease was highly correlated with task performance. Together, these findings suggest that this dampening of mPFC DA activity serves to filter environmental stimuli to allow selective attention towards a specific expected stimulus, which triggers an mPFC DA transient when detected.

Disclosures: **P.R. Melugin:** None. **S.O. Nolan:** None. **Z. Farahbakhsh:** None. **C.F. Ferrara:** None. **C. Siciliano:** None.

Poster

149. Addictive Substances and Memory Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 149.19

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH Grant R00DA04510
NIH Grant U01AA029971
Alkermes Pathways Research Award
Brain Research Foundation
Whitehall Foundation
Stanley Cohen Innovation Fund
NIH Grant F32DA051136

Title: Axonal and somatodendritic dopamine dynamics are governed by compartmentalized experience dependent mechanisms

Authors: S. O. NOLAN, K. R. ERICKSON, P. R. MELUGIN, M. H. KWON, H. CHEN, A. R. BROWN, B. A. CHRISTENSEN, H. E. BRANTHWAITE, E. S. CALIPARI, C. A. SICILIANO; Pharmacol., Vanderbilt Univ., Nashville, TN

Abstract: Substance use disorders (SUDs) are a debilitating set of disorders that have a societal cost of more than 700 million dollars per year in the US alone. Despite the prevalence and significant global financial burden of SUDs, the pathophysiology of these disorders is poorly understood, and current treatments have limited efficacy. After years of research, it is clear, however, that deficits in reward learning and motivation characteristic of substance use disorders can be directly linked to experience-induced alterations in dopamine transmission in the ventral tegmental area (VTA) to nucleus accumbens (NAc) pathway. The majority of this work has focused on *ex vivo* measurements of dopamine release in the nucleus accumbens terminals. Conversely, relatively little is known about the roles of non-canonical forms of release such as somatodendritic dopamine (sDA) release within the VTA, due to technical limitations which have largely prevented high fidelity temporally-specific recording of sDA signatures. Here, we utilized multisite fiber photometry and the optical sensor dopamine dLight1.2 to record *in vivo* somatodendritic dopamine kinetics at baseline as well as during a complex discriminative learning operant task and compare these to terminal release signatures. Our results revealed distinct activity-dependent signatures across contingency learning in the two compartments, characterizing these rapid time-locked sDA release signatures for the first time. Next, we characterized several potential mechanisms for this compartment-specific plasticity using widefield imaging of dLight dynamics and fast-scan cyclic voltammetry in *ex vivo* slices containing either the accumbal dopamine terminal fields or ventral tegmental area dopamine somata. Our results indicate enhanced high frequency evoked dopamine release in the NAc terminals in animals following contingency learning compared to naïve controls. However, in the VTA, the peak of evoked sDA release was unchanged in animals that underwent learning procedures. Together, these data suggest that sDA release is functionally decoupled from axonal release during motivated behavior and supports our burgeoning hypothesis that sDA release is activated by appetitive stimuli only after complex reinforcement learning has occurred. Further, the results of these experiments support temporally- and compartment-specific roles of dopaminergic plasticity in basal cognitive functions like reinforcement and motivated learning, and ultimately further extend our understanding of dopamine's role in both health and disease.

Disclosures: S.O. Nolan: None. **K.R. Erickson:** None. **P.R. Melugin:** None. **M.H. Kwon:** None. **H. Chen:** None. **A.R. Brown:** None. **B.A. Christensen:** None. **H.E. Branthwaite:** None. **E.S. Calipari:** None. **C.A. Siciliano:** None.

Poster

149. Addictive Substances and Memory Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 149.20

Topic: E.03. Basal Ganglia

Support: Parkinson's UK
ASAP

Title: Tonic activity facilitates striatal dopamine release during burst activity which is non-linearly related to intracellular calcium concentration

Authors: *Y. ZHANG, Y. HE, E. LOPES, M. CONDON, R. RAMACHANDRAN, S. J. CRAGG;
Univ. of Oxford, Oxford, United Kingdom

Abstract: Dopamine neurons play critical roles in reinforcement learning and action selection. Dopamine neurons spontaneously fire and have tonic low frequency and phasic high frequency spike activity at the cell body level. However, axons of dopamine neurons are not passive cables that faithfully convert neuronal activity into dopamine release. *Ex vivo* studies in mouse striatum show that isolated high-frequency stimuli (100 Hz) evoke dopamine release approximately linearly for small pulse numbers ($n > 4$), whereas intermittent low-frequency stimulation (≤ 40 Hz) shows short-term depression in dopamine release.
However, it is unclear how an ongoing background of tonic activity, as seen *in vivo*, impacts on how axons convert activity into dopamine release. To address this question, we applied a tonic-like electrical stimulation (2 Hz, 6 pulses) before a burst stimulation in *ex vivo* striatal slices from mouse brain. During tonic stimulation, dopamine release showed a strong initial depression and rapidly decreased to a steady level. Subsequent burst-evoked dopamine on a background of tonic activity was facilitated in a supra-linear manner with stimulation frequency. We investigated whether this supra-linear increase corresponds to calcium entry. By imaging GCaMP6f in dopamine axons, we found that calcium entry did not mirror the dopamine release pattern. There was no initial depression in calcium signals during tonic activity, and there was a sub-linear relationship between calcium entry and intra-burst frequency. A background of tonic activity had minimum impact on calcium entry during a burst. These findings indicate that calcium entry more efficiently triggers dopamine release during a high-frequency stimulation when a background of tonic activity is present. These findings reveal that tonic activity in dopamine neurons modulates the activity-dependence of dopamine during burst activity.
These findings will revise our understanding of dopamine function during phasic activity, such as in encoding reward-prediction errors. They also suggest that despite the potential energetic burden of handling Ca^{2+} entry to extensive arbors of dopamine axons, there are gains in function that enable greater levels of dopamine release to occur for a given level of intracellular calcium.

Disclosures: Y. Zhang: None. **Y. He:** None. **E. Lopes:** None. **M. Condon:** None. **R. Ramachandran:** None. **S.J. Cragg:** None.

Poster

150. Molecular Mechanisms Underlying Alcohol Use

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 150.01

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH Grant P60AA010760
NIH Grant R24AA019431
NIH Grant U01AA013510
NIH Grant P51OD011092

Title: Sex-dependent differences in ethanol self-administration in adult mice overexpressing neurobeachin in the prelimbic cortex

Authors: C. L. GARRETT[1], T. L. CARLSON[1], K. TERRY[2], R. P. CERVERA-JUANES[2], C. L. REED[3], T. J. PHILLIPS RICHARDS[3], K. A. GRANT[1], *V. C. CUZON CARLSON[1]; [1]ONPRC/OHSU, Beaverton, OR; [2]Wake Forest Univ., Winston-Salem, NC; [3]OHSU, Portland, OR

Abstract: Excessive alcohol use is involved in over 140,000 deaths per year. Despite known hazards, over 50% of US adults report drinking alcohol within the past 30 days. The corticostriatal limbic circuitry of cortical area 32/pre-limbic (PL) cortex to nucleus accumbens core (NAcc) has a role in motivated behavior and self-control, and is altered by chronic ethanol (EtOH) exposure. Here, we strive to identify discrete circuitry-related molecular/genetic differences between heavy and non-heavy drinkers. We have identified a list of differentially methylated regions (DMR) within the NAcc between heavy drinking (mean daily intakes >3 g/kg) and non-heavy drinking (mean daily intakes <3 g/kg) rhesus macaques given open access to 4% EtOH (w/v) for over 12 months. Modulating expression of genes from this list in the rodent may lead to identification of novel therapeutic targets for alcohol use disorder (AUD). One DMR was within the neurobeachin (NBEA) gene, which promotes receptor trafficking to the synaptic membrane and was hypermethylated in the NAcc of heavy drinking macaques. We previously found that knockdown of NBEA within the NAcc of the mouse increased EtOH preference ratio (EPR) in a two-bottle choice assay in mice and increased glutamatergic transmission onto NAcc medium spiny neurons. To further understand the role of NBEA in the impact of chronic EtOH consumption and glutamatergic transmission, adult mice selectively bred from the heterogeneous stock-collaborative cross to have high preference for EtOH were bilaterally injected into the PL with either a lentivirus containing NBEA-eGFP to promote NBEA overexpression or a control lentivirus carrying eGFP (n=15-16/sex/viral group). Following recovery, the mice were put through a continuous access 2-bottle choice for water vs. 10% EtOH experiment for 74 days to evaluate EPR and EtOH consumption. Behaviorally, our findings are two-fold. In males, NBEA overexpression resulted in a significant increase in EPR and EtOH consumption, beginning at day 48 compared to the control group. There was also a statistically significant, but transient reduction in EPR and EtOH consumption in females of the overexpression group beginning around day 12. Whole-cell patch clamp recordings will determine the effects of NBEA overexpression on the synaptic drive, or inhibitory/excitatory balance, in both the NAcc and PL. Coronal sections containing PL and NAcc were isolated for genetic and IHC experiments to confirm NBEA overexpression. Understanding how the modulation of genetic targets affects drinking behavior and synaptic drive via specific pathways related to motivated behavior could lead to novel, lifesaving treatments for AUD.

Disclosures: **C.L. Garrett:** None. **T.L. Carlson:** None. **K. Terry:** None. **R.P. Cervera-Juanes:** None. **C.L. Reed:** None. **T.J. Phillips Richards:** None. **K.A. Grant:** None. **V.C. Cuzon Carlson:** None.

Poster

150. Molecular Mechanisms Underlying Alcohol Use

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 150.02

Topic: G.09. Drugs of Abuse and Addiction

Support: VA Merit Review Award, I01BX004712
NIMH R01 MH122954
NIGMS U54GM128729

Title: Role of Neuronal Calcineurin in Immunosuppressant Induced Inhibition of Binge Alcohol Drinking

Authors: *P. RONAN[1], R. D. BURDINE[2], E. DORN[1], B. G. GOEDEN[1], P. SINNER[3], S. SEVERT[4], T. BERESFORD[5];
[1]Res. Service/Psychiatry and Basic Biomed. Sci., [2]Research/Psychiatry and Basic Biomed. Sci., Sioux Falls VA/USD Sch. of Med., Sioux Falls, SD; [3]Carleton Col., Northfield, MN; [4]Kent State Univ., Kent, OH; [5]Psychiatry, RMRVAMC-SOM U Colorado, Denver, CO

Abstract: We have found that the calcineurin mediated immunosuppressants cyclosporine and tacrolimus inhibit binge alcohol drinking in mice. Further, we have shown that this effect is mediated directly in brain, as intracerebroventricular administration also significantly decreases drinking. As these immunosuppressants have severe systemic toxic effects, our goal is to determine proximal mechanisms by which these immunosuppressants are working in order to develop effective treatments for alcohol use disorder (AUD) with fewer side effects. To this end, we are employing genomic, molecular, transcriptomic, metabolomic, anatomic, and behavioral approaches to explore the relationship between binge alcohol drinking and calcineurin mediated immunosuppressants in signaling and neuroinflammatory suppression. Since these immunosuppressants work through the inhibition of calcineurin, the question arises of what role does calcineurin play. Calcineurin is a somewhat ubiquitous phosphatase, involved in a wide range of signaling pathways - both in neurons and glia. One question is whether immunosuppressant effects are acting through neuronal signaling pathways, regulating reward and stress/anxiety pathways, or in glia, mediating neuroinflammatory effects. We have developed genetic models using a floxed calcineurin line (C57BL/6-Ppp3r1^{tm1Stl}/J) to decipher this by knocking out calcineurin in neurons and glia. Baseline drinking, both acute and chronic, in this line were not affected by CN knockout in this neuronal population. Though the CamkIIa-Cre line is often considered a way to get a pan brain neuronal knockout, CamKIIa expressing neurons represent only a subset of neurons. CamKIIa expressing neurons comprise around 50% of the total neuronal population in most brain regions. We are utilizing other strategies to address

this. We have developed a transgenic line with CN knockout in CRF neurons and are running these mice through our DID model. Other strategies being employed entail the use of AAV vectors with a Cre transgene expressed under an hSyn promoter. We have induced focal CN knockouts in both the central nucleus of the amygdala and nucleus accumbens and are investigating effects on drinking and immunosuppressants in our DID model.

Disclosures: **P. Ronan:** None. **R.D. Burdine:** None. **E. Dorn:** None. **B.G. Goeden:** None. **P. Sinner:** None. **S. Severt:** None. **T. Beresford:** None.

Poster

150. Molecular Mechanisms Underlying Alcohol Use

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 150.03

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH-COBRE P20GM103642
NSF 1736026
NIGMS P20GM103475
NIH-RISE 5R25GM061151-20
NIH-BP-ENDURE R25NS080687
NSF Grant 1633184
NSF Grant 2131647

Title: The role of histone acetyltransferase Tip60 in alcohol-induced neuroadaptations

Authors: *A. MONTES-MERCADO, C. DASTA-CRUZ, L. RAMOS-RODRIGUEZ, C. D. DEL VALLE COLÓN, M. KUCHIBHOTLA, J. L. AGOSTO, A. GHEZZI;
Biol., Univ. of Puerto Rico, Rio Piedras, San Juan, PR

Abstract: Alcohol Use Disorder (AUD) is a neuropsychiatric condition and a serious health problem characterized by an increased intake of alcohol accompanied by compulsive use. Alcohol consumption causes a homeostatic imbalance in the organism followed by the development of adaptations in the brain leading to alcohol tolerance and physiological dependence, or addiction. Recent evidence suggests that epigenetic mechanisms regulating gene expression and chromatin states are involved in such alcohol-induced neuroadaptations. However, most of these mechanisms are still unknown. The histone acetyltransferase Tip60, the mammalian homolog of Kat5 in the Drosophila melanogaster, has been linked to gene expression in neurons. We hypothesized that the histone acetyltransferase Tip60 activity in neurons mediates transcriptional dysregulation associated with alcohol tolerance. Thus, we employed the UAS-Gal4 System and RNAi to knockdown Tip60 in Drosophila neurons in vivo. To measure alcohol tolerance, we performed a behavioral assay using aged-matched female flies and quantified the difference in the rate of sedation between mock-treated and ethanol-sedated adult flies. To identify genome-wide transcriptional changes in these groups of flies, we performed

RNA sequencing of the whole brain. Our findings from the behavioral assay showed that Tip60 knockdown flies did not acquire alcohol tolerance. Differential expression (DE) analysis revealed that the top DE genes were involved in biological processes such as immune defense, gastrulation, muscle development, and metabolic processes involving hormones. This suggests that Tip60 might be a candidate regulator of specific processes, given that only a few genes were differentially expressed in our data set. A comprehensive study of the role of Tip60 activity in the brain illustrates mechanisms that may be involved in alcohol-induced neuroadaptations.

Disclosures: A. Montes-Mercado: None. **C. Dasta-Cruz:** None. **L. Ramos-Rodriguez:** None. **C.D. Del Valle Colón:** None. **M. Kuchibhotla:** None. **J.L. Agosto:** None. **A. Ghezzi:** None.

Poster

150. Molecular Mechanisms Underlying Alcohol Use

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 150.04

Topic: G.09. Drugs of Abuse and Addiction

Support: Collaborative Study on the Genetics of Alcoholism (COGA) U10 AA008401
Multi 'Omics Integration and Neurobiological Signatures of Alcohol Use Disorder (AUD) R01 AA027049
Integrating Epigenomics in Human Brain and Genomics of Nicotine Dependence R01 DA042090
UK Biobank Resource under Application Number 48123
Washington University Institute of Clinical and Translational Sciences TL1TR002344

Title: Alcohol associated cortical regions correlate with mRNA expression

Authors: *A. CHALOEMTOEM[1], V. THORNTON[2], J. SIEGEL[2], Y. CHANG[1], S. HARTZ[2], J. BIJSTERBOSCH[3], A. ANOKHIN[2], L. BEIRUT[2];
[1]Psychiatry, Washington Univ. in St. Louis, St. Louis, MO; [2]Psychiatry, [3]Radiology, Washington Univ. Sch. of Med., St. Louis, MO

Abstract: Rationale: Using the UK Biobank data, we recently found that alcohol consumption is associated with a spatial pattern of reduced cortical thickness. We hypothesized that regional differences in alcohol-associated thinning could be explained by regional differences in gene expression. Here we test this hypothesis by comparing alcohol-associated thickness with mRNA expression.
Data: UK Biobank imaging data is derived from 35054 male and female human participants between 40 to 80 years of age. Allen brain atlas represents in depth sequencing on 6 human brains.
Methods: Self-report data on alcohol consumption and MRI data on cortical thickness in 62 brain

regions of the Freesurfer Desikan-Killiany parcellation map were collected in accordance with published UK Biobank protocols. We performed linear regression in R to identify brain regions associated with alcohol use while controlling for covariates (systolic and diastolic blood pressure, waist hip ratio, BMI, income, education years, pack years, brain volume, site, sex, age, imaging date, head size, and in-scanner motion). Data on gene expression across brain regions were obtained from the Allen Brain atlas database. We tested for the correlation between the effect size of the association with alcohol and gene expression in 15633 genes across the 62 brain regions and determined functional enrichments using the ToppGene (https://toppgene.cchmc.org/) web portal.
Results: Analysis of the UK Biobank data showed that heavier alcohol use was significantly associated with reduced cortical thickness in 40 brain regions (Bonferroni corrected $p < 3.20*10^{-6}$). Across brain regions, alcohol-related differences in thickness correlated with differential expression of 206 genes (Bonferroni corrected $p < 3.20*10^{-6}$). Altered expression of these genes were enriched for molecular functions related to ion channel activity (FDR < 0.05).
Conclusion: Our results indicate that cortical regions showing association with alcohol consumption differ from non-associated regions at the mRNA level and shows functional enrichment for ion channel activity. We further demonstrate combining the UK Biobank with other data sets to approach questions that cannot be answered with either set alone.

Disclosures: A. Chaloemtoem: None. **V. Thornton:** None. **J. Siegel:** None. **Y. Chang:** None. **S. Hartz:** None. **J. Bijsterbosch:** None. **A. Anokhin:** None. **L. Beirut:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); U.S. Patent 8,080,371,“Markers for Addiction”.

Poster

150. Molecular Mechanisms Underlying Alcohol Use

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 150.05

Topic: G.09. Drugs of Abuse and Addiction

Support: FAPESP 2019/17065-4

Title: Context-induced reinstatement of ethanol seeking in rats is related to specific gene alterations in FACS-purified Fos-positive neurons

Authors: *P. C. BIANCHI, G. E. B. TAVARES, A. ANJOS-SANTOS, C. A. FAVORETTO, P. PALOMBO, E. L. CILLI, G. J. D. FERNANDES, F. C. CRUZ;
Dept. of Pharmacol., Univ. Federal de Sao Paulo (UNIFESP), São Paulo, Brazil

Abstract: Environmental contexts previously associated with drug use often provoke drug use relapse in humans and reinstate drug-seeking in laboratory animals. Here, we assessed unique molecular alterations within activated versus non-activated basolateral amygdala (BLA) neurons

after context-induced reinstatement of ethanol seeking. We trained Long-Evans male rats to self-administer ethanol in Context A and extinguished their lever-pressing in a distinct context (Context B). On test day, we assessed context-induced reinstatement in Context A or B (control group). We used fluorescent-activated cell sorting (FACS) to purify Fos-positive and Fos-negative neurons from BLA 90 min after the reinstatement test. In this method, neurons are labeled with NeuN (a marker of neurons) antibodies and activated versus non-activated neurons are identified according to their labeling with c-Fos antibodies. Exposure to Context A, but not Context B reinstated lever pressing (active lever presses: 11.3 ± 1.06, Context B and 29.3 ± 3.0, Context A; n=14 per group). RT-PCR data showed that exposure to Context A decreased the mRNA level of the genes GABAβ2 (1.04 ± 0.13, Fos^- and 0.55 ± 0.06, Fos^+), μ opioid (1.02 ± 0.24, Fos^- and 0.69 ± 0.12 Fos^+) and 5HT1-A (1.08 ± 0.19, Fos^- and 0.47 ± 0.06, Fos^+) and increased the expression of c-Fos gene (1.03 ± 0.1, Fos^- and 1.66 ± 0.17, Fos^+) in Fos-positive, but not Fos-negative, neurons. Otherwise, for Context B, we observed only a decrease in the mRNA level of the gene 5HT1-A (1.07 ± 0.16, Fos- and 0.48 ± 0.08, Fos+) in Fos-positive, but not Fos-negative, neurons. Our data indicate that context-induced reinstatement of ethanol seeking induces unique molecular alterations within activated BLA neurons that are distinct from those observed in the surrounding majority of non-activated neurons.

Disclosures: P.C. Bianchi: None. **G.E.B. Tavares:** None. **A. Anjos-Santos:** None. **C.A. Favoretto:** None. **P. Palombo:** None. **E.L. Cilli:** None. **G.J.D. Fernandes:** None. **F.C. Cruz:** None.

Poster

150. Molecular Mechanisms Underlying Alcohol Use

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 150.06

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH R21AA028352
NSF GRFP

Title: Different forms of ethanol tolerance are encoded by distinct transcriptional programs and brain circuits

Authors: *C. LARNERD, P. ADHIKARI, A. DEL TORO, A. VALDEZ, F. W. WOLF; Univ. of California, Merced, Merced, CA

Abstract: The way you drink alcohol influences how it alters your brain: we show that different patterns of initial ethanol intake encode ethanol experience through distinct molecular and circuit mechanisms. Understanding the molecular basis of how ethanol modifies the brain into a dysfunctional state is critical for understanding alcohol addiction. An early contributor of addictive progression is ethanol tolerance, that facilitates increased intake and that may set the stage for further maladaptive changes. The mechanistic distinctions between different forms of

tolerance and their relative contributions toward addiction are unknown. Here, we illuminate the biological phenomenon of chronic tolerance, that is induced by a long-term low dose of ethanol; as compared to rapid tolerance, that is induced by a short-term high dose. Both forms of tolerance manifest after the initiating ethanol dose is fully metabolized. Chronic tolerance is promoted by the activity of adult neurons located in the mushroom bodies, the primary learning and memory center in *Drosophila*. Chronic tolerance is suppressed by the gene *Sirt1*, encoding a conserved histone deacetylase (HDAC), specifically in mushroom body γ neurons. The immediate early gene (IEG) *Hr38*, homolog of mammalian *Nr4a* that is implicated in addiction plasticity, is not induced and is dispensable for chronic tolerance. HDACs encode chronic tolerance into the genome and block *Hr38* inducibility by short-term high dose ethanol. By contrast, rapid tolerance is promoted by the activity of mushroom body α/β neurons and is promoted by the gene *Sirt1* in those neurons. *Hr38* is induced and is required for rapid tolerance. Non-overlapping sets of IEG transcription factors are induced by chronic and rapid ethanol dosage patterns. Thus, different patterns of initial alcohol intake engage distinct molecular encoding mechanisms in different brain circuits. Changes in brain function associated with these forms of ethanol tolerance may have different priming effects for addiction liability via these signature molecular and cellular events.

Disclosures: C. Larnerd: None. **P. Adhikari:** None. **A. Del Toro:** None. **A. Valdez:** None. **F.W. Wolf:** None.

Poster

150. Molecular Mechanisms Underlying Alcohol Use

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 150.07

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH AA211597

Title: Heterogeneity of gene expression responses in different brain cell types after chronic alcohol consumption or/and innate immune activation in C57BL/6J male mice

Authors: *B. KISBY[1], M. MCMANUS[1], S. SHANMUGAM[1], I. PONOMAREV[2]; [2]Pharmacol. and Neurosci., [1]Texas Tech. Univ. Hlth. Sci. Ctr., Lubbock, TX

Abstract: Escalation of alcohol consumption is one of eleven criteria for alcohol use disorder (AUD). Previous work has shown the important role of neuroimmune signaling in regulating alcohol consumption in mice. For example, innate immune activation by repeated injections of the TLR3 agonist, Poly(I:C) (PIC), increases alcohol consumption in C57BL/6J male mice. We used this neuroimmune model of excessive alcohol consumption to investigate the role of different cell types in the transition from moderate to high alcohol drinking. The goal of this study was to identify cell types and cell-specific differentially expressed genes (DEGs) that are responsive to innate immune activation and/or excessive alcohol drinking. We used the every-

other-day two-bottle choice alcohol consumption paradigm that produces high levels of alcohol drinking in C57BL/6J male mice. Animals were randomly assigned to 4 drinking groups (n=4/group): saline drinking water (SW), saline drinking ethanol (SE), PIC drinking water (PW), and PIC drinking ethanol (PE). Animals were given a total of 9 injections of either saline or 10 mg/kg of PIC (one injection every 4 days) during the 5-week drinking procedure. Our results showed gradual increase in ethanol consumption and preference in the PE group compared to SE group, but no difference in total fluid intake. Brains were harvested twenty-four hours after the final alcohol session, flash frozen and subjected to whole-brain nuclei enrichment for single nuclei RNA-seq (snRNA-seq) analysis. Using 10x genomics Cell Ranger pipeline, we identified a total of 49,763 nuclei clustering into 40 discrete graph-based clusters representing specific cell types (based on molecular markers) including different types of neurons and glia. We used DESeq2 to perform pairwise comparisons for SW versus SE (effect of ethanol) and SE versus PE (effect of PIC) and identified cell-specific DEGs for each cluster/cell type. Based on the numbers of DEGs at FDR<5%, cell types most responsive to ethanol were VGLUT1- and VGLUT2-positive excitatory neurons (178 and 168 DEGs respectively), striatal Medium Spiny Neurons (264 and 110 DEGs for D1R- and D2R-positive respectively), Pvalb-positive GABA-ergic neurons (138 DEGs), and oligodendrocytes (185 DEGs). Cell types most responsive to immune activation by PIC were microglia (102 DEGs) and oligodendrocytes (449 DEGs). These preliminary results highlight the potential role of different cell types in the neuroimmune modulation of excessive ethanol consumption.

Disclosures: B. Kisby: None. **M. McManus:** None. **S. Shanmugam:** None. **I. Ponomarev:** None.

Poster

150. Molecular Mechanisms Underlying Alcohol Use

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 150.08

Topic: G.09. Drugs of Abuse and Addiction

Support: PVM competitive research fund

Title: Changes in protein signaling profiles of brain regions involved in drinking after a history of chronic binge-like drinking

Authors: *T. XIAO[1], Y. CHEN[2], A. BOISVERT,[3], E. KNORR[4], A. J. KIMBROUGH[5];
[1]purdue university, West Lafayette, IN; [2]Basic Med. Sci., Purdue Univ., Lafayette, IN; [3]BMS, [4]Purdue Univ., west lafayette, IN; [5]Basic Med. Sci., Purdue Univ., West Lafayette, IN

Abstract: Binge drinking is a significant societal problem that is defined as a pattern of drinking that brings blood alcohol levels (BALs) to 80 mg/dL or above. A history of chronic binge drinking may produce long term changes in the brain that result in increased susceptibility to alcohol and drug dependence. Many brain regions have been identified as critically involved in

alcohol drinking behavior. Recently the posterior cortical amygdala (pCOA), the ventrolateral periaqueductal gray (vlPAG), and the lateral habenula (Lh) have been identified as important in alcohol drinking behavior. However, we do not adequately understand the long-term protein signaling changes that occur binge-drinking after chronic binge-like drinking in the pCOA, vlPAG, and Lh. Thus, we sought to examine protein signaling changes in the pCOA, vlPAG, and Lh after 12 weeks of chronic binge-like drinking, using the 'Drinking in the Dark' (DID) mouse model, followed by Liquid Chromatography (LC)/Mass Spectrometry (MS) analysis of brain tissue. C57BL/6J mice (n=20; 10 male, 10 female) underwent 12 weeks of DID behavior. Each week consisted of drinking sessions beginning 3 hours into the dark cycle, with 3 days of 2-hour single-bottle access to 20% w/v alcohol, followed by 1 day of 4-hour single-bottle access to 20% w/v alcohol. The average amount of alcohol consumed on the final binge-like drinking day was 10.6±0.76 g/kg alcohol and the average BAL achieved each week was 104.87±10.24 mg/dL. After 12 weeks of chronic binge-like alcohol drinking, brains from the DID mice and age-matched alcohol naive control mice (n=16; 8 male, 8 female) were collected and snap frozen. Brain tissue from each target brain region (pCOA, vlPAG, and Lh) was then punched in order to process with LC/MS. Punches were stored at -80 degrees Celsius until processed by LC/MS for proteomic analysis. Brain tissue is currently being analyzed through Maxquant software to identify significant changes in protein signaling caused by chronic binge-like alcohol drinking. We expect to identify several proteins of interest that have had protein signaling significantly altered by binge-like drinking. The identified proteins of interest will be ideal targets for future binge-like drinking studies.

Disclosures: T. Xiao: None. **Y. Chen:** None. **A. Boisvert,:** None. **E. Knorr:** None. **A.J. Kimbrough:** None.

Poster

150. Molecular Mechanisms Underlying Alcohol Use

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 150.09

Topic: G.09. Drugs of Abuse and Addiction

Support: R01AA026256

Title: The role of endogenous neurosteroids in the bla mediating the effects of alcohol

Authors: *K. BLANDINO, J. MAGUIRE;
Tufts Med. Ctr., Boston, MA

Abstract: Alcohol use disorder is a major public health concern worldwide. In addition to causing a range of diseases such as liver disease and hypertensive disease, there is a high comorbidity with psychiatric disorders such as schizophrenia, anxiety and depression. The basolateral amygdala (BLA) has been implicated in both mood and alcohol use disorders; however, the mechanisms contributing to the shared pathophysiology remain unknown.

Extensive evidence indicates that ethanol modulates GABAergic signaling, including in the BLA, which has been suggested to mediate many of the behavioral effects, likely through actions on neurosteroid-sensitive, extrasynaptic $GABA_A$ receptors (δ-$GABA_A$Rs). Like alcohol, 5α-reduced neurosteroids, such as allopregnanolone, are potent modulators of $GABA_A$Rs, and studies have suggested that 5α-reduced neurosteroids mediate some of the behavioral effects of alcohol. This project leverages novel tools to directly examine the role of endogenous neurosteroid synthesis in mediating the effects of alcohol and contribution to withdrawal-induced anxiety. Here we employ a chronic intermittent ethanol (CIE) vapor model to establish alcohol dependence in mice and examine the impact on the capacity for endogenous neurosteroidogenesis. We demonstrate that CIE vapor induced dependence reduces the expression of 5α-reductase type 1 (5A1) both at the protein and mRNA level in the BLA. We also examine the impact of the reduced capacity for endogenous neurosteroid synthesis, using novel, conditional knockout mouse models of 5A1 and 5a-reductase type II (5A2) to examine the impact on the effects of alcohol and alcohol withdrawal-induced anxiety. This project provides insight into the role of endogenous neurosteroidogenesis in mediating the effects of alcohol from both a molecular and behavioral perspective.

Disclosures: K. Blandino: None. **J. Maguire:** None.

Poster

150. Molecular Mechanisms Underlying Alcohol Use

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 150.10

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH Grant R01AA016959
NIH Grant R01 AA025591
NIH Grant R01AG062716

Title: Neuroimmune effects of binge-like alcohol exposure in aged male rats

Authors: *E. R. CARLSON, J. K. MELBOURNE, C. ANASOOYA SHAJI, L. K. FONKEN, K. NIXON;
Pharmacol. and Toxicology, The Univ. of Texas at Austin, Austin, TX

Abstract: As the percentage of the global population age 65+ grows, and rates of problematic alcohol drinking in this group increase, understanding how alcohol interacts with the aging brain is of urgent concern. Neuroimmune activation is implicated in both natural aging as well as alcohol misuse, and its role in alterations to brain morphology and function may be exacerbated by excessive alcohol use in the aging brain. Here, we examined the Majchrowicz model of binge-like alcohol exposure in aged (25 mo) male F344BN rats, the preferred strain in the aging field due reduced neuropathology and increased longevity, to investigate microglia reactivity and neurodegeneration. Rats received alcohol (25% w/v in Vanilla Ensure Plus®) or isocaloric diet

every 8 h for 4 days with doses adjusted based on the severity of behavioral intoxication (initially 5 g/kg, i.g., 0-4 g/kg if more intoxicated). Peak blood alcohol concentrations were similar to young adult male Sprague Dawley rats in this model (368.1 ± 13.7 mg/dl), while behavioral intoxication scores appeared more varied. Hippocampal tissue collected two days post-ethanol revealed a surprising lack of active cell death (FJB+) across ethanol and vehicle (or unbinged) control groups. In hippocampal dentate gyrus molecular layer (DG-ML), soma size of Iba1+ microglia was increased with ethanol treatment. Further, MHC II+ cell number was decreased in the cornu ammonis layer 3 (CA3), which could reflect a loss of microglia as has been reported after binge exposure in young adult and adolescent rats. A preliminary survey of Iba1+ cell morphology in CA3 indicated the presence of some microglia with spheroidal swellings (initial stage of cytorrhexis/dystrophy) in both control and ethanol groups which may contribute to this loss of MHC II. Finally, a major change associated with aging is increased sensitivity and time to recovery following an insult, including alcohol use. Indeed, this model of binge alcohol use was not well tolerated in the aged rats, with greater attrition than typical. This preliminary study revealed several indices of a differential neuroimmune response following binge-like alcohol exposure in aged male rats, which may impact neurodegeneration and recovery from alcohol.

Disclosures: E.R. Carlson: None. **J.K. Melbourne:** None. **C. Anasooya Shaji:** None. **L.K. Fonken:** None. **K. Nixon:** None.

Poster

150. Molecular Mechanisms Underlying Alcohol Use

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 150.11

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH Grant R01AA025718
FONDECYT 1211082
FONDECYT 1201577
Beca Doctorado Nacional ANID 21190807

Title: The overexpression of glycine alpha 1 containing receptors in the nucleus accumbens reduces ethanol drinking in mice

Authors: *A. ARAYA MARTÍNEZ[1], S. S. GALLEGOS[1], A. MALDONADO[2], M. RIVERA[2], R. CHANDRA[3], M. LOBO[3], L. G. AGUAYO[1];
[1]Physiol., Univ. de Concepcion, Concepcion, Chile; [2]Dept. of Pharmacol. and Toxicological Chem., Univ. de Chile, Santiago, Chile; [3]Anat. and Neurobio., Univ. of Maryland Sch. of Med., Baltimore, MD

Abstract: The nucleus accumbens (nAc) is a critical region in the brain reward system since it integrates abundant synaptic inputs contributing to the control of neuronal excitability in the circuit. Alpha1 glycine receptors (alpha1GlyRs) are potentiated by ethanol through a mechanism

where ethanol increases free G beta-gamma dimers that interact with two basic lysine residues (385-386) from the intracellular domain responsible for producing the reversible enhancement of Cl^- conductance. The alpha1 Knock-In (alpha1KI) mouse model has a global mutation in the alpha1GlyRs in which lysine residues at position 385-386 are replaced with alanine resulting in an animal that exhibits an elevated ethanol consumption. The recent characterization of GlyRs present in the nAc have shown that they are sensitive to ethanol potentiation, but this characteristic was not found in the alpha1KI mouse model. These data support the idea that GlyRs expressed in the nAc play a protective role in controlling ethanol consumption. Using adeno associated virus (AAV) to overexpress the wild type (WT) alpha1GlyR subunit in the nAc of alpha1KI mice, or Cre-inducible AAV carrying an ethanol insensitive GlyR subunit to overexpress in the D1-Cre mice, we assessed ethanol consumption and electrophysiological properties. Injection of an Cre-inducible AAV carrying an ethanol insensitive alpha1 subunit, or alpha2shRNA, to knock down alpha2, in D1 Cre neurons was unable to affect sensitivity to ethanol in GlyRs or affect ethanol drinking. On the other hand, using an AAV that transduced WTalpha1GlyRs in GABAergic neurons in the nAc of high-ethanol consuming mice caused a reduction in ethanol intake as reflected by a decreased drinking in the dark and reduced blood ethanol concentration. As expected, the AAV increased the glycine current density by 5-fold without changing the expression of $GABA_A$ receptors. Ethanol sensitivity in dissociated accumbal neurons indicated that the GlyRs phenotype changed from an ethanol resistant to an ethanol sensitive type. These results support the conclusion that increased inhibition in the nAc can control excessive ethanol consumption and that selective targeting of GlyRs by pharmacotherapy might provide a mechanistic procedure to reduce ethanol abuse disorders.

Disclosures: **A. Araya Martínez:** None. **S.S. Gallegos:** None. **A. Maldonado:** None. **M. Rivera:** None. **R. Chandra:** None. **M. Lobo:** None. **L.G. Aguayo:** None.

Poster

150. Molecular Mechanisms Underlying Alcohol Use

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 150.12

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH-COBRE P20 GM103642
NSF 1736026
NIH-RISE 5R25GM061151
NIGMS P20GM103475
NSF Grant 1633184
NSF Grant 2131647

Title: The role of Tip60 in mechanisms of alcohol-induced sleep disruption

Authors: *C. D. DEL VALLE-COLÓN, S. I. MORALES-CANCIO, M. J. ÁLVAREZ-CORTÉS, A. MONTES-MERCADO, J. A. RODRÍGUEZ-CORDERO, J. L. AGOSTO, A.

GHEZZI;
Dept. of Biol., Univ. of Puerto Rico, Rio Piedras, San Juan, PR

Abstract: The uncontrolled consumption of alcohol affects neurological, physiological, and behavioral processes in the body that can affect young people and adults. Alcohol consumption leads to a homeostatic imbalance in the body, followed by the development of adaptations in the brain that lead to alcohol tolerance and physiological dependence. These adaptations can also affect the maintenance of circadian rhythms and sleep, which presents a major problem in the recovery from alcoholism. The modulation of gene expression has emerged as an important mechanism in the development of brain adaptations that produce alcohol-induced behavioral changes. Nonetheless, much of the epigenetic mechanisms that control the transcriptional reprogramming in alcohol-induced neuroadaptations remain unexplored. In this study, we aim to determine the role of the histone acetyltransferase Tip60 during alcohol-induced disorders using a *Drosophila* model. We focus our study on the lateral ventral neurons (LNv), which are a small group of neurons known for regulating sleep/wake cycles in *Drosophila*. We use the UAS-Gal4 genetic manipulation system and RNAi against Tip60 to knockdown Tip60 expression in the LNv neurons (pdf-Gal4/UAS-Tip60-RNAi). Using an activity monitor, we measured the effects of this manipulation in the sleep profile and alcohol sensitivity and tolerance in age-matched adult female flies. We found that Tip60 knockdown flies display significant sleep disruption, increased alcohol sensitivity and reduced alcohol tolerance. These results suggest that Tip60 is involved in the regulation of alcohol-induced sleep disruption and the development of alcohol tolerance. Collectively, this study can help identify new therapeutic targets for treating alcohol-induced sleep disorders.

Disclosures: C.D. Del Valle-Colón: None. **S.I. Morales-Cancio:** None. **M.J. Álvarez-Cortés:** None. **A. Montes-Mercado:** None. **J.A. Rodríguez-Cordero:** None. **J.L. Agosto:** None. **A. Ghezzi:** None.

Poster

150. Molecular Mechanisms Underlying Alcohol Use

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 150.13

Topic: G.09. Drugs of Abuse and Addiction

Support: AA020919
DA035958

Title: Role of a6-nicotinic receptors in alcohol-induced GABAergic synaptic plasticity in cholinergic interneurons in the nucleus accumbens

Authors: *H. A. WADSWORTH[1], E. Q. ANDERSON[1], J. T. WOOLLEY[1], J. W. RONSTRÖM[2], J. K. MOEN[5], A. M. LEE[6], J. MCINTOSH[7], J. T. YORGASON[3], S. C. STEFFENSEN[4];

[1]Brigham Young Univ., [3]Cell. Biol. and Physiol., [4]Dept of Psych and Neuro, [2]Brigham Young Univ., Provo, UT; [6]Pharmacol., [5]Univ. of Minnesota, Minneapolis, MN; [7]Univ. Utah, Salt Lake Cty, UT

Abstract: The prevailing view is that enhancement of dopamine (DA) transmission in the mesolimbic system, consisting of DA neurons in the ventral tegmental area (VTA) that project to the nucleus accumbens (NAc), underlies the reward properties of ethanol (EtOH) and nicotine (NIC). We have shown previously that EtOH modulation of DA release in the NAc is mediated by α6-containing nicotinic acetylcholine receptors (α6*-nAChRs), that α6*-nAChRs mediate low-dose EtOH effects on VTA GABA neurons and EtOH preference, and that α6*-nAChRs may be a molecular target for low-dose EtOH. Thus, the most sensitive target for reward-relevant EtOH modulation of mesolimbic DA transmission and the involvement of α6*-nAChRs in the mesolimbic DA reward system remains to be elucidated. The aim of this study was to evaluate EtOH effects on GABAergic modulation of VTA GABA neurons and VTA GABAergic input to cholinergic interneurons (CINs). Injecting DIO channel rhodopsin-2 (ChR2) viral constructs into the VTA of VGAT Cre mice, we found that VTA GABA neurons send an inhibitory projection to CINs, replicating what has been demonstrated by others. This study investigated the acute and chronic effects of EtOH at these inhibitory synapses. Low-dose EtOH enhanced GABAergic input to VTA GABA neurons via typical $GABA_A$ receptors that was blocked by knockdown of α6*-nAChRs by α6shRNA or superfusion of the α6-conotoxin MII[H9A;L15A]. VTA GABA neurons expressing α6*-nAChRs projected to NAc CINs and EtOH reduced GABAergic input to CINs via atypical $GABA_A$Rs. Ethanol enhanced CIN firing rate which was blocked by knockdown of α6*-nAChRs or MII. CIN-mediated light evoked DA release was decreased with application of EtOH, which effect was blocked by α6-conotoxin MII[H9A;L15A]. This study also investigated plasticity at this VTA-NAc GABAergic synapse. The baseline firing rate of CINs was markedly enhanced by knockdown of α6*-nAChRs, CINs were not activated by EtOH in EtOH-dependent mice, and low frequency stimulation (LFS; 1 Hz, 240 pulses) caused inhibitory long-term depression at this synapse (CIN-iLTD) which was blocked by knockdown of α6*-nAChRs, MII, atypical GABA receptor antagonists, and in EtOH-dependent mice. Taken together, these findings suggest that EtOH affects the VTA GABAergic projection to CINs via α6*-nAChRs and that atypical GABA receptors play a role in plasticity associated with chronic EtOH at this synapse.

Disclosures: H.A. Wadsworth: None. **E.Q. Anderson:** None. **J.T. Woolley:** None. **J.W. Ronström:** None. **J.K. Moen:** None. **A.M. Lee:** None. **J. McIntosh:** None. **J.T. Yorgason:** None. **S.C. Steffensen:** None.

Poster

150. Molecular Mechanisms Underlying Alcohol Use

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 150.14

Topic: G.09. Drugs of Abuse and Addiction

Support: AA020919
DA035958

Title: Peripheral mechanoreceptor activation alters chronic ethanol-induced changes to VTA GABA neurons, NAc dopamine release, & measures of withdrawal in rats

Authors: *S. C. STEFFENSEN[1], D. Z. OTTESON[2], G. C. JONES[3], C. A. SMALL[4], J. H. BATES[5], M. L. BLOTTER[1], K. B. BILLS[6];
[2]Biomed. Sci., [3]Neurosci., [4]Psychology, [1]Brigham Young Univ., Provo, UT; [5]Psychology, Brigham Young Univ. Neurosci. Ctr., Provo, UT; [6]Dept. of Biomed. Sci., Noorda Col. of Osteo. Med., Springville, UT

Abstract: There is growing evidence that mechanical stimulation (MStim) modalities (osteopathic and chiropractic manipulation, acupuncture & physical therapy) modulate substrates in the supraspinal central nervous system (CNS) that are outside the canonical somatosensory circuits. The aim of this study was to evaluate the effects of MStim applied to the cervical spine on neurons & neurotransmitter release in the mesolimbic dopamine (DA) system, an area implicated in reward & motivation. Utilizing electrophysiological, pharmacological, & neurochemical techniques, in male Wistar rats, we demonstrate that low frequency (45-80 Hz), but not higher frequency (115 Hz), peripheral MStim to the lower cervical spine depresses firing of ventral tegmental area (VTA) GABA neurons (52.8% baseline; 450 sec), increases VTA DA firing (248% baseline; 500 sec), increases both basal (178.43 % peak increase at 60 min) & evoked DA release in the nucleus accumbens (NAc; 135.03 % peak increase at 40 min), & enhances the expression and translocation of δ-opioid receptors on cholinergic interneurons in the NAc. Furthermore, MStim-induced DA release was mediated, in part, by endogenous opioid & acetylcholine release in the NAc, suggesting a role for cholinergic interneurons. Additionally, peripheral MStim administered concurrently with alcohol altered ethanol (EtOH)-induced desensitization of VTA GABA neuron firing rate in response to a reinstatement dose of EtOH (2.5 g/kg;IP) from 117.5 % of baseline to 32.3 %. Dopamine release in the NAc at 20 min post-injection was changed from 95.4% of baseline to 144.4 % & at 80 min from 104.1% to 138.2%. Further, behavioral indices of EtOH withdrawal (e.g., rearing, open-field crosses, tail stiffness, & gait) were substantively ameliorated with concurrent MStim treatment. These findings support the role of non-canonical somatosensory mechanoreceptor activation in modulating mesolimbic structures & the amelioration of EtOH withdrawal neuronal, neurochemical, & behavioral indices.

Disclosures: S.C. Steffensen: None. **D.Z. Otteson:** None. **G.C. Jones:** None. **C.A. Small:** None. **J.H. Bates:** None. **M.L. Blotter:** None. **K.B. Bills:** None.

Poster

150. Molecular Mechanisms Underlying Alcohol Use

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 150.15

Topic: G.09. Drugs of Abuse and Addiction

Support: NIAAA R01AA024434
NIAAA 1F31AA030219-01
IMSD: 5R25GM083270-11 (MPI
Robert J. and Nancy D. Carney Institute for Brain Science Innovation Award
Daniel C. Cooper Carney Graduate Award

Title: Alcohol-induced Alternative Splicing in Drosophila Memory Circuits

Authors: *T. M. BROWN[1], E. PETRUCCELLI[5], J. S. HERNANDEZ[2], S. J. GRATZ[2], A. G. WATERMAN[3], K. M. O'CONNOR-GILES[3], K. R. KAUN[4];
[1]Brown Univ., Brown Univ., PROVIDENCE, RI; [3]Neurosci., [2]Brown Univ., Providence, RI; [4]Neurosci., Brown Univ., Barrington, RI; [5]Biol. Sci., Univ. of Edwardsville, Illinois, Edwardsville, IL

Abstract: Repeated alcohol experiences produce long-lasting memories for sensory cues associated with intoxication. These memories can problematically trigger relapse in individuals recovering from alcohol use disorder (AUD). The molecular mechanisms underlying these sensory memories are not fully understood. We recently demonstrated that formation of ethanol-associated memories induces alternative splicing of the *Drosophila Dopamine 2-like receptor* (*Dop2R*) in mushroom body (MB) neurons, which encode odor memories in *Drosophila melanogaster*. Knocking down *Dop2R* or genes required for alternative splicing in MB neurons reduces ethanol-memory formation. This suggests that splicing of *Dop2R* impacts memory formation within MB neurons. In order to understand the functional consequences of *Dop2R* alternative splicing, we generated mutant *Drosophila* that have forced expression of the naive or trained isoform of *Dop2R*. We hypothesized that mutants expressing the isoform that is expressed after ethanol exposure would show greater motivational response for ethanol. We tested this using a new odor cue-ethanol Pavlovian three-choice test assay, and a novel operant ethanol vapor self-administration assay. From our preliminary results, we found that ethanol trained isoform mutants have greater preference for the ethanol-paired odor compared to the naïve isoform-expressing mutants (n = 120, 4-5-day-old males per strain). Similarly, mutants expressing the trained isoform escalate alcohol self-administration at a higher rate compared to mutants expressing the naïve isoform (n = 72, 6-day-old males per strain). Our results suggest that alcohol-induced alternative splicing of *Dop2R* in memory circuits enhances ethanol seeking and self-administration. These findings point to a functional role for the dynamic splicing of Dopamine 2 Receptors within the nervous system and its role in motivational response. This may provide a foundation for understanding the association between human polymorphisms associated with aberrant splicing of the Dopamine 2 Receptor, and higher susceptibility to developing AUD.

Disclosures: T.M. Brown: None. **E. Petruccelli:** None. **J.S. Hernandez:** None. **S.J. Gratz:** None. **A.G. Waterman:** None. **K.M. O'Connor-Giles:** None. **K.R. Kaun:** None.

Poster

150. Molecular Mechanisms Underlying Alcohol Use

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 150.16

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH Grant 5R01MH115604
NIH Grant 5R01NS105470

Title: Ethanol triggers motor attacks in a mouse model of episodic ataxia type 2 via a CK2-dependent mechanism

Authors: *J. O. TINDI, H. D. SNELL, K. KHODAKHAH;
Dominick P. Purpura Dept. of Neurosci., Albert Einstein Col. of Med., Bronx, NY

Abstract: Alcohol is the most used psychoactive drug in the world but its mechanism of action remains unknown. In a subset of movement disorders such as episodic ataxia type 2, ethanol triggers severe and debilitating motor attacks, whereas in others, for example myoclonus dystonia, ethanol improves motor function. As such, understanding the mechanism of action of ethanol is important from a global health perspective but also for elucidating mechanisms underlying trigger-induced motor dysfunction and developing therapies for other movement disorders. To begin to address this, we used the well-characterized *tottering* mouse model of episodic ataxia type 2 (EA2) that exhibits motor attacks in response to ethanol, stress or caffeine. Like in the human disorder, this model results from a loss-of-function mutation in the *CACNA1A* gene which encodes the P/Q-type voltage-gated calcium channel (Cav2.1). The cerebellum, and in particular Purkinje cells, are a key driver of motor dysfunction in *tottering* mice. A major target of ethanol in the cerebellum is γ-aminobutyric acid (GABA)-mediated transmission. Ethanol can increase the activity of δ-subunit containing type A GABA receptors (δ-$GABA_A$Rs) which mediate tonic inhibition, increase presynaptic release of GABA by inhibiting nitric oxide synthase, increase astrocytic production of GABA from ethanol metabolites, or directly decrease the activity of synaptic $GABA_A$Rs. We therefore hypothesized that ethanol may trigger motor attacks in *tottering* mice by modulating GABAergic transmission. Using pharmacology we found that manipulating GABAergic transmission at various nodes was not sufficient to trigger motor attacks. Stress triggers motor attacks in *tottering* mice through norepinephrine activation of α1 adrenergic receptors on Purkinje cells that in turn increase Purkinje cell irregularity via a Casein Kinase 2 (CK2)-dependent mechanism. CK2 regulates small calcium activated potassium channels (SK2) that control the regularity of Purkinje cell pacemaking and ability to encode information. We found that shRNA-mediated knockdown of CK2 in the cerebellum also blocks ethanol-induced attacks in *tottering* mice, suggesting that CK2 activity is required for ethanol to trigger motor attacks. Although ethanol readily enters cells and can directly affect enzymatic activity, we found that ethanol does not affect the kinase activity of recombinant CK2 *in vitro*, suggesting that ethanol triggers attacks by indirectly activating CK2. Further work is necessary to uncover the mechanism by which ethanol triggers CK2 activation. This may help elucidate the pathophysiology of EA2 and inform disorders where ethanol is therapeutic.

Disclosures: J.O. Tindi: None. **H.D. Snell:** None. **K. Khodakhah:** None.

Poster

150. Molecular Mechanisms Underlying Alcohol Use

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 150.17

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: AA024695
AA026665
AA027111

Title: Ethanol induced transcriptomic changes in the cerebellum during the onset and progression of fetal alcohol spectrum disorders using a postnatal mouse model

Authors: *K. HOLLOWAY[1], M. PINSON[2], J. DOUGLAS[1], T. RAFFERTY[1], R. MIRANDA[2], P. DREW[1];
[1]Univ. Of Arkansas For Med. Sci., Univ. Of Arkansas For Med. Sci. Dept. of Neurobio. and Develop. Sci., Little Rock, AR; [2]Texas A&M Univ. Col. of Med., Bryan, TX

Abstract: Fetal alcohol spectrum disorders (FASD) result from ethanol exposure *in utero*. FASD occur in up to 1-5% of live births in the United States and there currently is no cure. Ethanol is suggested to be an activator of neuroinflammation, resulting in widespread neuropathology, affecting learning, memory, impulse control, and motor function which can last a lifetime. Previously, we have shown that ethanol induces an increase in proinflammatory molecules in the cerebellum in a postnatal mouse model of FASD in which mice were treated with ethanol from P4-9 and cerebelli harvested on P10. In the current study, we utilized a similar third trimester equivalent neonatal mouse model of FASD to unveil changes in the cerebellum transcriptome during the onset and progression of FASD. C57BL/6 neonates were administered a daily gavage of 4g/kg ethanol or water vehicle on postnatal (PN) days 4-9 and cerebellar tissue was harvested on PN days 5, 6, 8, 10, 15, and 60. mRNA expression changes were analyzed by RNAseq and global biological pathway analysis. These analyses reveal increased expression in inflammatory and cell death related molecules and their associated pathways early during the time course. The expression of cell adhesion, cell migration, and cell cycle related molecules and their associated pathways were altered later in the time course. These results suggest that ethanol may alter the expression of specific molecules in a time-dependent manner that may contribute to the neuropathology associated with FASD.

Disclosures: K. Holloway: None. **M. Pinson:** None. **J. Douglas:** None. **T. Rafferty:** None. **R. Miranda:** None. **P. Drew:** None.

Poster

151. Nicotine: Neural Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 151.01

Topic: G.09. Drugs of Abuse and Addiction

Support: NIDA-IRP
FDA Grant NDA13001-001-00000

Title: Relationship between affective and behavioral composite factors and dynamic resting-state functional connectivity in sated and acutely abstinent smokers

Authors: *L. G. RODRIGUEZ[1], J. R. FEDOTA[1], T. J. ROSS[1], B. SALMERON[1], H. U. DESHPANDE[2], E. A. STEIN[1];
[1]Natl. Inst. on Drug Abuse, Baltimore, MD; [2]McLean Hosp., Harvard Med. Sch., Boston, MA

Abstract: In order to transition into long-term abstinence, cigarette smokers must overcome the severe affective and cognitive disruptions manifest during acute smoking abstinence. A better understanding of the neurobiological mechanisms and their relationship to various withdrawal symptoms could improve treatment efficacy and outcome success. Fedota et al. (2021) used time-varying functional connectivity (TVFC) of resting-state fMRI (rsfMRI) to assess nicotine state-related differences in communication between brain networks and related these to simple measures of affect and behavior. In order to accomplish this, they calculated two nodal-level measures of TVFC for 240 nodes at a nicotine-sated baseline and while 48hrs abstinent. Treating this as a discovery dataset, we applied Principal Component Analysis on these data to reduce the problem space and identify a smaller set of brain nodes that show significant changes with abstinence. One component from the TVFC data showed an effect of nicotine state, we selected the top 15 brain regions that preferentially loaded onto this component to focus on for subsequent analyses in our independent test dataset. In parallel, using the behavioral data from the discovery dataset, we used Factor Analysis to categorize 25 variables spanning multiple characterization questionnaires and behavioral tasks into composite factors to capture an abbreviated set of values that represent smokers' feelings and performance during smoking satiety and 48hrs abstinence. We identified several composite factors that changed as a function of nicotine state. Specifically, Factor 1 and Factor 2 significantly increased during abstinence with the first preferentially loading multiple non-craving related affective variables while the second loaded for multiple craving assessments. We hypothesized that there is a relationship between metrics of recurring connectivity states and the behavioral dimensions uncovered in the discovery dataset. To test this hypothesis in the test dataset, we employed a similar TVFC approach to obtain dynamic FC matrices where each cell represents the pairwise correlations between the activity time courses of brain nodes within a 40s window of the 8min rsfMRI scan. These matrices were clustered to obtain four recurring states of connectivity. We found significant effects of nicotine state on both the occurrence probability of states and on switching probabilities between them. Potentially, we could be identifying a set of nodes whose interactions during rest can characterize broad changes in affect during acute nicotine abstinence, which could inform new hypothesis and/or be tested as treatment targets.

Disclosures: L.G. Rodriguez: None. **J.R. Fedota:** None. **T.J. Ross:** None. **B. Salmeron:** None. **H.U. Deshpande:** None. **E.A. Stein:** None.

Poster

151. Nicotine: Neural Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 151.02

Topic: G.09. Drugs of Abuse and Addiction

Support: Oklahoma TSET; Grant # R2-02
NCI Support Grant P30CA225520

Title: Does neural activation mediate the relationship between iron status and smoking cessation? ERP evidence

Authors: *L. K. BOOZARY[1,3], L. A. DE STEFANO[4], S. F. NEWBOLDS[1], M. M. MORGAN[2], A. L. BARNETT[1], D. E. KENDZOR[3], M. J. WENGER[1];
[1]Cell. and Behavioral Neurobiology, Psychology, [2]Psychology, Univ. of Oklahoma, Oklahoma City, OK; [3]TSET Hlth. Promotion Res. Ctr., Univ. of Oklahoma Hlth. Sci. Ctr., Oklahoma City, OK; [4]Dept. of Psychiatry, Cincinnati Children's Hosp. Med. Ctr., Cincinnati, OH

Abstract: Some research suggests that women are more likely than men to respond to financial incentives to quit smoking, despite having lower overall rates of smoking cessation. Research suggests that iron deficiency, common in females, may alter dopaminergic pathways involved in both reward processing and addiction. This suggests a potential mechanism for the sex difference in cessation rates. Participants (n=54) were recruited from a local 6-month smoking cessation treatment program. Participants were seen before attempting to quit smoking, at which time they performed cognitive tests sensitive to reward processing, including the Probabilistic Selection Task (PST). At this appointment, task performance was recorded along with concurrent EEG, and a small sample of blood was taken. Smoking cessation at 4-weeks post-quit was used as the smoking outcome of interest. The iron status variable of interest was percentile rank of the NHANES III age-, race-, and sex-specific distributions of inflammation-adjusted serum ferritin (sFtP). The feedback-related negativity (FRN) is an established electrophysiological marker reflecting changes in dopamine levels, yet has not been analyzed in relation to iron status and smoking cessation. For the current protocol, incorrect feedback-locked FRN amplitude was extracted from the EEG data recorded during the PST task. Regression models examined the extent to which 1) iron predicted FRN amplitude and 2) the extent to which FRN amplitude, controlling for iron, predicted likelihood of smoking abstinence. The first model regressed FRN amplitude onto sFtP and showed that iron is a significant predictor of FRN amplitude ($B=0.02$, $p=0.04$, $R^2=0.10$). The second model regressed abstinence onto FRN amplitude, sFtP, FRN amplitude*sFtP interaction, income, and baseline heaviness of smoking. The results show that FRN amplitude may predict abstinence ($B=1.33$, $p=0.07$, $\rho^2=0.12$). In sum, changes to neural activation known to reflect dysfunction in central dopamine are significantly predicted based on sFtP, and neural activation may be a significant predictor of smoking cessation. Follow-up analyses should consider whether neural dynamics could mediate the relationship between iron status and smoking cessation.

Disclosures: **L.K. Boozary:** None. **L.A. De Stefano:** None. **S.F. Newbolds:** None. **M.M. Morgan:** None. **A.L. Barnett:** None. **D.E. Kendzor:** None. **M.J. Wenger:** None.

Poster

151. Nicotine: Neural Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 151.03

Topic: G.09. Drugs of Abuse and Addiction

Support: NDA Training Grant T-32 (PAR-19-342)

Title: Rewarding and aversive nicotine doses increase neural activity in the interpeduncular nucleus in vivo

Authors: *R. MANSOURI-RAD[1], D. S. MCGEHEE[2];
[1]Univ. of Chicago, Chicago, IL; [2]Anesthesia, Univ. of Chicago Committee On Neurobio., Chicago, IL

Abstract: Tobacco smoking is the leading cause of preventable death worldwide and this persists due to the primary addictive component: nicotine. A human's response their initial exposure to nicotine can predict their likelihood of future use and dependence. In mice, acute injection of a high dose of nicotine (1.5 mg/kg) reliably results in behavioral aversion. Ex vivo techniques demonstrate that this aversion is mediated by activation of the interpeduncular nucleus (IPN), but this has not been investigated in vivo. We recorded IPN neuronal activity to high dose nicotine in awake, freely behaving mice using fiber photometry and the genetically encoded intracellular Ca 2+ indicator, GCaMP6s. We expressed GCaMP pan neuronally in the IPN and implanted an optical fiber above the nucleus in nicotine-naïve mice. Three mice were exposed the aversive high nicotine dose as their first nicotine expose, while the other half was exposed to a rewarding low dose (0.5 mg/kg). Both groups were then subjected to the alternate dose 24 hours later. IPN calcium fluorescence responses to nicotine were compared to saline injections prior to nicotine on each experimental day. As expected, the high dose of nicotine induced an increase in IPN calcium fluorescence relative to saline. Contrary to ex vivo studies, however, IPN calcium fluorescence also increased relative to saline in response to the low dose of nicotine regardless of order of presentation. Future studies will examine changes in nicotine-induced IPN response with repeated drug exposure, which could have relevance to thedevelopment of tolerance to the nicotine's aversive effects. We are also exploring the IPN responses to nicotine in female mice. Our previous studies demonstrated that optogenetic inhibition of IPN projections to brainstem tegmental areas is anxiolytic. Extending those observations, we have observed profound increases in IPN activity in response to natural anxiogenic stimuli, such as looming stimuli and novel objects. These studies are providing insight into the behavioral impact of IPN activity independent of nicotine exposure, which may provide a more complete understanding the determinants of nicotine's behavioral valence and the progression to addiction.

Disclosures: **R. Mansouri-Rad:** None. **D.S. McGehee:** None.

Poster

151. Nicotine: Neural Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 151.04

Topic: G.09. Drugs of Abuse and Addiction

Support: DePauw University

Title: Acetylcholine receptors in nicotine-seeking and avoidance behavior of larval zebrafish

Authors: *H. SCHNEIDER, D. RHODES, L. ARAYA, T. N. T. NGUYEN, L. WILLIAMS, I. AMALARAJ, A. BUTTON, Z. CAPPEL, E. KENNEDY;
Dept. of Biol., DePauw Univ., Greencastle, IN

Abstract: The first consumption of nicotine products can result in the liking or the avoiding of nicotine. A diminished aversive response to nicotine could lead to a continued use and potentially a dependence on nicotine. Nicotinic acetylcholine receptors appear to be involved in neural mechanism underlying the aversive response to nicotine. Mice with a gene knock-out of the alpha 3 nicotinic acetylcholine receptor (Chrna3) have been shown to have an increased consumption of nicotine. We explored if the chrna3 receptor could have a similar role in larval zebrafish. In an acute nicotine response test using Daniovision (Noldus), pre-treatment of larval zebrafish (wild-type) with the chrna3 antagonist SR16584 resulted in a reduced spontaneous movement activity. The relative increase of nicotine-induced (10 microM) movement activity in the acute nicotine response was stronger in SR16584 treated larval wild-type zebrafish. To better understand the role of the chrna3 receptor, we started to test a chrna3 mutant zebrafish line with a premature stop codon in a behavioral choice test using a gradient maze. The analysis of the tracks in gradient maze experiments using EthovisionXT (Noldus) has pointed to a stronger nicotine-seeking behavior compared to wildtype larval zebrafish. A single nucleotide polymorphism (SNPs) in the human CHRNA3 gene that had been associated with nicotine use could not be confirmed in the zebrafish chrna3 gene. The results indicate that the chrna3 gene could have a deciding role in the nicotine-choice behavior and whether a larval zebrafish is a nicotine-seeker or avoider.

Disclosures: **H. Schneider:** None. **D. Rhodes:** None. **L. Araya:** None. **T.N.T. Nguyen:** None. **L. Williams:** None. **I. Amalaraj:** None. **A. Button:** None. **Z. Cappel:** None. **E. Kennedy:** None.

Poster

151. Nicotine: Neural Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 151.05

Topic: G.09. Drugs of Abuse and Addiction

Support: Oklahoma TSET; Grant # R2-02
NCI Support Grant P30CA225520

Title: Neural correlates of iron status & smoking cessation: ERP evidence from the Iowa Gambling Task

Authors: *M. M. MORGAN[1], L. K. BOOZARY[2,3], L. A. DE STEFANO[4], S. F. NEWBOLDS[2], A. L. BARNETT[2], D. E. KENDZOR[3], M. J. WENGER[5];
[1]Psychology, [2]Cell. and Behavioral Neurobiology, Psychology, Univ. of Oklahoma, Norman, OK; [3]TSET Hlth. Promotion Res. Ctr., Univ. of Oklahoma Hlth. Sci. Ctr., Oklahoma City, OK; [4]Psychiatry, Cincinnati Children's Hosp. Med. Ctr., Cincinnati, OH; [5]Ctr. for Applied Social Res., Univ. of Oklahoma Cell. and Behavioral Neurobio., Norman, OK

Abstract: Some research suggests that women are more likely than men to respond to financial incentives to quit smoking, despite having lower overall rates of smoking cessation. Research suggests that iron deficiency, most commonly occurring in females, may alter dopaminergic pathways involved in both reward processing and addiction. This suggests a potential mechanism driving the sex difference in cessation rates. The present study examines the extent to which iron status predicts variations in neural dynamics, and whether both of these can predict smoking cessation outcomes. Participants (n=54) were recruited from a local smoking cessation clinic and followed for 6 months post-quit (PQ). Participants completed a baseline visit before their scheduled quit date (QD; the first target date of cessation which occurs about 7 days after enrollment), at which they performed cognitive tests sensitive to reward processing, including the Iowa Gambling Task (IGT). At this appointment, task performance was recorded alongside concurrent EEG. Participants also gave a small sample of blood. Smoking cessation at 4-weeks PQ was used as the smoking outcome of interest. The iron status variable of interest was percentile rank of the NHANES III age-, race-, and sex-adjusted distributions of serum ferritin (sFtP). The error-related negativity (ERN) is an established electrophysiological marker reflecting changes in dopamine levels (i.e. reduced amplitude corresponding to decreased dopaminergic activity following error response and error feedback), yet has not been analyzed in relation to iron status. For the current protocol, CRN (correct-related negativity), ERN, and FRN (feedback-related negativity) were extracted from the EEG data recorded during the IGT task, locked to correct responses, error responses, and loss/gain feedback, respectively. Regression models examined 1) iron status as a predictor of CRN/ERN/FRN, and 2) iron status and CRN/ERN/FRN as predictors of smoking cessation. The results from these analyses were consistent with the hypothesis that iron status predicts neural dynamics, which supports inferences about dopamine levels. Additionally, both iron status and neural dynamics could predict smoking cessation at 4-weeks PQ. Thus, follow up analyses should consider whether neural dynamics mediate the relationship between iron status and smoking cessation. In sum, being low in iron may represent an additional burden to females attempting to quit smoking.

Disclosures: **M.M. Morgan:** None. **L.K. Boozary:** None. **L.A. De Stefano:** None. **S.F. Newbolds:** None. **A.L. Barnett:** None. **D.E. Kendzor:** None. **M.J. Wenger:** None.

Poster

151. Nicotine: Neural Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 151.06

Topic: G.09. Drugs of Abuse and Addiction

Support: Basic Science Research Program through the National Research Foundation (NRF) of Korea funded by the Ministry of Science, ICT, & Future Planning 2018R1C1B3007313
National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) 2021M3E5D2A0102249311
Creative Pioneering Researchers Program through Seoul National University

Title: Alterations in striatal resting state functional connectivity are associated with successful smoking cessation outcome

Authors: *J. J. IM[1], H. KIM[1], J.-H. LEE[1], H. PARK[3,4], H.-K. JOH[5,6], W.-Y. AHN[1,2]; [1]Dept. of Psychology, [2]Dept. of Brain and Cognitive Sci., Seoul Natl. Univ., Seoul, Korea, Republic of; [3]Dept. of Family Med., SMG-SNU Boramae Med. Ctr., Seoul, Korea, Republic of; [4]Dept. of Family Med., Seoul Natl. Univ. Hlth. Service Ctr., Seoul, Korea, Republic of; [5]Dept. of Med., Seoul Natl. Univ. Col. of Med., Seoul, Korea, Republic of; [6]Dept. of Family Med., Seoul Natl. Univ. Hosp., Seoul, Korea, Republic of

Abstract: Tobacco smoking is a major cause of death and diseases globally. Despite the negative consequences, the success rate of smoking cessation is very low. Developing an effective treatment for nicotine dependence is a public health priority, yet relatively little is known about the neural mechanisms that contribute to successful smoking cessation. The striatum has been identified as a critical hub for reward processing and motivation and has been considered to play an important role in addictive disorders, including nicotine dependence. The goal of this study was to investigate whether smokers who abstained during a quit attempt show different striatum-based functional connectivity compared to those who relapsed. In the present study, 48 smokers underwent resting state functional magnetic resonance imaging (fMRI) scans before and after a 5-week smoking cessation program where they received medication-assisted outpatient treatment. After a 5-week quit attempt, 38 participants relapsed and 10 participants did not relapse to smoking. A mixed ANCOVA was conducted with group (relapse vs non-relapse) as a between-subjects factor and time (pre vs post) as a within-subjects factor, controlling for age and gender. Significant interaction effects were found: (1) between right putamen and right superior frontal gyrus, (2) between left putamen and right medial superior frontal gyrus, (3) between left caudate and left supramarginal gyrus, and (4) between left caudate and left middle temporal gyrus. Post-hoc analysis revealed that these interactions were mainly driven by a

decrease in striatal functional connectivity post-treatment compared to pre-treatment in the non-relapse group. These findings suggest that modulation of striatal connectivity may be associated with smoking cessation outcomes.

Disclosures: **J.J. Im:** None. **H. Kim:** None. **J. Lee:** None. **H. Park:** None. **H. Joh:** None. **W. Ahn:** None.

Poster

151. Nicotine: Neural Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 151.07

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH Grant DA044242

Title: Dopamine D2-like receptor-mediated dopamine transmission is involved in reinforcing effects of cotinine in rats

Authors: *Z. DING, X. TAN, E. NESLUND;
Penn State Univ. Col. of Med., Hershey, PA

Abstract: Background: Previous research from our lab indicates that activation of mesolimbic dopamine system is involved in the reinforcing effects of cotinine, the major metabolite of nicotine. Passive administration of cotinine into the ventral tegmental area or systemically increased extracellular dopamine levels in the nucleus accumbens (NAc). However, it remains unknown whether active self-administration of cotinine would alter NAc extracellular dopamine levels. Pharmacological blockade of dopamine D1-like receptors reduced intravenous self-administration of cotinine, but the involvement of dopamine D2-like receptors has not been determined. The objective of the current study is to further characterize the role of mesolimbic dopamine system in cotinine reinforcement. **Method:** Effects of cotinine self-administration on NAc extracellular dopamine levels were examined with microdialysis during ongoing self-administration of cotinine. Nicotine self-administration was used as a positive control. Both nicotine and cotinine were self-administered at 0.03 mg/kg/infusion. To determine the involvement of dopamine D2-like receptors in cotinine reinforcement, a D2-like receptor antagonist, eticlopride (0, 5, 10 μg/kg), was tested during cotinine self-administration and cue-induced reinstatement of cotinine seeking. **Results:** Both nicotine and cotinine induced comparable active responses and number of infusions during self-administration. Microdialysis data indicate that NAc extracellular dopamine levels increased during self-administration of nicotine or cotinine. Maximal extracellular dopamine levels were 156% and 132% above baseline during nicotine and cotinine self-administration, respectively, with greater increase in nicotine than cotinine self-administration ($p < 0.05$). Systemic administration of eticlopride reduced number of infusions during cotinine self-administration (e.g., saline vs 10 μg/kg: 23 vs 7, $p < 0.05$) and attenuated active responses during cue-induced reinstatement of drug seeking

(e.g., saline vs 5 µg/kg: 58 vs 18, $p < 0.05$). **Conclusions:** These results indicate that ongoing self-administration of cotinine increased NAc extracellular dopamine levels, which was less robust than nicotine self-administration. Pharmacological blockade of D2-like receptors reduced reinforcing effects of cotinine. These data provide additional evidence that activation of mesolimbic dopamine system plays a critical role in mediating cotinine reinforcement.

Disclosures: Z. Ding: None. **X. Tan:** None. **E. Neslund:** None.

Poster

151. Nicotine: Neural Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 151.08

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH R01 DK109930
NIH DP1 AT010971
Pew Charitable Trusts
NIH T32 GM007753

Title: Interoceptive representations of nicotine dependence and withdrawal in the insular cortex

Authors: *K. E. EVANS[1,2], D. GUARINO[2], M. PICCIOTTO[3], M. L. ANDERMANN[1,2]; [1]Neurobio., Harvard Univ., Boston, MA; [2]Endocrinol., Beth Israel Deaconess Med. Ctr., Boston, MA; [3]Dept Pyschiat, Yale Univ., New Haven, CT

Abstract: The insular cortex (InsCtx) integrates sensory, visceral, and limbic information and is implicated in interoception: the sensing of internal bodily states. Interoception is critical to addiction because the rewarding effects of addictive drugs and the aversive aspects of withdrawal are largely experienced as bodily sensations. Functional imaging in human smokers has shown that InsCtx responses to smoking-related cues increase with self-reported craving intensity and with the expectancy of receiving nicotine. Nevertheless, it remains unclear how the InsCtx encodes nicotine-replete and withdrawal states during nicotine dependence. This gap in understanding is due in part to our inability to track the activity of large numbers of neurons throughout the development of dependence on and withdrawal from addictive drugs. I have overcome this challenge by adapting our lab's conceptual and technical framework for chronic two-photon calcium imaging of hundreds of InsCtx neurons during shifts in hunger/thirst to investigate InsCtx encoding of nicotine states and nicotine-predicting cues. To induce physiological nicotine dependence, I have implemented a model of chronic nicotine exposure via home-cage drinking water. *I have found that the InsCtx response to nicotine-predicting cues and oral nicotine delivery is distinct from the InsCtx response to water-predicting cues and water delivery.* Because nicotine has direct effects *centrally* on the brain as well as *peripherally* on bodily physiology, I am using natural and pharmacological manipulations to describe how the ongoing InsCtx activity patterns reflect both the central and peripheral actions of nicotine. These

experiments will advance our understanding of how InsCtx activity patterns change during the emergence of nicotine dependence, and how the neural representations associated with 'physiological satiety' change during the development of dependence.

Disclosures: K.E. Evans: None. **D. Guarino:** None. **M. Picciotto:** None. **M.L. Andermann:** None.

Poster

151. Nicotine: Neural Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 151.09

Topic: G.09. Drugs of Abuse and Addiction

Support: R37DA020686

Title: Nicotine CCK-ing: evidence for brain-body interactions underlying drug addiction

Authors: *K. M. BRAUNSCHEIDEL, M. R. ISHMAM, L. WILLS, P. J. KENNY;
Icahn Sch. of Med. at Mt. Sinai, NEW YORK, NY

Abstract: Background: Nicotine addiction in the form of habitual tobacco use is the leading cause of premature death in the United States. In addition to the direct effects of nicotine on hedonic neurocircuitry, recent evidence implicates aversion neurocircuitry and peripheral structures in nicotine habit formation. For instance, circulating cholecystokinin (CCK), an upper-gut satiety-signaling hormone, levels are disrupted in smokers following meal consumption. Yet, a causal relationship between the CCK system and smoking has not been explored. Here, we investigate the effect of CCK receptor (CCKR) manipulation on nicotine intake and hypothesize that CCKRs in gut-innervating vagal sensory neurons potentiates nicotine signal transmittance similar to CCK's regulation of appetite.
Methods: We used an enzyme immunoassay to detect plasma CCK levels in mice injected with either nicotine (1.5 $mg*kg^{-1}$,sc) or periphery-restricted nicotine receptor agonist, methylnicotinium (1.64 $mg*kg^{-1}$,sc). We then stimulated CCK receptors using the periphery-restricted agonist, CCK-8 (10 $\mu*kg^{-1}$,ip) or inhibited CCKRs with dexamethonium (200 $\mu g*kg^{-1}$,ip) and measured the effect on nicotine self-administration and conditioned place aversion. In a separate study, CCKR+ nodose ganglia were selectively ablated using CCK-saporin prior to testing nicotine-related behaviors. Finally, snRNAseq was performed on the nodose ganglia following a single nicotine or methylnicotinium injection.
Results: Nicotine and methylnicotinium increased postprandial, but not fasting plasma CCK concentrations. Enhancing peripheral CCKR signaling decreased, whereas systemic CCK receptor blockade or selective nodose CCK receptor-expressing neuronal knockout increased, nicotine related behaviors. Finally, a single nicotine injection drastically altered the transcriptional profile of the nodose ganglia.
Conclusions: Peripheral CCK receptors regulate nicotine intake due in part to actions on vagal

sensory afferents. The existence of this novel “bottom-up” regulation of nicotine intake by circulating hormones and the nodose ganglia may prove useful for the development of novel addiction therapies for two reasons: first, direct vagal stimulation has been validated as a treatment for other neurological disorders; and second, CCK levels & vagal activity can be altered by non-invasive means.
Funding: R37DA020686 (PJK)

Disclosures: **K.M. Braunscheidel:** None. **M.R. Ishmam:** None. **L. Wills:** None. **P.J. Kenny:** None.

Poster

151. Nicotine: Neural Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 151.10

Topic: G.09. Drugs of Abuse and Addiction

Support: R21 DA046184

Title: Inhibition of GABAergic interpeduncular nucleus neuronal projections to laterodorsal tegmental nucleus relieves nicotine withdrawal symptoms

Authors: *A. MONICAL[1], D. S. MCGEHEE[2];
[1]Med. Scientist Training Program, The Univ. of Chicago, Chicago, IL; [2]Anesthesia, Univ. of Chicago Committee On Neurobio., Chicago, IL

Abstract: SIGNIFICANCE: Understanding the neural mechanisms of nicotine withdrawal is important for developing more effective smoking cessation interventions. Previous research has shown that medial habenula (MHb) excitatory output to GABAergic neurons in the interpeduncular nucleus (IPN) is a key mechanism in development and maintenance of the nicotine withdrawal state. While IPN activity is enhanced, suppression of ventral tegmental area (VTA) dopamine (DA) signaling is one consequence of withdrawal. We hypothesize that IPN activation results in depressed dopamine signaling during nicotine withdrawal through suppression of the laterodorsal tegmental nucleus (LDTg), a presynaptic regulator of VTA DA neuron firing. **METHODS:** Chronic nicotine was administered to GAD2-Cre mice via drinking water for four weeks. After mecamylamine induced withdrawal, behaviors were monitored with and without optogenetic inhibition of the IPN GABAergic neurons synapsing within the LDTg. Activity of LDTg neurons was monitored using fiber photometry during nicotine withdrawal. Rabies virus mediated transsynaptic tracing was used to label the IPN neurons projecting to LDTg. **RESULTS:** Inhibition of IPN-LDTg projections in one chamber of a real-time preference apparatus during nicotine withdrawal resulted in more time spent in that chamber, which indicates a decrease in the negative affective state. This effect persists over three days of testing. Conditioned place testing revealed that preference was state-dependent, as the animals preferred the previously inhibition-paired chamber only when they were experiencing withdrawal. In

addition, optogenetic inhibition of IPN GABAergic terminals in LDTg normalized exploratory behavior, novel object interaction, social odor preference, and somatic withdrawal signs towards nicotine-naïve levels, suggesting a role of this circuit in withdrawal associated affective and physical behaviors. Fiber photometry recordings reveal an attenuation of LDTg activity to novelty following nicotine withdrawal that may be a result of enhanced GABAergic drive onto excitatory neurons within the LDTg. Consistent with this idea, rabies tracing of inputs to inhibitory neurons in the LDTg revealed only sparce labeling of IPN neurons.
CONCLUSIONS: GABAergic projections from IPN to LDTg mediate affective and somatic nicotine withdrawal in mice, as optogenetic inhibition of these terminals decreases severity of the withdrawal state.

Disclosures: A. Monical: None. **D.S. McGehee:** None.

Poster

151. Nicotine: Neural Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 151.11

Topic: G.09. Drugs of Abuse and Addiction

Support: Swedish Research Council Grant 2020-00559
Stiftelsen Wilhelm och Martina Lundgrens Vetenskapsfond Grant 2021-3870
Göteborgs Läkaresällskap Grant GLS-961765
Fredrik O Ingrid Thurings Stiftelse Grant 2020-00634

Title: Nicotinic modulation of neurotransmission in female rats -electrophysiological and behavioral measurements

Authors: *O. LAGSTRÖM, M. ERICSON, L. ADERMARK;
Inst. of Neurosci. and Physiol., Univ. of Gothenburg, Gothenburg, Sweden

Abstract: Nicotine is a highly addictive substance, and cigarette smoking is the leading preventable cause of death worldwide. Yet, most who try to quit relapse and available intervention approaches are limited. Great effort has been made to understand the nicotinic mechanisms, but mostly in male animals. However, tobacco use amongst women has increased for several years, and epidemiological studies have shown sex-differences in nicotine sensitivity, that may influence the vulnerability to tobacco addiction in a sex specific manner. Amongst smokers, men are suggested to be more reinforced by nicotine itself, whereas women report more negative effects, more cue-induced craving and more difficulties quitting. Progressive nicotine-induced adaptations in amygdalo-striatal circuits are suggested to reflect an increasing risk of relapse. This study aims to shed light on how chronic nicotine administration affects neurotransmission in striatal and amygdalar brain regions in female animals, and if the possible changes are persistent over time. To this end, 45 adult female rats were injected with nicotine (0.36mg/kg, subcutaneous), or saline, with a total of 15 injections, followed by a three-month

abstinence period. Behavioral effects of nicotine were assesed using locomotor activity measurements and elevated plusmaze, while neurophysiological changes were defined using e*x vivo* electrophysiological field potential recordings in striatal subregions and in the central nucleus of the amygdala. Behavioral assessments demonstrated a robust sensitization to the locomotor stimulatory properties of nicotine, while anxiogenic behavior was not affected during acute withdrawal. Electrophysiological recordings revealed a selective increase in excitatory transmission in the dorsomedial striatum and nucleus accumbens during the acute abstinence phase. Following protracted abstinence, however, these regions demonstrated a depression of neurotransmission, with a concomittant hyperexcitability of the central nucleus of the amygdala. Together, these findings suggest that nicotine-induced modulation of neurotransmission partly separate from previous findings in male animals, in brain regions associated with drug addiction. Understanding how nicotine transforms the brain in female animals allows us to more fully grasp the complexity of nicotine dependence and, in extension, provides new means to challenge nicotine addiction.

Disclosures: O. Lagström: None. **M. Ericson:** None. **L. Adermark:** None.

Poster

151. Nicotine: Neural Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 151.12

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH NIDA U01043802

Title: Mapping of modifiers that alter oral nicotine consumption in Chrna5 knockout mice

Authors: *H. L. MATHEWS[1], S. BELLATI[1], E. MYERS[1], Z. WERNER[1], M. BROWN[2], P. STARBUCK[2], J. A. STITZEL[3], R. A. RADCLIFFE[4];
[1]Univ. of Colorado Boulder - Inst. for Behavioral Genet., Boulder, CO; [3]Univ. of Colorado Boulder, [2]Univ. of Colorado Boulder, Boulder, CO; [4]Univ. of Colorado, Univ. of Colorado, Aurora, CO

Abstract: Expression of the α5 nAChR subunit, encoded by the gene Chrna5, is believed to play a role in the regulation of sensitivity to nicotine. In humans and rodents, reduced or complete loss of function of Chrna5 is associated with increased consumption of nicotine. Recently, we published a study examining nicotine consumption in a panel of C57BL/6J-Chr#A/J/NAJ chromosome substitution strains (CSS) in which the Chrna5 knockout (KO) allele was introgressed. The goal of this study was to screen for A/J chromosomes that possess alleles that modify the increase in consumption caused by Chrna5 deletion in mice with a C57BL/6J (B6) background. Results indicated that A/J chromosomes 1, 5 & 11 possess genetic modifiers that eliminate increased nicotine consumption caused by Chrna5 deletion in B6 background mice. A/J chromosome 1 also produced an overall reduction in nicotine consumption that was

independent of Chrna5 genotype. We also found that chromosome 17 likely possesses an allele or alleles that increase nicotine consumption independent of Chrna5 genotype. To narrow the chromosomal regions possessing the A/J alleles that impact nicotine consumption in these CSS Chrna5 KO mice, B6 Chrna5KO x CSS Chrna5KO F2 intercross mice were generated for 3 CSS of interest (CSS1, CSS11, CSS17) and these animals were assessed for oral nicotine consumption using a two-bottle choice paradigm. Genotyping was then performed for each appropriate chromosome and QTL mapping was conducted to localize chromosomal regions linked to nicotine consumption. Two significant QTL were identified in CSS1 F2 mice (Chr1:98.05 Mbp, LOD = 5.65, CI = 87.05-131.05 Mbp; Chr1:162.05 Mbp, LOD = 3.67, CI = 139.87-168.05 Mbp). Interestingly, one of the QTLs detected for CSS1 (162.05 Mbp) maps to the same location as a QTL we previously mapped for nicotine consumption in a different population of mice (B6 x C3H/HeJ F2) suggesting the the general effect of chromosome 1 on nicotine consumption may be driven by this QTL. Significant QTLs were also detected in both CSS 11 (Chr11:79.14 Mbp, LOD = 5.78, CI = 69.19-89.3 Mbp) and CSS17 (Chr17: 29.43 Mbp, LOD = 6.63, CI = 19.43-36.43 Mbp). Therefore, results of this study confirmed the effect of A/J chromosomes 1, 11 and 17 on Chrna5 KO-dependent and independent nicotine consumption and narrowed the regions of these chromosomes that harbor the modifier loci. Although more work is required to identify the specific genes responsible for the modifier effects, these results suggest that a genetic approach may be a tractable way in which to gain insight into the mechanism through which loss of function of Chrna5 impacts nicotine consumption.

Disclosures: H.L. Mathews: None. **S. Bellati:** None. **E. Myers:** None. **Z. Werner:** None. **M. Brown:** None. **P. Starbuck:** None. **J.A. Stitzel:** None. **R.A. Radcliffe:** None.

Poster

151. Nicotine: Neural Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 151.13

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH Grant SC2DA052119

Title: Adolescent nicotine vapor exposure increases motivation for rewards in male rats

Authors: L. MAYNEZ-ANCHONDO, M. A. URBINA, O. ROHRER, *I. A. MENDEZ;
The Univ. of Texas at El Paso Sch. of Pharm., El Paso, TX

Abstract: In recent years, there has been a dramatic increase of nicotine vapor consumption via electronic nicotine delivery systems, such as e-cigarettes, particularly in adolescents. Preclinical studies have investigated the rewarding and withdrawal effects of nicotine through traditional routes of administration, such as intravenous self-administration. While there is an increase of investigation on the effects of nicotine vapor exposure on global health, its effects on the brain and behavior remain unclear. The goal of this project is to assess changes in motivation for

rewards following adolescent and/or adult nicotine vapor exposure in rats. Male Sprague-Dawley rats (N = 24) were passively exposed to vehicle control (50/50 propylene glycol/vegetable glycerin, PG/VG) or 24 mg/mL nicotine vapor for 10 daily 90-minute session during adolescence (PND 58-67) and/or adulthood (PND 159-168). To assess motivation for food rewards instrumental responding for 45 mg grain pellets was assessed in the Progressive Ratio Task immediately after adolescent and adult passive vapor exposure. Approximately 25 weeks later, motivation for drug rewards was assessed by training and testing the rats for 6 mg/mL nicotine vapor self-administration. Results reveal that adolescent, but not adult, exposure to 24 mg/mL nicotine vapor causes increases in total lever presses for food rewards in the Progressive Ratio Task, relative to controls. Tests of nicotine vapor self-administration following prior nicotine vapor exposure demonstrate that adolescent, but not adult, exposure causes significant increases in nicotine vapor self-administration later in adulthood, relative to rats with no history of nicotine vapor exposure. Our findings demonstrate that adolescent exposure to nicotine vapor causes short-term and long-term increases motivation for rewards, including nicotine. Future experiments should investigate neurobiological and environmental mechanisms driving the effects of adolescent nicotine vapor exposure on motivation and drug seeking behavior. A better understanding of the unique effects of nicotine vapor on the brain and behavior will help drive much needed policy reform and educational campaigns related to the use of e-cigarettes.

Disclosures: L. Maynez-Anchondo: None. **M.A. Urbina:** None. **O. Rohrer:** None. **I.A. Mendez:** None.

Poster

151. Nicotine: Neural Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 151.14

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH Grant SC2DA052119

Title: Nicotine vapor exposure causes short term increases in impulsive and risky choice in adult male rats

Authors: *P. GINER[1], L. MAYNEZ-ANCHONDO[1], A. LILEY[2], R. J. FLORES GARCIA[3], K. P. URIBE[4], G. A. FRIETZE[5], N. W. SIMON[6], L. E. O'DELL[4], I. A. MENDEZ[5];
[1]Psychology, The Univ. of Texas At El Paso, El Paso, TX; [2]Psychology, Univ. of Memphis, Memphis, TN; [3]Unit on Neuromodulation and Synaptic Integration, Natl. Inst. of Mental Hlth., Bethesda, MD; [4]Psychology, The Univ. of Texas at El Paso, El Paso, TX; [5]Pharmaceut. Sci., The Univ. of Texas at El Paso Sch. of Pharm., El Paso, TX; [6]Psychology, Univ. of Pittsburgh, Memphis, TN

Abstract: Increased frequency of use, higher nicotine concentrations, and unique additive chemicals associated with electronic nicotine delivery systems (i.e., e-cigarettes) results in

different pharmacokinetics and pharmacodynamics, relative to that seen with traditional cigarettes. Targeted advertising, addition of palatable flavors, and misconceptions about safety has led to a recent dramatic increase in recreational consumption of nicotine. While the cognitive enhancing effects of nicotine have been well documented, it has also been shown to impair decision making. The goal of these studies was to determine if exposure to nicotine vapor increases impulsive and risky decision making. These studies also aimed to investigate possible long-term effects of nicotine vapor exposure on the expression of genes coding for cholinergic and dopaminergic receptors in brain. Fifty-six adult male Sprague Dawley rats were exposed to vehicle control, 12 mg/mL, or 24 mg/mL nicotine vapor immediately followed by testing in the delay discounting (Experiment 1) or probability discounting (Experiment 2) tasks for 10 consecutive days. For Experiment 1 serum cotinine levels were analyzed on nicotine exposure days 1, 5, and 10 using enzyme-linked immunosorbent assay (ELISA). Fifty-four days after testing in the probability discounting task, animals in Experiment 2 were sacrificed and expression of genes coding for the α4 and β2 cholinergic receptor subunits, and dopamine D1 and D2 receptors, were analyzed using RT-PCR. Exposure to nicotine vapor caused an immediate and transient increase in both impulsive and risky choice. Rats exposed to 12 and 24 mg/mL nicotine vapor displayed higher serum cotinine levels than control rats exposed to vapor vehicle. Analyses of gene expression identified significant reductions in *CHRNB2* and *DRD1* in the nucleus accumbens core and *CHRNB2* and *DRD2* in the medial prefrontal cortex of rats previously exposed to nicotine vapor, relative to vehicle controls. Results provide data on the negative cognitive effects of nicotine vapor exposure and identify cholinergic and dopaminergic mechanisms that may be affected with repeated use. A better understanding of the distinct effects of nicotine vapor on the brain and behavior is necessary for the development of policies and educational campaigns aimed at addressing this novel drug phenomena.

Disclosures: P. Giner: None. **L. Maynez-Anchondo:** None. **A. Liley:** None. **R.J. Flores Garcia:** None. **K.P. Uribe:** None. **G.A. Frietze:** None. **N.W. Simon:** None. **L.E. O'Dell:** None. **I.A. Mendez:** None.

Poster

151. Nicotine: Neural Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 151.15

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH
CIHR

Title: Hedgehog-interacting protein acts in the habenula to regulate nicotine intake

Authors: *S. P. B. CALIGIURI[1], W. M. HOWE[6], L. WILLS[1], A. SMITH[7], M. LEI[8], P. BALI[2], M. P. HEYER[3], J. K. MOEN[9], J. L. ABLES[10], K. ELAYOUBY[9], M. WILLIAMS[11], C. FILLINGER[4], Z. OKETOKOUN[9], V. E. LEHMANN[5], A. G. DIFELICEANTONIO[12], P. M.

JOHNSON[13], K. BEAUMONT[9], R. SEBRA[9], I. IBANEZ-TALLON[14], P. J. KENNY[5]; [1]Icahn Sch. of Med. At Mount Sinai, [3]Dept. of Neurosci., [4]Neurosciences, [5]Neurosci., [2]Icahn Sch. of Med. At Mount Sinai, New York, NY; [6]Virginia Tech. Sch. of Neurosci., Virginia Tech. Neurosci. PhD Program, Blacksburg, VA; [7]Med. Univ. of South Carolina (MU Neurosci. Inst. - Grad., Charleston, SC; [8]Icahn Sch. of Med., New York, NY; [10]Psychiatry, [9]Icahn Sch. of Med. at Mount Sinai, New York, NY; [11]Ichan Sch. of Med. At Mount Sinai, New York, NY; [12]Yale Univ. Sch. of Med., Roanoke, VA; [13]D-ITET, ETH Zurich, Zurich, Switzerland; [14]The Rockefeller Univ., New York, NY

Abstract: Genetic variations in Hedgehog Interacting Protein (HHIP) are associated with the risk of chronic obstructive pulmonary disease (COPD) and other tobacco-related respiratory diseases. The role of HHIP in lung development has been accepted as the pathophysiological mechanism linking HHIP to COPD. However, *in situ* hybridization reveals dense expression of Hhip in the medial habenula (MHb), a brain region involved in nicotine aversion; this suggests a possible role of HHIP in nicotine reinforcement, tobacco smoking, and the risk for COPD. Thus, we aimed to investigate the role of HHIP in nicotine reinforcement using cell type specific transcriptomics and *in vitro* and *in vivo* manipulations of HHIP. Firstly, using single-cell sequencing, MHb cholinergic neurons were observed to be transcriptionally responsive to systemic nicotine. Using Targeted Purification of Polysomal mRNA (TRAP) sequencing, HHIP expression was highly enriched in MHb cholinergic neurons that regulate aversive behavioral responses to nicotine. An HHIP haploinsufficient mouse model exhibited perturbed expression of genes involved in MHb cholinergic signaling. Knockdown of HHIP via CRISPR and shRNA in HEK cells stably expressing α4β2α5 nicotinic acetylcholine receptors (naChRs), disrupted the function of nAChRs and intracellular calcium response to nicotine. To investigate how HHIP may influence nAchR function, downstream mediators were assessed. HHIP functions as a decoy receptor to sequester Hedgehog ligands and promote PATCHED-1 (PTCH-1) activity. ShRNA knockdown of *PTCH-1* or CRISPR/Cas9-mediated genomic cleavage of PTCH1 decreased nAChR signaling similar to HHIP depletion. How HHIP and PTCH-1 might function together in MHb neurons to regulate nAChR signaling was next investigated. PTCH-1 controls hedgehog signaling by regulating cholesterol concentration gradients in the plasma membrane and cholesterol is known to exert a direct inhibitory effect on nAChR signaling. A PTCH-1 mutant that contained three amino acid substitutions to prevent conformational changes required for PTCH-1-mediated cholesterol transport without impacting the binding of Hedgehog ligands was transfected into HEK cells stably expressing α4β2α5. This PTCH-1 mutant induced a striking deficit in nAChR signaling in response to nicotine. Together, these findings suggest that HHIP may influence vulnerability to smoking-related respiratory diseases by influencing cholinergic transmission in the medial habenula and thus influence reinforcement to nicotine.
Funding: NIH & CIHR

Disclosures: S.P.B. Caligiuri: None. **W.M. Howe:** None. **L. Wills:** None. **A. Smith:** None. **M. Lei:** None. **P. Bali:** None. **M.P. Heyer:** None. **J.K. Moen:** None. **J.L. Ables:** None. **K. Elayouby:** None. **M. Williams:** None. **C. Fillinger:** None. **Z. Oketokoun:** None. **V.E. Lehmann:** None. **A.G. DiFeliceantonio:** None. **P.M. Johnson:** None. **K. Beaumont:** None. **R. Sebra:** None. **I. Ibanez-Tallon:** None. **P.J. Kenny:** None.

Poster

152. Attention: Cognitive and Psychological Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 152.01

Topic: H.01. Attention

Title: Investigating the Neural Mechanisms of Attention Shifting

Authors: *E. ALTAMIRANO[1], M. DASTJERDI[2];
[1]Loma Linda Univ., Loma Linda, CA; [2]Neurol., Loma Linda Med. Ctr., Loma Linda, CA

Abstract: The brain receives an overwhelming amount of information across various sensory modalities while having a limited information processing capacity. To overcome this limitation, the brain exploits its attention system to dynamically allocate neural resources to process survival-relevant information preferentially. The effect of attention on ongoing information processing is well-studied in different sensory modalities. However, the mechanism of shifting attention from one spotlight to another is largely unknown in humans. In this study, we introduce a novel attention control task to measure cognitive errors during shifting attention in patients undergoing intracranial EEG. We hypothesize that attention shift is a cognitive process that interferes with ongoing information processing. To test this hypothesis, we have designed a dichotic listening task where the laterality of attention changes after the presentation of a visual cue. We speculate that the task performance and the reaction time significantly interact with attention shifts in comparison to overall behavioral responses. Accordingly, the differential neural responses of the attention network will provide insight to the neural mechanisms of attention shifts. We recorded behavioral and neural data from two patients. Our preliminary behavioral analysis from one patient shows a high task performance, with a high hit rate (90%) and a low false alarm rate (6-10%) averaged over three runs of the task. In addition to the high performance rate, the reaction time (1±0.3 sec) was significantly shorter than the allowed response time (1.5 sec) further indicating the subject's active participation in the task. We found that most of the trials with a reaction time above the average (1±0.3 sec) occurred after an attention shifting cue. In conclusion, the high-performance rate in our preliminary behavioral analysis shows active subject participation in the task. We are currently looking at differential responses of the nodes of the attention network obtained with intracranial EEG data during the attention shifts.

Disclosures: E. Altamirano: None. **M. Dastjerdi:** None.

Poster

152. Attention: Cognitive and Psychological Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 152.02

Topic: H.01. Attention

Support: NIH Grant R21MH120784
NIH Grant EY025172
Tab Williams Fund
Johnston Family Foundation

Title: Temporal dynamics of exogenous and endogenous contributions to saccadic choices resolved under time pressure

Authors: *A. GOLDSTEIN, T. R. STANFORD, E. SALINAS;
Neurobio. and Anat., Wake Forest Sch. of Med., Winston Salem, NC

Abstract: Saccadic eye movements result from decision processes that simultaneously weigh the salience of exogenous sensory events and one's endogenously defined goals. Where and when one looks is determined by the relative potency, congruence, and timing of these distinct attentional pointers. The present study deploys urgent variants of pro- and anti-saccade tasks to provide a detailed mechanistic account of how these factors interact to dictate saccadic choices. Experiment 1 examines how the congruency between exogenous and endogenous signals determines pro- (congruent) and anti-saccade (incongruent) performance. Experiment 2 independently manipulates stimulus salience and endogenously defined task rules to further delineate their respective contributions to saccadic choices. In both cases, urgency is key: under time pressure, performance varies sharply with cue viewing time (i.e., processing time, PT), which yields a psychometric function with the temporal precision essential to resolving the contributions of exogenous and endogenous influences as they unfold in time. In Experiment 1, we found that when a lone, salient stimulus appears, saccades made after little viewing time (PT ~100 ms) are nearly always directed toward it, regardless of whether a pro- or an anti-saccade was requested. This exogenous (involuntary) capture was extremely potent but very brief, as it could be reliably (voluntarily) overcome after ~40 ms of additional PT. Thus, the characteristic performance curves for pro- and anti-saccades were strongly determined by the exogenous pull of the visual cue during early PTs. To more clearly resolve the evolution of the endogenous signal that guides target selection, in Experiment 2, two stimuli were shown, a cue on one side and a noncue on the other, and cue color instructed the participant to look toward (pro-saccade) or away from the cue (anti-saccade). Cue location was always known, so covert attention could be deployed in advance. The results from 19 human participants revealed two key findings. First, both relevant and irrelevant stimuli produced an exogenous response, but capture was always dominated by the more salient regardless of relevance. Symmetric, isoluminant stimuli produced weak or no capture and minimal directional bias. Second, absent a strong exogenous bias, the PT dependence of pro- and anti-saccade performance was very similar. Advance allocation of attention to the eventual target (pro case) yielded only a small advantage of ~20 ms, suggesting that selection of the next saccade target is constrained less by the speed at which endogenous attention can shift than by its congruency with the direction of exogenous pull.

Disclosures: A. Goldstein: None. **T.R. Stanford:** None. **E. Salinas:** None.

Poster

152. Attention: Cognitive and Psychological Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 152.03

Topic: H.01. Attention

Support: NIH Grant R21 MH120784
NIH Grant R01 EY025172
Johnston Family Fund Foundation
Tab Williams Fund

Title: Attentional contributions to visuomotor performance under dynamic viewing conditions

Authors: *E. A. KATTNER, E. SALINAS, T. R. STANFORD;
Wake Forest Sch. Of Med., Wake Forest Sch. Of Med., Winston-Salem, NC

Abstract: Visuospatial attention helps parse visual information and choose objects worth examining more carefully. It is known that, along with exogenous (stimulus-driven) and endogenous (goal-driven) mechanisms, history effects due to prior experience determine when and where attention is deployed. However, it is unclear how these mechanisms interact and what their effective contributions are under natural viewing conditions, when stimuli are unpredictable and eye movements are not constrained by the long fixation and delay requirements typical of laboratory tasks. To assess the interplay between different attention mechanisms in a dynamically realistic context, we developed a gamified visual task in which participants make saccadic choices continuously, at their own pace. The 'game' is played in runs of fixed duration (90 s), with points accrued by looking at colored stimuli with known point values (e.g., red = 3, yellow = 1, blue = 0 points), and the goal is to maximize the high score across runs. Critically, because the targets change color at random times and because the high score increases with both accuracy and speed, the optimal strategy is to respond rapidly and guess often — but not too rapidly/often. Given such high urgency, perceptual performance can be comprehensively characterized via a 'tachometric' curve, a function that relates choice accuracy to time relative to the onset of a relevant visual cue, i.e., processing time (PT). Human participants (n=19, aged 21-57, 12 female) performed the dynamic task, and separate tachometric curves were generated for choices following the appearance of either a high- (red) or a low-value (blue) stimulus. The corresponding curves were similar to those obtained in prior experiments with urgent pro- and antisaccade tasks: they demonstrated chance performance for very short PTs (< 100 ms), strong exogenous capture shortly after a cue onset (PT ≈ 100 ms), and endogenous guidance toward the correct target slightly (~50 ms) later. Thus, we were able to rigorously characterize perceptual capacity under highly dynamic viewing conditions. In three further experiments, we found that (1) involuntary capture due to stimulus salience occurred very briefly but was always present, (2) consistent with the so called premotor theory, the covert deployment of spatial attention led to strong, idiosyncratic motor biases and to perceptual benefits, and (3) stimulus statistics had a profound impact on performance, altering processing speed, the effective salience of stimuli, and asymptotic accuracy. We conclude that although attention effects are qualitatively robust, viewing dynamics have a dramatic influence on their strength.

Disclosures: E.A. Kattner: None. **E. Salinas:** None. **T.R. Stanford:** None.

Poster

152. Attention: Cognitive and Psychological Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 152.04

Topic: H.01. Attention

Support: CIHR Grant MOP-FDN-148418
Queen's University Department of Psychiatry Internal Faculty Grant

Title: Oculomotor and attentional biases in bipolar disorder during naturalistic free viewing of emotional faces

Authors: *R. YEP[1], B. J. WHITE[1], D. C. BRIEN[1], B. C. COE[1], L. ITTI[3], A. MARIN[2], D. P. MUNOZ[1];
[1]Ctr. for Neurosci. Studies, [2]Dept. of Psychiatry, Queen's Univ., Kingston, ON, Canada; [3]USC, Los Angeles, CA

Abstract: Bipolar disorder (BD) is a heterogeneous and debilitating psychiatric illness for which objective, neurobiologically-based indices of disease progression and treatment response have yet to be identified. Individuals with BD have previously been characterized by deficits in oculomotor, attentional, and emotional control, however, these processes are often investigated independently using behavioral paradigms with limited ecological validity. Video-based eye tracking during the unstructured viewing of naturalistic video may provide a simple and more sensitive means of probing the frontal-subcortical circuitry underlying deficits in BD. Here we contrasted eye movement behavior between healthy adults and adults diagnosed with BD (n=50, n=30, aged 18-50) while they performed a novel unstructured paradigm, the Free Viewing Faces task. In this task, participants freely viewed 10 min of naturalistic video that randomly changed in content every 2-5 s, and for which 40% of the video clips featured human faces expressing positively, neutrally, or negatively valenced emotions. Saccade and blink behavior was pre-processed using a standardized pipeline and analyzed (i) averaged across clips and (ii) aligned to clip onset. Averaged across clips, BD participants had higher center gaze bias and lower blink rate relative to control participants. Aligned to clip onset, all participants had saccade rate suppression and rebound measures that were faster and greater in magnitude on face vs. non-face clips. BD participants had slower saccade rate measures on non-face clips, but faster saccade rate measures on face clips relative to control participants. Separating face clips by valence revealed that the first three saccades made by BD participants on positively and neutrally valenced faces were earlier than those of control participants. These findings suggest that during naturalistic free viewing, individuals with BD engage less in explorative behavior, have an abnormal blink rate, and exhibit differential attentional biases toward positively, neutrally, and negatively valenced faces. The timing and magnitude of these behaviors across the duration of clips suggests the involvement of both fast, subcortical neural mechanisms, and slower, cortical neural mechanisms. We propose that this simple and naturalistic paradigm may provide important insight into dysregulated frontal-subcortical circuitry mediated by psychopathology and medication effects in BD. More broadly, our work demonstrates that this paradigm is highly

amendable for the investigation of oculomotor, attentional, and emotional processing across a range of healthy and clinical populations.

Disclosures: R. Yep: None. **B.J. White:** None. **D.C. Brien:** None. **B.C. Coe:** None. **L. Itti:** None. **A. Marin:** None. **D.P. Munoz:** None.

Poster

152. Attention: Cognitive and Psychological Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 152.05

Topic: H.01. Attention

Support: NSERC

Title: Exploring the Powers of Mindfulness-Based Training on Enhanced Executive Function

Authors: *S. CHAMBERS[1], R. STAINES[2];
[1]Hlth., [2]Univ. of Waterloo, Waterloo, ON, Canada

Abstract: Humans are flooded with a large number of visual stimuli at any moment, and to act efficiently, we filter information based on how relevant it is to us and avoid stimuli that may be considered distracting. Research has demonstrated that those who meditate have improved executive functioning compared to controls. Visual event-related potentials (ERPs) can be used to assess visual selective attention. Specifically, in response to lateralized attended stimuli the N2pc (posterior contralateral) is associated with top-down attentional selection and the distractor positivity (Pd) with bottom-up selection. We hypothesized that those who have been meditating consistently can draw their attention more efficiently towards a target, represented by a larger N2pc, and suppressing distractors, represented by a larger Pd. Additionally, we hypothesized that the meditators would respond more accurately than controls and would have a reduction in interference post-error indicated by a larger error-related negativity (ERN). EEG was collected from 27 participants (15 control, 12 meditators; 20-35 yrs). Meditators had to be meditating for at least the past year with an average of 45 minutes spent in meditation each week. ERPs were measured using EEG to investigate mechanisms. Using a modified flanker task where two sets of three letter arrays were arranged vertically, one in either visual hemisphere, one green array, the other red. Participants were instructed to indicate whether the middle letter of the attended array (red/green) is a consonant or a vowel via keypad. Participants were instructed to attend to either array across 10 blocks (5 attend green; 5 attend red) with 100 trials presented per block. ERPs were extracted via subtracting contralateral-ipsilateral electrodes relative to the attended visual target (O1/2, P3/4, P7/8) and quantified via mean wave amplitude over a time window of 200-300ms after stimulus onset. ERN was extracted by subtracting correct from incorrect trials and taking the peak negative amplitude within 50-150ms after response onset at the FCz site. Latency was recorded and accuracy was measured via correct vs error trials (excluding missed trials). Preliminary analysis suggests that meditators tend to focus more on accuracy than speed. EEG

data indicates markers for improvement in cortical areas responsible for attentional selection (N2pc/Pd) and changes in the anterior cingulate cortex regarding error processing (ERN). The relationship between meditators and mechanisms of attention are being investigated. These findings may inform about the way meditation improves our attention and how it can be adapted for the most effective outcome.

Disclosures: S. Chambers: None. **R. Staines:** None.

Poster

152. Attention: Cognitive and Psychological Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 152.06

Topic: H.01. Attention

Support: NSF CAREER BCS 1151805

Title: Probing attentional modulation of biological motion processing at various temporal stages: a modified event-related potential paradigm

Authors: *S. ZHANG, A. P. SAYGIN;
Cognitive Sci., Univ. of California San Diego, La Jolla, CA

Abstract: Perceiving the motion of other living beings (biological motion, BM) is crucial to our life. Literature suggests both top-down and bottom-up mechanisms contribute to the successful processing of BM. However, few studies have addressed the following questions. Does attention modulate BM perception differently at various stages of an attention task? What will happen when BM co-presents with a visual competitor(s)? Conventional ERP paradigms could only partially answer these questions. Time-locking to the overall stimulus onset adds challenges to exploring the ongoing aspects of BM processing. Also, it is hard to isolate object-specific ERPs in a multi-object display. Hence, we developed a modified ERP paradigm using biological (BM) and scrambled (SM) point-light walkers (PLWs) as stimuli. This novel paradigm features applying sparse visual events to dynamic displays. Canonical PLWs depict locomotion with black dots corresponding to the joints of a moving body. A brief contrast reversal (black dots to white) was randomly applied to individual frames of the walker to induce a feed-forward wave of visual processing without disturbing the motion. Brain potentials were computed by time-locking to these sparse pulse events instead of the onset. Fourteen healthy adults (ten females) participated in this study. In each trial, two PLWs were presented simultaneously on each side of the visual field with a non-overlapping pulse sequence to each PLW. Subjects needed to focus on the center fixation and detect a yellow dot by pressing the corresponding key when the target appeared either on the left or right PLW as soon as they detected the target. Pulse-locked ERPs on contralateral electrodes were sorted and averaged into three phases. The pre-target phase includes pulses preceding the target dot frame (excluding the onset). In this phase, an interaction between pulse location and competitor type was evidenced by a more negative deflection in 100-

200 ms ($p<0.05$) elicited by SM pulses with a BM competitor condition. The pre-key phase includes pulses between the target frame and the key press. Similar patterns as in the previous phase were found ($p<0.01$) only when the pulses were on the target walker. Phase 3 includes frames after the button pressing. Pulses on BM walkers evoked a greater positivity from 0-200ms ($p<0.01$) with an SM competitor regardless of whether the pulse location matches the target position. This novel paradigm allows us to compare brain activities of co-presented objects as the task progresses from anticipation to execution to completion, providing new insights into the dynamic interplay between attention and biological motion processing.

Disclosures: S. Zhang: None. **A.P. Saygin:** None.

Poster

152. Attention: Cognitive and Psychological Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 152.07

Topic: H.01. Attention

Title: Oddly anxious: an examination of oddball errors with symptoms of depression and anxiety

Authors: *N. MOHAMMED, J. S. JACKSON, C. KHAJADOURIAN, A. ROBY, L. E. KNOX, S. A. DREW;
Psychology, California State University, Northridge, Northridge, CA

Abstract: The onset of the COVID-19 pandemic saw an increase in reports of anxiety and depression (COVID-19 Mental Disorders Collaborators, 2021). Previous literature suggests that individuals with major depressive disorder present a counterproductive allocation of visio-attention resources (Desseilles et al., 2010). Similarly, it has also been reported that high-anxiety participants shift their visual attention towards differing stimuli when compared to low-anxiety participants (Fox, 1993). Due to the aforementioned increased prevalence of anxiety and depression and their potential impact on visual attention, it is of interest to better understand how attentional research may be impacted. Given the high utilization of the OddBall task as a standard measure of sustained attention, we sought to investigate whether psychometrically assessed levels of anxiety and depression would predict changes in performance on the Oddball task. We hypothesized that participants experiencing higher anxiety levels and/or depression would exhibit lower sustained visual attention as quantified by increased OddBall errors. Participants (N = 127) were students recruited from California State University, Northridge, through the university SONA subject pool. They were directed to LabVanced, an online experimental program, where they completed the oddball task (Squires, Squires & Hillyard, 1975) and the number of errors were recorded. Participants additionally completed measures for anxiety and depression as part of a larger experimental protocol. Results from our regression analysis ($R2 = .005$, $F(2,123) = .308$, $p = .735$) revealed no significant relationship between sustained visual attention (i.e. oddball errors) and the levels of anxiety ($\beta = .006$, $p = .957$) or depression ($\beta = -.074$, $p = .519$). This study demonstrates the nonsignificant relationship between

anxiety/depression and sustained visual attention, providing preliminary evidence that additional screening for anxiety and depression is not warranted for researchers utilizing the OddBall task. It must be noted however that our sample reflected mild levels of anxiety and depression and further study is needed that examines the relationship between sustained visual attention in moderate to severe cases of depression and anxiety.

Disclosures: N. Mohammed: None. **J.S. Jackson:** None. **C. Khajadourian:** None. **A. Roby:** None. **L.E. Knox:** None. **S.A. Drew:** None.

Poster

152. Attention: Cognitive and Psychological Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 152.08

Topic: H.01. Attention

Support: PAPIIT-UNAM #IN217221
PAPIIT-UNAM #IA205218
PAPIIT-UNAM #IN215218
CONACYT #1083933

Title: Suppression attentional mechanism, but not amplification, predicts working memory accuracy across adulthood

Authors: *E. LÓPEZ-GONZÁLEZ[1], U. CABALLERO SANCHEZ[2], A. POLO-ROMERO[5], D. ZENTENO[3], Z. ESPINOSA[7], A. G. GARCÍA[8], J. CERVANTES-ROSAS[6], M. MENDEZ DIAZ[9], O. PROSPERO-GARCIA[10], A. E. RUIZ-CONTRERAS[4];
[1]Univ. Nacional Autonoma de Mexico, Ciudad de México, Mexico; [2]Univ. Nacional Autonoma de Mexico, Mexico City, Mexico; [3]Facultad de Psicología, Univ. Nacional Autonoma de Mexico, Coyoacán, Mexico; [4]Univ. Nacional Autonoma de Mexico, D.F., Mexico; [5]Facultad de Psicología, [6]Univ. Nacional Autónoma de México, Ciudad de México, Mexico; [7]Lab. de Neurogenómica Cognitiva, Facultad de Psicologia, Ciudad de México, Mexico; [8]Inst. De Fisiología Celular UNAM, México, Mexico; [9]Univ. Nacional Autonoma De Mexico, Mexico DF, Mexico; [10]Physiol., Inst. De Neurobiología, UNAM Inst. De Neurobiologia, CDMX, Mexico

Abstract: Attention allows selecting only the relevant stimuli to prioritize their processing and inhibit the processing of irrelevant stimuli. Some stimuli attract the individual's attention and divert it from goal-directed behaviour, generating attentional capture. Two mechanisms have been described for attention: amplification of relevant information and suppression of irrelevant information. Attention ability can impact working memory (WM) performance. This last is defined as the ability to maintain and manipulate information, even when it is no longer available, to impinge on goal-directed behaviour. Attention and WM are two interacting functions with limited cognitive resources that can be affected by attentional capture. Faces are

more attention-grabbing than other kinds of stimuli (i.e., scenes). It has been documented that attention, particularly, selective attention, and WM decline in older adults (i.e., more than 60 years). And they are less efficient at preventing interference and suppressing the processing of distracting stimuli, which in turn is associated with a decline in the efficiency of attention and WM performance. Noteworthy, their amplification mechanism seems relatively conserved compared with young adults. As far as we know, the way amplification and suppression mechanisms change across adulthood has not been described. The aim of this research was to assess changes in both amplification and suppression attentional mechanisms (by means of reaction times, RT), and their impact on WM efficiency (measured by d'), across adulthood. Here, 78 adults, ages between 20 and 80 years, participated in an online session using RealEye (Lewandowska, 2019) running counterbalanced three-conditions tasks: "remember faces and ignore scenes", "remember scenes and ignore faces" and "passive view" in a WM task. Age negatively predicted WM accuracy only for the "remember faces" tasks, but not for "ignoring faces". On the other hand, the amplification index associated to face processing (i.e., RT for the "remember scenes" condition - RT for the "passive view" condition) did not predict WM performance. However, the suppression index (i.e., RT for the "passive view" condition - RT for the "ignoring faces" condition) did positively predict WM performance, independently of age. Thus, WM accuracy did not always decline across adulthood, but it seems to depend on the type of stimuli (i.e., faces vs. scenes). On the other hand, WM accuracy was predicted by the suppression attentional mechanism but not by the amplification mechanism. Thus, the suppression mechanism was found to prevent attentional capture of task-irrelevant faces, favouring efficiency in WM.

Disclosures: **E. López-González:** None. **U. Caballero Sanchez:** None. **A. Polo-Romero:** None. **D. Zenteno:** None. **Z. Espinosa:** None. **A.G. García:** None. **J. Cervantes-Rosas:** None. **M. Mendez Diaz:** None. **O. Prospero-Garcia:** None. **A.E. Ruiz-Contreras:** None.

Poster

152. Attention: Cognitive and Psychological Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 152.09

Topic: H.01. Attention

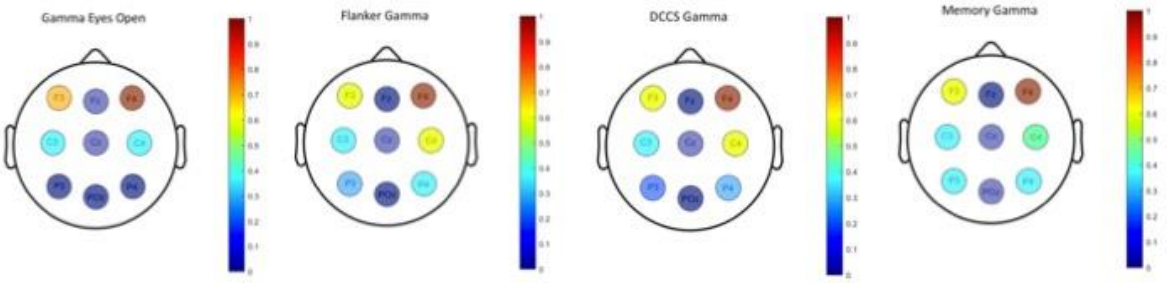
Support: LMU Faculty Research Grants

Title: Unable to Attend -Electroencephalographic (EEG) gamma-band activity differences during 3 distinctive cognitive tasks in young adults

Authors: *M. R. FOY, J. G. FOY;
Dept. of Psychological Sci., Loyola Marymount Univ., Los Angeles, CA

Abstract: Electroencephalograph (EEG) recordings from scalp locations measure voltages generated by underlying neural currents. In applied and basic research, EEG can be used to study

neural functioning in naturalistic settings. EEG waveforms are sensitive to real-time changes in brain activity, and can provide a temporal resolution that links brain activity with changes in mental activity. We examined sensor site differences in power spectral densities (PSD) during clinically relevant executive function (EF) tests. By recording from 9 scalp locations, we explored whether a coarse-grained analysis would be sensitive to shifts in brain activity from task to task. The participants in this study were 29 healthy undergraduate (18-22 yr) volunteers. Using wireless EEG, PSDs were examined over frontal, central and parietal brain regions (left, center, right) in 5 EEG frequency bands (delta, theta, alpha, beta, gamma) during a baseline, relaxed eyes open resting state, and during a series of 3 EF tasks (NIH Toolbox Cognitive Battery), which included the Flanker Test, Dimensional Change Card Sort (DCCS) Test, and Picture Sequence Memory (PSM) Test. Here we report gamma-band activity PSD differences. Recordings taken during the resting state revealed that gamma-band PSD was maximal at F4 and minimal at P0z (p=.016). During the EF tests, gamma-band PSD was maximal at F4 and minimal at Fz (p<.05 for Flanker and PSM tests, *ns* for DCCS test). There was an anteriorization of gamma-band PSD during the resting state (C4 vs. P4, p=.003) and for the Flanker test (C4 vs. P4, p=.022) but not for the other two EF tests, suggesting that gamma-band activity is more widespread for more challenging cognitive tests. A coarse-grained analysis of gamma-band PSD activity is sensitive to localized neural differences in EF tests compared to resting state. Furthermore, gamma-band PSD may be lower in posterior than central locations (right hemisphere) in resting state and the Flanker Test (test of inhibitory control), but is more widespread in tests of DCCS and PSM (tests of cognitive flexibility and episodic memory).



Standardized comparisons of gamma-band EEG activity across baseline (eyes open) and 3 cognitive tasks

Disclosures: **M.R. Foy:** None. **J.G. Foy:** None.

Poster

152. Attention: Cognitive and Psychological Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 152.10

Topic: H.01. Attention

Title: Musical attention decoding

Authors: *Y. AMIN[1], P. LARROUY-MAESTRI[2], C. PELOFI[3];
[1]Psychology, Krosch Lab, Cornell Univ., Ithaca, NY; [2]CLaME, Max Planck Inst. for Empirical Aesthetics, Frankfurt am Main, Germany; [3]Psychology, CLaME, New York Univ., New York, NY

Abstract: Auditory Scene Analysis (ASA) is a set of principles modeling the way cognitive systems process complex auditory stimuli. ASA has been studied mostly in the context of multi-talker scenes (the famous cocktail party problem); however, music perception also constitutes a relevant context for ASA studies, as most people spontaneously and regularly engage with music, an activity that entails perceiving "melodic voices" from different instruments simultaneously. To tackle this gap, we adapted music pieces from the Baroque repertoire, composed of two melodic voices to investigate how melodic voice entries and content affect the dynamics of attention during music listening. To that aim, 80 online participants (M_{age} = 19.7, *SD* = 1.3; 70% female) of varying musical expertise were exposed to piano MIDI versions of four Bach pieces. Each of the two voices were separated and presented dichotically. Participants were asked to continuously report to which ear they were mostly attending. We identified the main predictors of attentional switches and assessed whether they were consistent across participants using a randomness test. For each piece, we created density distributions of participants' switches using a sliding window that provided a moving-averages of switches. We then regressed switches on acoustical and musical content. To derive the acoustical content, we used techniques such as feature extraction (e.g., chroma, loudness, tempo) and a model predicting a continuous surprisal measure (D-Rex; Skeritt-Davis & Elhilali, 2018). We also used theoretically-driven approaches to extract musical content; namely, Lerdhal and Jackendoff's (1983) grouping rules. We addressed multicollinearity of these features by performing LASSO Regression. Wald-Wolfowitz runs tests demonstrate that attention switches dynamically between ears in a non-random and consistent way across participants (*ps* < .001). Attentional switches were time-locked to acoustical and musical features such as the proximity and change rules (Lerdahl & Jackendoff, 1983). Additionally, when voices entered simultaneously, participants attended to the voice which shared or resembled the same contours of prior voice entries. Our study provides a novel and well-controlled viable paradigm to explore ASA using ecologically-valid stimuli. We highlight the cognitive and attentional salience of specialized compositional techniques, such as the varying of repeated melodic contours across time. By exploring the perception of melodic voices, we identified cues that consistently trigger attentional switches and put forward new components of ASA in the relevant and unexplored context of music listening.

Disclosures: Y. Amin: None. **P. Larrouy-Maestri:** None. **C. Pelofi:** None.

Poster

152. Attention: Cognitive and Psychological Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 152.11

Topic: H.01. Attention

Support: NIH National Institute on Aging Grant R01 AG065255
Wu Tsai Human Performance Alliance at Stanford University

Title: Readiness-to-remember: On the relationship between recognition memory, recollection precision, and moment-to-moment fluctuations in preparatory sustained attention

Authors: *S. T. SCHWARTZ[1,2], K. P. MADORE[1], A. D. WAGNER[1,2];
[1]Dept. of Psychology, Stanford Univ., Stanford, CA; [2]Wu Tsai Neurosciences Institute, Stanford Univ., Stanford, CA

Abstract: Episodic memories afford us both a window into the past and the ability to make predictions about the future. Sustained attention is considered necessary for the successful goal-directed expression of episodic memories, with recent evidence indicating that moment-to-moment fluctuations in preparatory sustained attention, as assayed by scalp EEG (posterior alpha power) and pupillometry, predict goal-directed item recognition and source memory failures when measured in the tonic periods immediately preceding goal coding during retrieval. Despite the apparent predictive power of neural measures of pre-goal fluctuations in attention lapsing on behavioral forgetting, it is unknown whether these same assays predict recognition memory and recollection precision in the absence of varying retrieval goals. Here, we investigated how trial-to-trial tonic fluctuations in sustained attention, in the moment just prior to remembering, relate to item recognition and recollection precision for visual objects previously encoded in an associated color. Trial-level recognition memory was assayed via hits/misses from high-/low-confidence old/new judgements made on previously learned objects (presented in grayscale), which were intermixed with new objects. For objects recognized as "old" - regardless of confidence - participants were probed to indicate their memory of the color the object had been presented in at encoding, using a well-established, perceptually uniform 360-AFC color-wheel precision task. Initial analyses suggest that tonic fluctuations in sustained attention, in the 1-second prior to the onset of the recognition memory probe, predict item recognition memory performance (i.e., whether studied objects were recognized with high-confidence memory). The effects of attention lapsing on recognition memory were greater than that on subsequent perceptual recollection precision. These initial findings highlight the predictive role of attention lapsing on memory, raise the possibility of differential effects depending on the nature of memory expression, and set the stage for exploration of the causal influence of readiness-to-remember attentional processes on the retrieval of mnemonic evidence and/or on memory-guided decision making.

Disclosures: S.T. Schwartz: None. **K.P. Madore:** None. **A.D. Wagner:** None.

Poster

152. Attention: Cognitive and Psychological Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 152.12

Topic: H.01. Attention

Title: Smartphone presence and the electrophysiology of attention: effects on oddball P3 and beta power

Authors: R. L. SHEETZ, G. THOMPSON, C. A. GLAND, E. L. KERR, M. L. GAWLITTA, C. E. KIDWELL, C. N. LE, A. J. GRZYBOWSKI, ***D. S. LELAND**;
Psychology, Univ. of Wisconsin-Eau Claire, Eau Claire, WI

Abstract: Given concerns about how distracting smartphones can be, we are interested in how they affect attention-related brain electrical activity. Previous research suggests that the mere presence of one's smartphone can negatively impact behavioral performance on an attention-related task. The aim of our ongoing study is to investigate whether simply having one's smartphone present and visible (although shut off) influences attention-related EEG (electroencephalographic) activity. We are assessing this in two ways. First, subjects perform an oddball task, which requires attention and responses to occasional target stimuli ("oddballs") among many task-irrelevant stimuli ("standards"). The P3, a late component of the event-related potential (ERP), is typically larger to oddballs (which receive more attention) than standards; we predict an attenuation of this oddball effect in the presence of one's phone versus a control non-phone object (tile). Second, we are looking at EEG power in the beta range (13-30 Hz) as subjects passively view their phone versus the control object. Since beta activity is positively correlated with alertness and attention, we predict greater beta power in the phone condition. Furthermore, we predict a correlation between beta power in response to one's phone and attenuation of the P3 oddball effect by one's phone; that is, the more attention is garnered by one's phone the more we think their phone will distract from a phone-irrelevant attention task. Analysis of preliminary data suggests replication of the classic P3 oddball effect, with larger late positivity over centro-posterior sites to target stimuli, but does not provide evidence for a significant impact of smartphone presence.

Disclosures: R.L. Sheetz: None. **G. Thompson:** None. **C.A. Gland:** None. **E.L. Kerr:** None. **M.L. Gawlitta:** None. **C.E. Kidwell:** None. **C.N. Le:** None. **A.J. Grzybowski:** None. **D.S. Leland:** None.

Poster

152. Attention: Cognitive and Psychological Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 152.13

Topic: H.01. Attention

Support: NIH P60 AA011605-21

Title: Mindfully acting with awareness moderates the relationship between alcohol misuse and behavioral inflexibility

Authors: *E. VIDRASCU[1], M. M. ROBERTSON[1], M. SHERIDAN[2], D. L. ROBINSON[3], C. A. BOETTIGER[1];

[1]Psychology & Neurosci., [2]Psychology and Neurosci., [3]Bowles Ctr. for Alcohol Studies, Univ. of North Carolina at Chapel Hill, Chapel Hill, NC

Abstract: Automatic responses to stimuli allow efficient navigation of the world, but optimal behavior requires the ability to flexibly countermand automatic responses. Growing evidence suggests that adolescent alcohol exposure impairs such behavioral flexibility, with effects persisting into adulthood; moderators of this relationship remain unclear. We hypothesized that high trait mindfulness would weaken the association between alcohol misuse and behavioral inflexibility. This hypothesis is based on the fact that mindfulness meditation training increases momentary awareness of the self and environment by orienting attention onto an object of focus while letting go of salient stimuli that capture and hold attention. Moreover, higher trait mindfulness among adults in recovery from alcohol use disorder (AUD) predicts less attentional bias towards alcohol cues. We used Prolific to collect data representative of the US population (*n*=1074; mean age: 35.4 yrs, range:18-83). We used PROCESS (Models 1 and 3) to investigate the relationships between adolescent ($\leq$ age 21) alcohol use, past year alcohol misuse, trait mindfulness (acting with awareness subscale of the Five-Facet Mindfulness Questionnaire), and two questionnaire measures of behavioral flexibility: value-driven attentional capture, and the Creature of Habit subscales. We regressed the interaction of adolescent and past year alcohol misuse on behavioral flexibility and decomposed this interaction by estimating conditional effects of alcohol use for those with average, low (-1 SD), and high (+1 SD) levels of mindfulness. Controlling for age, sex, race/ethnicity, family history of AUD and socioeconomic status, we found similar significant interacting effects of adolescent and past year alcohol misuse on automatic responses and attentional capture by rewarding stimuli; both were higher among those with high past year drinking. Among people with low to average past year alcohol use, greater adolescent alcohol misuse predicted greater automaticity or attention to reward. Attention to reward was significantly moderated by awareness: average to high levels of awareness was associated with weaker effects of adolescent misuse or past year drinking on attention to reward. In contrast, awareness did not moderate the relationship between alcohol use and automatic behavior. Behavioral inflexibility is an AUD risk factor. Our finding that acting with greater awareness associates with less attentional capture by rewarding stimuli suggests that increasing this mindfulness facet may specifically reduce attention to reward cues.

Disclosures: E. Vidrascu: None. **M.M. Robertson:** None. **M. Sheridan:** None. **D.L. Robinson:** None. **C.A. Boettiger:** None.

Poster

152. Attention: Cognitive and Psychological Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 152.14

Topic: H.01. Attention

Support: USDA National Needs Fellowship
University of Illinois Graduate College Fellowship

University of Illinois Division of Nutritional Sciences
National Dairy Council
Hass Avocado Board

Title: The relationships between body composition and attentional inhibition across the lifespan

Authors: *S. SETHI[1], C. N. CANNAVALE[1], S. KEYE[1], A. L. MCMATH[2], A. D. M. WALK[5], S. M. DONOVAN[2], N. A. BURD[1,2], H. D. HOLSCHER[1,2,3], N. A. KHAN[1,2,3,4];
[1]Dept. of Kinesiology and Community Hlth., [2]Div. of Nutritional Sci., [3]Dept. of Food Sci. and Nutr., [4]Neurosci. Program, Univ. of Illinois, Urbana-Champaign, Urbana, IL; [5]Dept. of Psychology, Eastern Illinois Univ., Charleston, IL

Abstract: Body composition is associated with executive function across the lifespan, but no studies have compared the associations between body composition and attentional inhibition in different age-groups. Accordingly, the current exploratory analyses used pooled baseline data from six studies to investigate the relationship between body composition and inhibitory control across the lifespan. Participants (*n*=447) were divided into four age-groups: preschoolers (3-5 years, *n*=90), school-aged children (6-12 years, *n*=125), early adults (18-35 years, *n*=133) and middle-aged adults (35-46 years, *n*=86). In each study, dual energy X-ray absorptiometry was used to assess visceral adipose tissue (VAT), the percentage of whole-body fat (%FAT) and lean mass (LEAN). Inhibitory control was measured with a modified Eriksen Flanker task, during which event-related potentials (P3 & N2 components) were recorded to assess the neural underpinnings of behavioral outcomes. In the whole sample, partial Spearman correlations adjusting for age, sex and diet quality revealed positive associations between LEAN and accuracy in congruent and incongruent trials. By contrast, LEAN was negatively related to reaction time, coefficient of variation (CV, intra-individual variability in response time), peak N2 amplitude (response inhibition) and P3 latency (cognitive processing speed) in congruent and incongruent trials. Congruent reaction time was negatively associated with VAT, body mass index (BMI) and %FAT, whilst peak N2 amplitude was negatively related to VAT, waist:height ratio (WHtR), BMI and %FAT. In preschoolers, VAT was negatively associated with CV, but in middle-aged adults, VAT, WHtR, BMI and %FAT were positively related to CV. The association between VAT and consistency in response times is hence age-dependent; VAT in children did not have the same deleterious effects on variability in response times as it did in adults. Furthermore, VAT, WHtR and %FAT were negatively related to accuracy and positively related to congruent P3 latency in middle-aged adults. Fisher r-to-z transformations revealed that the negative relationship between %FAT and incongruent accuracy was stronger in middle-aged adults compared to school-aged children ($z=2.29$, $p=0.02$). In conclusion, higher lean mass is related to greater inhibitory control, whilst VAT, WHtR, BMI and %FAT are related to poorer inhibitory control across the lifespan, regardless of task complexity. The body composition marker most strongly associated with cognitive function varies with age. Although adiposity is related to executive function, the negative influence of adiposity appears to be more pronounced with age.

Disclosures: S. Sethi: None. **C.N. Cannavale:** None. **S. Keye:** None. **A.L. McMath:** None. **A.D.M. Walk:** None. **S.M. Donovan:** None. **N.A. Burd:** None. **H.D. Holscher:** None. **N.A. Khan:** None.

Poster

152. Attention: Cognitive and Psychological Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 152.15

Topic: H.01. Attention

Support: Bio-Design & Bio-Engineering Initiative (BBI2) Phase 2, Department of Bio-Technology (DBT), Government of India

Title: Dynamic variations in P300 Attention and Working Memory components in Males and Females, in an Indian cohort

Authors: H. HARIHARAN[1], A. TAK[2], R. K. JOSHI[3], B. BUDIHAL[5], S. THOMAS[1], K. SRINIVASAN[1], H. J. PANDYA[3], *M. JAYACHANDRA[4,1];
[1]Divison of Mental Hlth. and Neurosciences, St. John's Res. Inst., Bangalore, India; [2]Physiol., Rajmata Vijaya Raje Scindia Med. Col., Bhilwara, India; [3]Dept. of Electronic Systems Engin., [4]Ctr. For BioSystems Sci. And Engin. BSSE, Indian Inst. of Sci., Bangalore, India; [5]BGS Global Inst. of Med. Sci., Bangalore, India

Abstract: We studied male-female variations in P300 event-related potentials in an Indian population (n=24;m=12,f=12) in the Visual and Auditory systems, in a 64-channel *Neuroscan, Natus*, EEG system. We focused on Attention (P300a - no response required) and Working Memory (P300b - response required), components of the P300 response, using the classic 3-stimulus visual P300 paradigm (Polich, 2007). The recorded wave-forms followed the canonically described P300 components. The P300a was earlier and monophasic, while the P300b had a later rise, plateau and fall *(ibid).* Wavelet de-noising allowed identification of single-events (P300a and P300b), and showed slowing of all P300 responses, possibly indicating cognitive fatigue and/or habituation over the duration of the experiment (16.7min).
There were no statistically significant differences in the latencies and amplitudes in P300a and P300b components between males and females. However, a point-to-point statistical analysis elicited periods of statistically significant differences between males and females ($p<0.05$), within the P300 epochs (350-500ms). LORETA EEG analysis of male female grand averages amplified this differential cortical area activation, during P300 epochs (350ms - 450ms).
Attention tasks in males: At the peak of the P300a (reflecting Attention), multiple cortical areas were activated: Bilateral Frontal, Left Temporal, Left Visual, Centro-frontal, and Right Visuo-Parietal areas. By contrast in females, the main area activated was the Left Inferior Parietal area.
Working Memory tasks in males: P300 activation was largely confined to the Visuo-Parietal area, first at right and then spreading bilaterally, later. By contrast in females, during the peak and plateau of the P300b (Working Memory) multiple brain areas were activated including: Bilateral Central, Bilateral Frontal, Left Visuo-Parietal, and Centro-Parietal.
Auditory P300 responses occurred earlier than Visual and also showed differences between males and females.
This pilot study underscores the importance of EEG data imaging (e.g., LORETA) to increase resolution of brain cortical areas activated during ERPs. The resultant richer view of dynamic EEG data, hints at functional cortical connectivity patterns at different times, on the millisecond

scale. It also argues against grouping male and female brain wave data when using the P300 in a clinical situation, e.g., Acute Stroke monitoring.
Polich J. (2007) Updating P300: an integrative theory of P3a and P3b. Clinical Neurophysiology 118(10):2128-2148.

Disclosures: H. Hariharan: None. **A. Tak:** None. **R.K. Joshi:** None. **B. Budihal:** None. **S. Thomas:** None. **K. Srinivasan:** None. **H.J. Pandya:** None. **M. Jayachandra:** None.

Poster

152. Attention: Cognitive and Psychological Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 152.16

Topic: H.01. Attention

Support: NEDO Grant JPNP20006

Title: Auditory perceptual performance during dual task Wii virtual skateboarding is related to pre and post stimulus gamma band EEG power in auditory brain regions

Authors: *D. CALLAN[1,2], T. FUKADA[3,1], F. DEHAIS[2,4], S. ISHII[3,1];
[1]Brain Information Communication Res. Lab., Advanced Telecommunications Res. Inst. Intl., Kyoto, Japan; [2]Dcas, ISAE-SUPAERO, Univ. of Toulouse, Toulouse, France; [3]Grad. Sch. of Informatics, Kyoto Univ., Kyoto, Japan; [4]Sch. of Biomed. Engineering, Sci. and Hlth. Systems, Drexel Univ., Philadelphia, PA

Abstract: Studies have shown that individuals often experience a type of 'inattentional deafness' in which they do not report hearing otherwise audible sounds under high workload multi-task conditions. The goal of the research is to detect performance-related changes in localized electroencephalographic EEG (Cognionics Quick 32R, utilizing 29 channels) gamma band power both before and after stimulus presentation on an auditory change identification task while concurrently playing the Wii Skateboard Arena balance board game. The auditory task required participants (N = 14) to push a button when the current audio stimuli being played was different from the previous one played. In total there were 400 of the two stimuli presented randomly every 2 to 3 seconds. Auditory performance during Wii game levels consisting of single repetitive tasks (levels 1 to 5 Hit Rate HR = 0.21) was significantly higher ($T = 2.96$, $p < 0.05$, $df = 13$) than that during the Wii game level consisting of combining multiple tasks (level 6 HR = 0.16), thought to require greater task dependent attentional processing. The EEG data was preprocessed (EEGLAB) using artifact subspace reconstruction and ICA upon which only brain components were selected using ICLabel. LORETA (LORETA Key Software) time frequency analysis in the Gamma band (30 to 50 Hz) showed a significant positive correlation with overall participant performance (HR) for hits relative to misses on the auditory task in the left auditory cortex and inferior parietal lobule prior to stimulus onset (one-second segment) ($r = 0.80$, $p <$ 0.05 corrected) and in the left auditory cortex post- stimulus onset (500 msec segment) ($r = 0.75$,

$p < 0.05$ corrected). Contrasting auditory stimuli played during the Wii game level requiring multiple tasks compared to the levels only requiring single tasks showed that participant level decrements in differential performance were correlated with post-stimulus gamma band power in left premotor cortex ($r = -.84$, $p < 0.05$ corrected). Greater Gamma band power in brain regions involved with planning and organization of movement is correlated with worse participant auditory performance. Results suggest that participants that performed worse are likely actively attending to the skateboarding task. Together these results are consistent with participant related attentional modulation of auditory perception during dual-task implementation by showing a relationship between 1. auditory task performance and relative increases in gamma band power in auditory processing regions as well as 2. auditory task performance and relative decreases in gamma band power in premotor cortex that is related to skateboarding task difficulty.

Disclosures: D. Callan: None. **T. Fukada:** None. **F. Dehais:** None. **S. Ishii:** None.

Poster

152. Attention: Cognitive and Psychological Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 152.17

Topic: H.01. Attention

Title: Spatial attention control mechanism modulated by subliminal stimuli: Evidence from electroencephalography

Authors: *A. LIU, M. A. PITTS;
Psychology Dept., Reed Col., Portland, OR

Abstract: The relationship between attention and consciousness has been at the center of a long-lasting debate. Considerable evidence suggests that it is possible to attend to a stimulus without being aware of it. Here we investigated the role of awareness in the control of visual spatial attention. Event-related potentials (ERPs) and event-related time-frequency spectra were used to investigate the effect of a subliminal distracting prime on the temporal dynamics of the spatial attention control system.
Metacontrast masking rendered the subjects either objectively aware or unaware of a task-irrelevant prime that provided consistent or conflicting information to the task. The task was a Posner cueing paradigm that facilitated subjects' endogenous orienting of attention to a location, signaled via a symbolic cue. The control mechanism of spatial attention was examined via two ERPs, Anterior Directing Attention Negativity (ADAN), Late Directing Attention Positivity (LDAP), and via the topography and latency of alpha-band frequency, observed during the time interval between the cue and the target.
Preliminary results revealed that a task-irrelevant invisible prime that provided conflicting information to the task-relevant cue created a greater disturbance to the endogenous orienting of attention, compared to an incongruent but visible prime, reflected by a polarity reversal of the ADAN. Further, the disruptive effect of the prime was transient, as the subsequent LDAP

component was left unaffected. These findings add novel evidence to our understanding of the temporal dynamics of attention control mechanisms and the complex relationship between attention and awareness. In addition, the pattern of results we observed is also one of the first electrophysiological evidence that supports one of the key hypotheses proposed by Graziano and colleagues' "Attention Schema Theory" of consciousness.

Disclosures: A. Liu: None. **M.A. Pitts:** None.

Poster

152. Attention: Cognitive and Psychological Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 152.18

Topic: H.01. Attention

Title: The temporal cost of deploying top-down attention limits accurate target identification in rapid serial visual presentation

Authors: *A. R. KIMATA[1,3,4], B. ZHENG[2], T. WATANABE[5], W. F. ASAAD[6,3,7];
[1]Anna Kimata, [2]Warren Alpert Med. Sch. of Brown Univ., Providence, RI; [3]Dept. of Neurosurg., Rhode Island Hosp., Providence, RI; [4]Dept. of Neurosci., Brown Univ., Providence, RI; [5]Brown Univ., Brown Univ., Westwood, MA; [6]Brown Univ. / Rhode Island Hosp., Brown Univ., Providence, RI; [7]Carney Inst. for Brain Sci., Providence, RI

Abstract: Rapidly processing the visual world is a skill that requires people to deploy attention to detect relevant, often fleeting information. Prior work has produced estimates ranging from 13 to 500ms for the time needed to activate attention. Some of these discrepancies may be related to confounding from attentional shift paradigms, which require spatial reorienting of attention, or tasks that involve semantic, lexical, or exogenous cue stimuli, which trigger distinct processing mechanisms. In the present study, we developed a unique single-stream rapid serial visual presentation (RSVP) task to investigate the time needed to activate attention to a single, novel target. This image-based paradigm allowed us to more directly measure the temporal limitations on activating attention to visual items that may not have an overlearned template to guide detection or identification. Our results from experiment 1 demonstrated that the time needed to reliably engage top-down attention to a salient target lies around 74 ms. Comparing top-down and bottom-up attentional processes also revealed a 19 ms cost for top-down attention activation. In experiment 2, systematically varying image presentation rate versus image duration demonstrated that faster presentation rates yielded lower RSVP performance, whereas decreased duration of individual item presentation did not on its own impair target detection. Furthermore, in experiments 3 and 4, when given sufficient time to activate attention, accuracy improved over subsequent trials, demonstrating a learning effect; however, for presentation rates below the temporal threshold, performance accuracy was capped at an initial ceiling. Experiment 4 also revealed that when the cue was a constant 4-image sequence within the RSVP stream, performance remained high if sufficient time from the onset of the sequence to the target was

provided, despite rapid presentation rates. These results demonstrate that accurate target identification in RSVP was limited by the time needed to engage attention, rather than by perceptual processes prior to activating attention such as insufficient experience with novel images in the stimulus stream or interference from the accumulation of information within the field of attention. Without enough time to activate attention, performance accuracy may depend on native fluctuations in visual temporal attention to coincidentally capture the target. These findings inform our understanding of how the human visual system deploys and adapts attention under challenging temporal constraints.

Disclosures: **A.R. Kimata:** None. **B. Zheng:** None. **T. Watanabe:** None. **W.F. Asaad:** None.

Poster

152. Attention: Cognitive and Psychological Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 152.19

Topic: H.01. Attention

Support: Australian Research Council (ARC) DP210101093
Australian Research Council (ARC) DP220100803
Australia Defence Innovation Hub P18-650825
US Office of Naval Research Global under Cooperative Agreement Number ONRG - NICOP - N62909-19-1-2058
AFOSR – DST Australian Autonomy Initiative 10134
NSW Defence Innovation Network and NSW State Government of Australia DINPP2019 S1-03/09
NSW Defence Innovation Network and NSW State Government of Australia DINPP21-22.03.02

Title: Neural correlates of inattentional blindness under the interference of different sensory modalities within an immersive environment

Authors: *Y. TIAN, Y.-K. WANG, N. DO, C.-T. LIN;
Sch. of Computer Science, Fac. of Engin. and IT, Univ. of Technol. Sydney, Sydney, Australia

Abstract: Inattentional blindness (IB) occurs when an unexpected stimulus goes unnoticed when attention is engaged in a separate demanding task due to limited attention. Exploring the potential methods to attenuate the occurrence of IB is significant and has been addressed via manipulating the factors that might affect IB. To date, little evidence has been illustrated on exploring specific sensory modality interference to manipulate the IB occurrence and compare the neural correlates of IB within the ecological realistic virtual reality. Here in this study, we aim to investigate how different interference of sensory modalities, including unimodal and cross-modal, affect neural correlates of IB in an immersive environment. Two experimental phases were included with electroencephalography (EEG) to record neural responses: i) phase 1

(IB): participants were unaware of the unexpected task-irrelevant patterns and attended to the target detection task with target stimulus that appeared in auditory, visual or congruent visual-auditory manners, then followed by an awareness assessment of the unexpected patterns; ii) phase 2: participants were aware of the unexpected patterns but continued performing the target detection task. 30 participants (male: 20, female: 10) participated in this study, with 15 in the IB group (unaware of the patterns in phase 1); and the others belonging to the Aware group (aware of the patterns in phase 1). Target detection performance varied across different sensory modalities, with cross-modal showing higher accuracy and shorter response time than unimodal conditions. The unattended patterns elicited a negativity response post-stimulus around 300 ms in the parieto-occipital regions, which was absent under IB. Interestingly, the visual awareness negativity of conscious awareness varied across different presentation sensory modalities, with auditory and visual-auditory conditions showing more negativity differences but not under the visual condition. These findings might indicate that introducing cross-modal sensory information could affect the performance and neural changes of IB, and it might be due to the attention shift and reallocation across sensory modalities. These findings also supported our aims to explore the potential methods to manipulate the occurrence of the IB effect via adapting the information in different sensory modalities.

Disclosures: **Y. Tian:** None. **Y. Wang:** None. **N. Do:** None. **C. Lin:** None.

Poster

152. Attention: Cognitive and Psychological Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 152.20

Topic: H.01. Attention

Support: The National Research Council of Thailand
The Thailand Science Research and Innovation
The Asahi Glass Foundation
The KMUTT Partnering Initiative
The KMUTT's Frontier Research Unit Grant for Neuroscience Center for Research and Innovation

Title: Increased conflict resolution precise to cardinal orientation

Authors: *K. BENJASUPAWAN[1,2], T. SUDAYUWORN[1], P. SOOKPRAO[1,2], S. ITTHIPURIPAT[2], C. CHUNHARAS[1,3];
[1]Cognitive Clin. & Computat. Neurosci. Lab, Fac. of Med., Chulalongkorn Univ., Bangkok, Thailand; [2]Neurosci. Ctr. for Res. and Innovation, Learning Inst., King Mongkut's Univ. of Technol. Thonburi, Bangkok, Thailand; [3]Chula Neurosci. Ctr., King Chulalongkorn Mem. Hospital, Thai Red Cross Society, Bangkok, Thailand

Abstract: Selective attention is a complex behavioral and cognitive process often intertwined and multifaceted with perception. A well-known phenomenon in perception is the visual anisotropy, oblique effect, now novally explored in attention. This effect refers to the increase of orientation discriminability and neural sensitivity towards stimuli located in the cardinal directions (0°, 90°, 180°, 270°). While past research reported increased effective attention deployment to certain positions, the cause of such elevation remains unclear. We hypothesize that the attentional oblique effect is related to the increase in conflict resolution in cardinal positions. To test this, we measured the spatial resolution and conflict resolution of cardinal-oblique and vertical-horizontal anisotropy in healthy subjects using a modified spherical Ericksen Flanker task. We assessed the subject's reaction time (RT) to target onset in twelve (12) different clock-like positions during incongruent and congruent trials which are thought to reflect conflict resolution in selective attention. Oblique positions were separated into counter-clockwise and clockwise positions relative to the cardinals to take into account the precision of resolution. Consistent with previous research, we found a significant elevation of attention with targets located in the cardinal and vertical directions. When further explored into conflict resolution, we found a more precise attentional receptive field in cardinal compared to off-side oblique. We also found interactions between oblique effect and vertical-horizontal bias in which vertical cardinal is significantly more precise than horizontal cardinal. Together, our findings suggested that visual orientations are beneficial across spatial conflict resolution due to the narrowing of attentional receptive fields in cardinal degrees.

Disclosures: K. Benjasupawan: None. **T. Sudayuworn:** None. **P. Sookprao:** None. **S. Itthipuripat:** None. **C. Chunharas:** None.

Poster

152. Attention: Cognitive and Psychological Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 152.21

Topic: H.01. Attention

Support: NIH Grant R01MH106520
NIH Grant R01MH118847

Title: The computational consequences of parietal cortical surface area variation and its relationship to visual perception

Authors: *S. O. MURRAY, T. KOLODNY;
Univ. of Washington, Seattle, WA

Abstract: Cortical surface area within specific cortical subregions varies across individuals. However, how differences in surface area affect neural computation and specifically contribute to behavior is unknown. Here we examine how individual differences in cortical surface area in subregions of the parietal cortex relate to visual behavior. Parietal cortex is known to contribute

to spatial attention and have neurons with spatiotopically tuned "gain fields" which make this region amenable to computational modeling. For example, differences in the spatial width of attentional gain fields can be incorporated into well-established models of early sensory processing. These models provide important constraints on the expected relationships between behavior and cortical surface area of attentional control regions. The key assumption we make is that feedback circuits from parietal regions to early sensory areas are constrained in their anatomical extent. The predicted consequence of this assumption is that a person with a relatively large attentional control region in parietal cortex will have a relatively narrow spatial gain field. We present results analyzing behavior in a visual motion task in a sample of 52 adult participants. The task involves discriminating rightward versus leftward motion of briefly presented visual stimuli and the minimum duration threshold is identified for each participant. We first assessed whether cortical surface area in any subregion of the human connectome project multimodal parcellation atlas (HCPMMP) was associated with behavioral thresholds. Using cross-validation predictive modeling, we found that the surface area of subregions of the parietal cortex were inversely related to perceptual thresholds - larger surface area was associated with lower thresholds. In a subsequent model-constrained analysis, the optimal spatial gain field was fit for each subject to best account for their behavioral thresholds. We found that the model parameter that determines the width of spatial gain was inversely related to cortical surface area in subregions of parietal cortex. Overall, the results reveal key regions in parietal cortex where variations in surface area associate with performance in the visual motion task, and suggest a computational consequence of variation in cortical surface area.

Disclosures: S.O. Murray: None. **T. Kolodny:** None.

Poster

152. Attention: Cognitive and Psychological Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 152.22

Topic: H.01. Attention

Title: Engaging with information: Using EEG to enhance measures of engagement during an informational video

Authors: *R. D. TORRENCE, M. LEDERER, K. DOUGHERTY, S. B. BARNETT; ThinkAlike Labs., Northbrook, IL

Abstract: One of the most common methods of measuring engagement with audiovisual content is to simply ask viewers if a video was engaging. However, this method is subjective and lacks temporal precision; researchers are still left to ask which moments or scenes engaged the participant. Therefore, neuroscientists have sought to develop techniques for measuring viewer engagement objectively, with temporal precision, and without interruption to pose survey questions. One such technique utilized electroencephalography (EEG) to calculate cross-brain correlation (CBC) among moviegoers (Barnett & Cerf, 2017). The researchers found that CBC

measures engagement, which predicted movie trailer recall and opening weekend ticket sales. The CBC method measures the neural similarity (alpha waves) across participants. We used CBC to measure participant engagement in informational videos. We collected EEG data from 20 participants while watching a publicly available airline safety video. Additionally, we asked the participants, using a 1-10 Likert psychometric scale, if the video was engaging and informative. Ratings of engagement and informativeness were positively correlated with each other (Spearman's rank correlation), $r(18) = .79$, $p < .001$. We formed two groups based on rated informativeness, high informativeness (HI) rated the video 7 or more, and low informativeness (LI) rated it 6 or less. The HI group ($Mdn = 7$) rated the video as more engaging than the LI group ($Mdn = 5$), $U(N_{HI} = 13, N_{LI} = 7) = 83.50$, $p = .003$. The HI group ($M = 0.015$) had increased mean CBC compared to the LI group ($M = -0.008$), $t(582) = 8.61$, $p < .001$, indicating an overall increase in engagement across the video. However, the incremental benefit of CBC analysis is examining moment-to-moment engagement. The safety video provides important information to airline passengers, generally delivered by a single individual in frame with a simple background. The video creators used distractor scenes to transition from one informative topic to the next. During the informative scenes, the HI group ($M = 0.023$) had significantly higher peaks of CBC than the LI group ($M = -0.014$), $t(18) = 2.85$, $p < .01$. Additionally, CBC for the HI group increased during informative scenes compared to distractor scenes, $t(19) = -1.73$, $p < .05$, but the LI group's CBC did not differ between informative and distractor scenes. These results suggest that CBC measures moment-to-moment engagement during an informative video without relying on subjective self-report methods. These findings extend CBC's applications beyond the previously studied domain of entertainment to the important use case of informational videos.

Disclosures: R.D. Torrence: None. **M. Lederer:** None. **K. Dougherty:** None. **S.B. Barnett:** None.

Poster

152. Attention: Cognitive and Psychological Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 152.23

Title: WITHDRAWN

Poster

153. Decision Making Under Motivational Conflict: Neural Circuitry and Pharmacology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 153.01

Topic: H.03. Decision Making

Support: NSERC (RGPIN-2018-04295)

Title: Modulation of active and inhibitory avoidance by anxiogenic and depressive treatments

Authors: *I. DALY, G. L. DALTON, R. M. TODD, S. B. FLORESCO;
Psychology, Univ. of British Columbia, Vancouver, BC, Canada

Abstract: Flexibly initiating or withholding actions in a context-appropriate manner to minimize aversive outcomes is essential for survival. Altered avoidance profiles are associated with various neuropsychiatric disorders in humans, such as anxiety, PTSD, and depression. In previous rodent studies, brain areas relevant to the neurobiological expression of anxiety have been linked to the mediation of avoidance. Further investigations using rodent models of disorders like anxiety could be utilized to better understand the mechanisms that can underlie impairments in avoidance. In the present study, we investigated how pharmacological manipulations that induce “anxious” or “depressed” states in humans and rodents affect active and inhibitory avoidance in male and female Long-Evans rats. To this end, rats were well-trained on an aversive go/no-go task that required subjects to shift flexibly between active and inhibitory avoidance strategies to avoid receiving foot shocks. Trials began with insertion of a lever into a chamber and presentation of one of two distinct auditory cues. On 12 of these trials, one cue signaled an “active avoidance” trial, requiring a lever press within 15 s of insertion to avoid a shock. On the remaining 12 “inhibitory avoidance” trials, another cue signaled that responding must be withheld for 15 s, as a press during these trials resulted in the immediate delivery of shock. Separate groups of rats received treatment with either the inverse benzodiazepine FG-7142 (1, 5, and 10 mg/kg), the alpha-2 adrenergic antagonist yohimbine (10 mg/kg), or the monoamine depleting tetrabenazine (0.5 and 1 mg/kg). We hypothesized that anxiogenic drugs like FG-7142 and yohimbine would selectively impair active avoidance responses and our results support this hypothesis. Thus, treatment with either FG-7142 or yohimbine both reduced the number of active, but not inhibitory, avoidance. Notably, the effects of FG-7142 were considerably more reliable in male vs female rats, whereas the effects of yohimbine were comparable across sexes. In contrast, treatment with the monoamine depleter tetrabenazine, which can induce depressive-like symptoms, had no effect on either active or inhibitory avoidance. These findings provide insight into the mechanisms which underlie maladaptive patterns of avoidance in anxiety and could inform future translational and clinical studies of neurochemical basis of anxiety and avoidance.

Disclosures: I. Daly: None. **G.L. Dalton:** None. **R.M. Todd:** None. **S.B. Floresco:** None.

Poster

153. Decision Making Under Motivational Conflict: Neural Circuitry and Pharmacology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 153.02

Topic: H.03. Decision Making

Support: CIHR grant (PJT-162444)

Title: D1 and D2 dopamine receptor subtypes in nucleus accumbens core and shell exert differential effects on cue-guided risk-reward decision-making

Authors: *S. SCHOFIELD-LEWIS[1], S. B. FLORESCO[2];
[1]Univ. of British Columbia, Univ. of British Columbia, Vancouver, BC, Canada; [2]Univ. British Columbia, Univ. British Columbia, Vancouver, BC, Canada

Abstract: The ability to integrate cues to guide efficient decision making is a central behavioral adaptation in many organisms, and disorders involving pathophysiology of the dopamine (DA) system are associated with sub-optimal decision making. Prior research into dopamine modulation of decision-making has used probabilistic discounting tasks where internal representation of probability guide choice. Yet, real-world decision-making often involves using information provide by external cues to guide choice. To measure this, our group has developed a rodent assay known as the "Blackjack" task, requiring rats to use external stimuli to guide optimal decisions. Each trial involves the presentation of one of two auditory cues, followed by the extension of two levers. Rats choose between the small/certain lever (1 pellet at 100% probability) and the large/risky lever (4 pellets, probabilistically). The auditory stimuli signals if the large/risky lever will have good (50%) odds or poor (12.5%) odds of delivering the large reward. Separate groups of rats were trained on a control, conditional auditory discrimination task, wherein the same two cues were used to inform animals that a response on either the lever or right lever would deliver reward with 100% certainty, thereby removing the probabilistic component embedded in the Blackjack task. Using these task, we investigated the influence of intracranial D1 and D2 antagonists in the nucleus accumbens core/shell in male and female rats. Animals were well-trained on the tasks and then received intracranial infusions of either D1 or D2 antagonists prior to testing. Previous work by our group has shown that a D1 blockade reduces risky choice during probabilistic discounting guided by internal representations of reward history. In contrast, a recent study by our group using systemic DA manipulations on the Blackjack task found that D1 antagonism did not affect choice on the Blackjack task. This suggests recruitment of distinct underlying decision-making circuits between the tasks. Preliminary data show that infusion of either DA antagonist into the accumbens shell had no effect on performance of the conditional auditory discrimination. The current study aims to highlight both the functional heterogeneity of the nucleus accumbens core and shell, and investigate potential sex differences between our male and female subjects on how D1 and D2 antagonism affects risk/reward decision making guided by external cues.

Disclosures: S. Schofield-Lewis: None. **S.B. Floresco:** None.

Poster

153. Decision Making Under Motivational Conflict: Neural Circuitry and Pharmacology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 153.03

Topic: H.03. Decision Making

Support: CIHR grant (PJT-162444)

Title: Modulation of reward-related risky decision making and response inhibition involving punishment by different types of acute stress

Authors: *G. LAINO CHIAVEGATTI[1], G. L. DALTON[2], A. SAMS[1], S. B. FLORESCO[1]; [1]Psychology, Univ. of British Columbia, Vancouver, BC, Canada; [2]Psychology, Univ. of British Columbia, VANCOUVER, BC, Canada

Abstract: Effective decision making entailing evaluation of the potential costs and benefits associated with different actions is essential for survival. Recent studies in rodents have indicated that stressors can differentially alter reward-related decision-making depending on the type of costs being evaluated. For example, acute restraint stress does not alter preference for larger/uncertain or delayed rewards *vs*. smaller certain/immediate ones, but does shift preference away from larger rewards linked to greater physical effort costs. Yet, how stress may modulate decisions where rewards are linked to punishment has yet to be fully explored. We examined how acute restraint and pharmacological stress influenced action-selection on two tasks involving reward-seeking under risk of punishment in male and female rats. In one study, we adopted a risky decision-making task involving choice between a small/safe lever always delivering one reward pellet and a large/risky option delivering three pellets but that could also deliver foot shock with an increasing probability across blocks of trials (0, 25, 50, 75, 100%). In well-trained rats, one-hour restraint increased risk aversion and punishment sensitivity, reducing preference for the larger yet potentially punished rewards in both sexes. Stress also increased response latencies and trial omissions in both sexes, with females generally showing lower levels of task engagement overall. In contrast, the α-2 noradrenergic antagonist yohimbine had minimal effects on choice. A second study used a go/no-go "behavioral control" task that assessed ability to inhibit approach towards a readily available reward associated with punishment. Here, a food pellet was delivered in a cup, and on 30/60 trials the rat merely had to approach and retrieve reward. On the other 30 trials, a 12-s visual/auditory warning cue signaled food retrieval also delivered foot shock and that approach must be withheld until cue termination. Both restraint stress and yohimbine had comparable effects which differed across sexes. These stressors made males more impulsive on test day, as they were less likely to suppress reward retrieval for the full 12 s, and received more punishment. In contrast, females were unaffected by stress on the test day, and were actually less impulsive when tested 24 hr later. These findings suggest acute restraint enhances the effects of punishment on choice between different rewards while differentially altering sensitivity to punishment-associated cues in males and females. The mechanisms underlying this effect may relate to the increased risk aversion observed in individuals with depression.

Disclosures: G. Laino Chiavegatti: None. **G.L. Dalton:** None. **A. Sams:** None. **S.B. Floresco:** None.

Poster

153. Decision Making Under Motivational Conflict: Neural Circuitry and Pharmacology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 153.04

Topic: H.03. Decision Making

Support: NSERC (RGPIN-2018-04295)

Title: Prelimbic prefrontal dopamine D1 and D2 receptors modulate discrimination of conditioned cued fear

Authors: *M. ZHAO, G. CAPUZZO, S. B. FLORESCO;
Psychology, Univ. of British Columbia, Vancouver, BC, Canada

Abstract: Threat and safety are often signaled by environmental cues, and adaptive behaviour relies on learning and discriminating between these cues. While fear and avoidance are appropriate responses to life-threatening stimuli, persistence of these behaviours in the absence of danger maladaptively prevents an animal from tending to other survival needs, such as food-seeking. Both human and rodent studies have shown medial prefrontal cortex engagement in this threat/reward decision conflict. Pharmacological blockade of $GABA_A$ receptors in the prelimbic region (PL) of the rat medial prefrontal cortex reduces an animal's fear response to a threat cue, while increasing its fear response to an innocuous cue. Dopamine transmission modulates prefrontal excitatory/inhibitory tone through its actions on GABA interneurons and has been implicated in the encoding of threat-predictive cues. To further study the role of prefrontal dopaminergic signaling, we performed intracranial infusions of either the D1 receptor antagonist, SCH 23390, or D2 receptor antagonist, eticlopride, into the PL in a fear discrimination task. Animals first learned to lever press for reward on a VI60 schedule. Then, animals were conditioned to associate an aversive footshock (US) with an auditory and visual "threat" cue (CS+), and an innocuous "safety" cue (CS-) with the absence of any event. Two days later, these cues were presented while rats were again lever pressing for food, and discriminative fear behaviour was measured as the conditioned suppression of pressing in response to the CS+ and CS-. Preliminary findings indicate that PFC D1 receptor blockade prior to the discriminative fear expression test tended to heighten the conditioned fear response to both the CS+ and CS- compared to saline controls. D2 receptor blockade made animals lever press less in response to the CS+, but more in response to the CS-, reflecting more adaptive threat/safety discrimination. In light of the fact that D1 and D2 receptors facilitate and attenuate GABA signaling on prefrontal neurons, respectively, these findings suggest that dopaminergic signaling in the prefrontal cortex may modulate the expression of fear discrimination via. GABA-mediated inhibition.

Disclosures: **M. Zhao:** None. **G. Capuzzo:** None. **S.B. Floresco:** None.

Poster

153. Decision Making Under Motivational Conflict: Neural Circuitry and Pharmacology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 153.05

Topic: H.03. Decision Making

Support: CIHR grant (PJT-162444)

Title: Investigating the temporal dynamics of mesocortical and mesoaccumbens dopamine signaling in motivation and decision making

Authors: *J. SCHUMACHER, D. A. BERCOVICI, M. ZHAO, M. HALL, S. B. FLORESCO; Psychology, Univ. of British Columbia, Vancouver, BC, Canada

Abstract: Dopamine is a critical modulator of motivation and decision making. However, mesoaccumbens vs mesocortical dopamine projections differentially modulate performance on many motivation and decision making tasks. For example, probabilistic discounting tasks requires a decision maker to choose between a small/certain and a large/risky reward with the odds associated with the large/risky reward changing systematically in blocks of trials. Using this task, our group has demonstrated that nucleus accumbens dopamine, acting on D1 receptors, promotes preference for large/uncertain rewards whereas cortical dopamine release refines choice through opposing actions at D1 vs. D2 receptors. Microdialysis studies complement these findings, showing that dopamine efflux in the nucleus accumbens and cortex tracked reward uncertainty and overall reward rates, respectively. While these studies are informative, dopamine signaling manifests as temporally discrete, phasic bursts of activity that occur prior to action selection or in response to outcomes of those actions. As such, pharmacological manipulations cannot provide information about how temporally discrete activity of the dopamine system may influence behavior during different phases of the decision process. To address this gap, we are using optogenetic silencing of nucleus accumbens or medial prefrontal cortex projecting VTA dopamine neurons in male and female rats performing a probabilistic discounting task. These experiments silence either pathway prior to choice as well as after different choice outcomes (risky wins, risky losses, certain wins) or during the ITI. A parallel set of experiments have been investigating the role of mesoaccumbens dopamine transmission in a more basic measure of motivation - progressive ratio responding. Preliminary data from the progressive ratio task suggests that terminal silencing of accumbens dopamine inhibition at the beginning of a ratio increases latency to reengage in lever pressing whereas inhibition at the end of a ratio has no effect on latency to collect reward. Finally, inhibition at the beginning of a bout of lever pressing decreased the total number of presses and the maximum breakpoint achieved. Collectively these data will elucidate the precise temporal dynamics of dopamine signaling supporting motivation and risk-based decision making.

Disclosures: J. Schumacher: None. **D.A. Bercovici:** None. **M. Zhao:** None. **M. Hall:** None. **S.B. Floresco:** None.

Poster

153. Decision Making Under Motivational Conflict: Neural Circuitry and Pharmacology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 153.06

Topic: H.03. Decision Making

Support: NSERC (RGPIN-2018-04295)

Title: Monoaminergic modulation of inhibitory impulse control in the context of punished reward-seeking

Authors: *S. B. FLORESCO, G. LAINO CHIAVEGATTI;
Psychology, Univ. British Columbia, Vancouver, BC, Canada

Abstract: Making and withholding responses appropriately to achieve a goal is essential when dealing with threatening stimuli and achieve the best outcome possible, and is a critical skill for survival. Situations involving threat often require the integration of multiple cues that are predicting of a negative outcome to guide action-selection, or they may be also avoided by withholding behavior in response to cues. It is well established that certain aspects of impulse control are regulated by different monoamines, although the specific manner in which pharmacological manipulations of monoaminergic transmission may alter impulsive choice or action can vary considerably, depending on the particular cognitive and emotional processes being taxed. Here we examined how monoaminergic transmission influenced action-selection on an operant assay involving reward-seeking under risk of punishment in male and female rats. To this extent, we adopted a behavioural control task that entailed positively reinforcing active responses intermixed with punishment. In this task, a food pellet was delivered in a cup, and on 30/60 trials the rat merely had to approach and retrieve reward. On the other 30 trials, a 12-s visual/auditory warning cue signaled food retrieval also delivered foot shock, and that reward retrieval must be withheld until cue termination to avoid punishment. Rats were well-trained on this task for ~12 days and were then given 1.0 mg/kg of the psychostimulant and monoamine releaser D-amphetamine. Treatment with amphetamine induced an expected increase in overall locomotor activity. Yet, these treatments exerted a pronounced and seemingly opposite effect on impulse control. Specifically, these treatments markedly reduced impulsive responding, as rats were more likely to wait 12 s for the warning cue to terminate and then retrieve reward without being shocked compared to control conditions. Amphetamine also reduced the proportion of trials where food was retrieved in females on both non-punished and potentially punished trials. These findings suggest that increased monoamine transmission can markedly enhance the ability of cues signaling potential punishment to suppress impulsive reward-seeking under threat. Future studies will use more selective pharmacological approaches to dissect the contribution of dopaminergic, noradrenergic and serotonergic transmission to these processes.

Disclosures: S.B. Floresco: None. **G. Laino chiavegatti:** None.

Poster

153. Decision Making Under Motivational Conflict: Neural Circuitry and Pharmacology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 153.07

Topic: H.03. Decision Making

Support: NJBIR Grant CBIR20PIL004
NJBIR Grant CBIR19IRG025
Osteopathic Heritage Foundation for Primary Care Research

Title: Sex-specific variation of catecholamine regulatory proteins may underlie increased risky choice preference following repetitive mild traumatic brain injury

Authors: *C. P. KNAPP[1], E. PAPADOPOULOS[1], J. A. LOWETH[1], C. M. CORBETT[1], S. B. FLORESCO[2], B. D. WATERHOUSE[1], R. L. NAVARRA[1];
[1]Cell Biol. and Neurosci., Rowan Univ. Sch. of Osteo. Med., Stratford, NJ; [2]Univ. British Columbia, Vancouver, BC, Canada

Abstract: Mild traumatic brain injury (mTBI) can disrupt cognitive processes that influence risk-taking behavior. The medial (mPFC), orbitofrontal (OFC), and anterior cingulate (ACC) regions of the PFC play prominent roles in risk/reward decision making. Currently, little is known regarding the effects of repetitive injury (rmTBI) on risk/reward decision making or whether these outcomes are sex-specific. Here we examined how rmTBI affects risk/reward behavior in rodents using a probabilistic discounting task (PDT) that mimics risky gambling behavior in humans. Rats are required to choose between small/certain rewards delivered with 100% certainty and large/risky rewards delivered with decreasing probabilities over a session. Rats were first trained on the PDT and then exposed to sham surgery (no mTBI), a single injury (smTBI), or a series of three closed-head control cortical impact (CH-CCI) injuries over the course of one week. Rats then returned to the PDT for testing for four weeks. RmTBI increased risky choice in females, but not males, during the first two weeks post-injury. Choice behavior normalized by week 3 indicating that these effects are transient. Previous reports have demonstrated catecholamine imbalances within the PFC following TBI, which may underlie TBI-induced behavioral outcomes. To further investigate our observations and potential mechanisms of catecholamine imbalance within the PFC, Western blotting was used to measure levels of the synthetic enzyme, TH, packaging enzyme, VMAT2, reuptake transporter, NET, and degradation enzymes, COMT and MAO-A, in PFC sub-regions 48 hours following rmTBI. No injury-induced differences were detected within the mPFC or ACC; however, sex-specific TBI-induced changes were observed within the OFC. Levels of TH were increased in the OFC of injured females suggesting increased catecholamine synthesis. Levels of VMAT2 were reduced in the OFC of rmTBI males and females indicating a lower capacity for packaging and release. NET and COMT were reduced in the OFC of rmTBI males and females, while MAO-A was only reduced in the OFC of rmTBI females. Reduced levels of NET indicate lower reabsorption of catecholamines from the synapse, while decreased COMT and MAO-A may reflect a decreased need for degradation. The sex-specific decrease of MAO-A in the OFC of rmTBI females may serve as a novel variable to further elucidate differential rmTBI-induced mechanisms of increased risky choice preference. As such, combining the CH-CCI model of rmTBI, PDT, and Western blotting creates an innovative model for studying the effects of TBI on male vs. female subjects and the neural mechanisms underlying those behavioral changes.

Disclosures: **C.P. Knapp:** None. **E. Papadopoulos:** None. **J.A. Loweth:** None. **C.M. Corbett:** None. **S.B. Floresco:** None. **B.D. Waterhouse:** None. **R.L. Navarra:** None.

Poster

153. Decision Making Under Motivational Conflict: Neural Circuitry and Pharmacology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 153.08

Topic: H.03. Decision Making

Support: Whitehall Foundation 2019-08-82
Brain and Behavior Research Foundation 2843
NIMH, 1R21MH121888-01A1

Title: Role of D1- and D2-receptor prefrontal-accumbens circuits in mediating cognitive flexibility and stress pathology.

Authors: *A. WAKHLU, E. ANDERSON, S. DEMIS, A. CZYZ, A. EDWARDS, M. HEARING;
Dept. of Biomed. Sci., Marquette Univ., Milwaukee, WI

Abstract: Deficits in cognitive flexibility is one of the most consistently documented cognitive problems in neuropsychiatric disorders and contributes to reduced emotional control and development of maladaptive behaviors (i.e., substance abuse) and increased susceptibility to negative life events (e.g., stress). This dynamic behavior requires coordinated activity of principle output pyramidal neurons in the prelimbic region of the medial prefrontal cortex (PrL-PFC) to brain regions such as the mediodorsal thalamus (MDT) and nucleus accumbens core (Core). Within these circuits lie subcircuits comprised of pyramidal neurons that selectivity express dopamine type 1 (D1) and type 2 (D2) receptors that are thought to differentially contribute to processing of information related to flexible decision-making, however their exact contributions remain unknown. Here, we combined a clinically relevant model of attentional set-shifting to assess cognitive flexibility with Cre-dependent retrograde viral targeting in male and female D1- and D2-Cre transgenic mice on a C57bl6/j background to promote expression of the inhibitory DREADD, hM4Di or mcherry control in PrL-Core subcircuits (D1-Core, D2-Core). In male mice, intra-PrL infusion of 1mM clozapine-n-oxide (CNO; 0.5uL into each hemisphere) increased the mean number of trials to reach criteria during an extradimensional set-shift test of flexibility in D1-Core but not D2-Core mice compared to mcherry controls. In females, neither inhibition D1-Core or D2-Core circuits altered performance versus mcherry controls. Follow up studies in females using a similar circuit-specific approach to retrogradely target the PrL-Core circuit as a whole in wild-type (C57bl6/j) mice also showed no effect on trials to criteria versus control mice however inhibiting PrL pyramidal neurons regardless of downstream projection showed increased trials to criteria versus controls. These data suggest that D2-Core circuits in males play a larger role in regulating flexible behavior. Further, as a majority of studies to date studying the role of the PrL in flexibility have almost exclusively used males, our findings

highlight a previously unknown sex difference in the neural circuits required for flexibility. Ongoing studies are examining the impact of globally inhibiting the PrL-Core circuit in males, targeting alternate circuits in females and examining a link between D2-Core circuit dysfunction in stress-mediated reductions in cognitive flexibility in males.

Disclosures: **A. Wakhlu:** None. **E. Anderson:** None. **S. Demis:** None. **A. Czyz:** None. **A. Edwards:** None. **M. Hearing:** None.

Poster

153. Decision Making Under Motivational Conflict: Neural Circuitry and Pharmacology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 153.09

Topic: H.03. Decision Making

Support: 2020R1A2C2014830
2021M3E5D2A01023887
2020R1A2C2102134
2017H1A2A1044665

Title: Heterogenous encoding of spatial and non-spatial information by the medial prefrontal cortex in rats during naturalistic foraging

Authors: *J. JEONG, S. LIM, J.-S. CHOI;
Sch. of Psychology, Korea Univ., Seoul, Korea, Republic of

Abstract: The medial prefrontal cortex (mPFC) has been implicated in goal-directed spatial navigation tasks due to its role in working memory and planning. In this regard, several studies attempted to predict animals' location using neural activity within the mPFC. However, the accuracy of the spatial information decoded from mPFC ensemble activity varies across different studies. Here we subject food-deprived rats to a naturalistic foraging situation where an opportunity to acquire food resources and a threat posed by a predatory attack coexist. The foraging arena was composed of three distinct sections: Nest zone (N), Foraging zone (F), and Threat zone (T). Initially, the rats were free to explore and approach the sucrose solution dispenser within T. Next, they were trained to shuttle between N and T across F until they consistently acquired rewards. In the following days, they were faced with a striking attack by Lobsterbot, named after its fast-closing jaw, 3 or 6 s after the first lick while approaching for sucrose. The attack immediately evoked a withdrawal response. This paradigm continued to produce a mixture of approach and avoidance behavior during which neuronal activities were recorded using implanted tetrodes micro-drive. Single unit activities from 635 units were analyzed based on their firing rate. Among them, 56 % showed significant modulation of approach-related activity, 46 % avoidance, and 37% both. To further investigate the ensemble encoding of their behavioral relevance, we implemented a 4-layer artificial neural network (ANN) to predict the head position from simultaneously recorded neural activity. The results

show a striking discrepancy in encoding accuracy depending on the zone. The L1 error of the ANN position predictor was 15.78 cm (distance from Lobsterbot), which was significantly lower than the predictor based on shuffled unit activity. On the other hand, the error rate of the ANN predictor significantly increased compared to F when animals were moving in N or facing the robot in T. Considering the modulation of approach and avoidance-related firing within T, these data suggest that neurons in mPFC encode goal-relevant spatial information only when the location is moderately distant and perhaps switch to a different encoding mode when the task demand changes.

Disclosures: **J. Jeong:** None. **S. Lim:** None. **J. Choi:** None.

Poster

153. Decision Making Under Motivational Conflict: Neural Circuitry and Pharmacology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 153.10

Topic: H.03. Decision Making

Support: NIMH K08 MH122733
VA National Center for PTS
BBRF NARSAD Y.I.
NIH/NINDS R00NS114166

Title: Synergistic dynamics of norepinephrine, dopamine, and serotonin in mouse frontal cortex during naturalistic decision-making

Authors: *J.-H. YANG[1], R.-J. LIU[1], S. M. STASZKO[1], A. BASU[1], A. YU[1], J. RONDEAU[1], S. GLAESER-KHAN[1], Y. LI[2], A. CHE[1,3], A. P. KAYE[1,3];
[1]Dept. of Psychiatry, Yale Univ., New Haven, CT; [2]Peking Univ., Beijing, China; [3]Clin. Neurosciences Div., VA Natl. Ctr. for PTSD, West Haven, CT

Abstract: In nature, animals must forage for food under environmental danger to survive. Neuromodulators including norepinephrine (NE), dopamine (DA), serotonin (5HT) play a fundamental role in this process, enabling flexible switching between motivational drives. The question of how neuromodulators synergistically encode motivational state is thus fundamental to systems neuroscience, yet the interplay between these neuromodulators during naturalistic decision-making are not fully understood. Here, we developed a naturalistic approach/avoidance task in mice involving a tradeoff between seeking reward versus safety in the presence of predation risk (looming stimuli). We utilized whole-brain cFos mapping, slice electrophysiology, computational behavior tracking, and multifiber photometry in this task. The results indicate that mice who experienced looming stimuli showed increased cFos expression in regions including frontal cortex, amygdala, and locus coeruleus but decreased expression in dorsal nucleus raphe. To directly examine neuromodulatory interactions, an *ex vivo* slice physiology experiment suggests that 5HT induces local inhibition on subset of locus coeruleus NE neurons.

Furthermore, multiple neuromodulators were recorded simultaneously using multifiber photometry of GPCR-based sensors (DA, 5HT, NE) to investigate the representations of motivational drives both individually and collectively. We found that DA, NE, and 5HT each showed distinct encoding of innate reward and threat from one another, while remaining highly correlated at other times. Although 5HT trace *per se* does not encode threat, 5HT interacts with NE to increase prefrontal NE in a receptor-dependent manner. These findings indicate the importance of cross-talk between different neuromodulatory circuits in representing approach/avoidance conflict. In conclusion, monoamines such as NE, DA, 5HT can converge in their encoding of naturalistic motivated behaviors as well as dissociate from one another. By utilizing this approach, interactions between motivational drives may be delineated in terms of basis in neurochemical signaling events during natural behavior.

Disclosures: **J. Yang:** None. **R. Liu:** None. **S.M. Staszko:** None. **A. Basu:** None. **A. Yu:** None. **J. Rondeau:** None. **S. Glaeser-Khan:** None. **Y. Li:** None. **A. Che:** None. **A.P. Kaye:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Transcend therapeutics, inc..

Poster

153. Decision Making Under Motivational Conflict: Neural Circuitry and Pharmacology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 153.11

Topic: H.03. Decision Making

Support: Natural Science and Engineering Research Council of Canada (NSERC)
UBC Djavad Mowafaghian Centre for Brain Health (DMCBH) Innovation Fund
Kickstart Research Grant

Title: Comorbid depression and anxiety symptoms impair active but not inhibitory avoidance in the presence of motivational conflict

Authors: *R. J. TOMM, L. KALENTERIDIS, L. CLARK, T. CHAKRABARTY, S. B. FLORESCO, R. M. TODD;
Univ. of British Columbia, Vancouver, BC, Canada

Abstract: Alternating between avoidance and reward-seeking behaviors requires the prioritization of actions that are relevant to an individual's current and overarching goals. Achieving the appropriate balance between avoidance and reward-seeking is critical to minimize aversive outcomes while maximizing beneficial outcomes. Maladaptive avoidance and reward-seeking behaviors have been associated with anxiety and depressive disorders, respectively. However, research has traditionally focused on these disorders in isolation with little emphasis on how they might interact to regulate avoidance and reward-seeking behaviors. Indeed, anxiety and depressive disorders are highly comorbid and are associated with worse treatment outcomes.

Furthermore, neuropsychiatric research has relied heavily on self-report measures of behavior - making it difficult to translate findings with pre-clinical animal models. Using a transdiagnostic approach, we aim to investigate how anxiety and depressive symptoms interact to regulate avoidance and reward-seeking behaviors in humans using a Go/No-Go task with cross-species translational utility. Undergraduates (N = 68) ranging in anxiety symptom (Beck Anxiety Inventory, BAI; Range = 1-37) and depressive symptom (Beck Depression Inventory-II, BDI; Range = 0-46) severities completed an uninstructed orthogonalized go/no-go task. Four cues indicated the type of response (go/active vs. no-go/inhibitory) and the motivational context (avoidance vs. reward-seeking) to either avoid an unpleasant noise or obtain monetary rewards. The task consisted of two stages: 1) An acquisition stage required the learning of active avoidance and active reward-seeking responses; 2) An intermixed stage required the flexible learning of both active and inhibitory responses. Participants demonstrated reduced accuracy on trial types where the correct response conflicted with the prepotent response normally instigated in a particular motivational context, in that performance was better on inhibitory vs active avoidance and active vs inhibitory reward-seeking. Furthermore, a regression analyses revealed a negative relationship between anxiety scores and active reward-seeking accuracy, but only in participants high in depressive symptoms. These findings highlight the utility of using a transdiagnostic approach to further our understanding of the relationship between anxiety and depressive symptoms in regulating avoidance and reward-seeking behaviors.

Disclosures: R.J. Tomm: None. **L. Kalenteridis:** None. **L. Clark:** None. **T. Chakrabarty:** None. **S.B. Floresco:** None. **R.M. Todd:** None.

Poster

153. Decision Making Under Motivational Conflict: Neural Circuitry and Pharmacology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 153.12

Topic: H.04. Executive Functions

Support: R01 MH053851
T32 NS082145

Title: Role of paraventricular thalamus to orbitofrontal cortex pathway in the effects of stress on reversal learning

Authors: *K. M. TUITE, K. TAPIA MENCHACA, M. GIROTTI, D. A. MORILAK;
The Univ. of Texas Hlth. Sci. Ctr. At S, UT Hlth. San Antonio, San Antonio, TX

Abstract: Stress-related psychiatric disorders, such as major depressive disorder and anxiety disorders, have cognitive flexibility deficits that persist even after other symptoms of these disorders go into remission. Reversal learning, a form of cognitive flexibility necessary to adapt to a changing environment, is disrupted in stress-related psychiatric disorders. The orbitofrontal cortex (OFC) mediates reversal learning, and hyperactivity in the OFC is associated with

depression and obsessive-compulsive disorder in humans. Using a reward-based discrimination digging task to assess reversal learning in rodents, we have previously reported that chronic stress impairs reversal learning and potentiates responses to excitatory input in the OFC, and that inducing long-term depression in the mediodorsal thalamus to OFC pathway reverses these deficits, indicating that increased activity in projections to the OFC is detrimental to reversal learning. However, the circuit-level mechanisms underlying stress-induced reversal learning deficits are not well established. Preliminary data using Fos immunohistochemistry, showed a significant decrease in Fos in the lateral OFC following reversal learning, and Fos expression in paraventricular thalamus (PVT). Converging evidence from other laboratories suggests that the PVT projects to the OFC and that the PVT is activated by chronic stress, as shown by ΔFosB expression. Therefore, we next tested the hypothesis that input to the OFC from the PVT, when activated chemogenetically or by chronic stress, will disrupt reversal learning. We used an adeno-associated virus to deliver an excitatory (Gq) DREADD, an inhibitory (Gi) DREADD, or GFP control into the PVT under the control of the CaMKII promoter, and implanted guide cannulae into the lateral OFC for pathway specific in/activation. Animals received microinjections of the DREADD agonist clozapine-N-oxide (300 μM, i.c. 0.75 μL) directly preceding the reversal learning task. Activating the PVT-OFC pathway with the Gq DREADD significantly impaired reversal learning in non-stressed animals, while inhibiting the PVT-OFC pathway with the Gi DREADD in chronically stressed animals reversed the stress-induced deficits in reversal learning. These results suggest that increased activation in the PVT to OFC pathway is detrimental to reversal learning, and this potentially contributes to the detrimental effects of chronic stress. This indicates a circuit not yet investigated in the role of chronic stress in disruptions in cognitive flexibility. Future experiments will determine how dysfunction in the PVT-OFC pathway may disrupt other OFC-related circuits.

Disclosures: K.M. Tuite: None. **K. Tapia Menchaca:** None. **M. Girotti:** None. **D.A. Morilak:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); H. Lundbeck, Copenhagen, Denmark. Other; South Texas Veteran's Health Care System, San Antonio TX.

Poster

153. Decision Making Under Motivational Conflict: Neural Circuitry and Pharmacology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 153.13

Topic: G.07. Post-Traumatic Stress Disorder

Support: VA BX004727-01

Title: Effect of acute stress and stress-conditioned cues on matrix metalloproteinases in the nucleus accumbens core

Authors: *R. HODEBOURG[1], C. GARCIA-KELLER[2], P. W. KALIVAS[1];
[1]Neurosci., Med. Univ. of South Carolina, Charleston, SC; [2]Pharmacol. and Toxicology, Med. Univ. of South Caroline, Milwaukee, WI

Abstract: Post-traumatic stress disorder (PTSD) is a psychiatric disease that is seen in a subpopulation of people experiencing a traumatic event. It is well established that there is a strong comorbidity between PSTD and substance use disorders. Preclinical studies have shown that acute stress produces long-lasting neuroadaptations at glutamatergic synapses in the nucleus accumbens core (NAcore) that parallel those produced by drug self-administration. Thus, 2h of restraint stress followed by 3 weeks induces an increase in the AMPA/NMDA ratio and dendritic spine density, and downregulates the glutamate transporter (GLT-1) in the NAcore. Furthermore, a stress-conditioned stimulus (CS) is able to reinstate drug seeking behavior. Based on these data we hypothesized that, like drug-associated cues, a stress-CS induces transient-synaptic potentiation (t-SP) in the NAcore. Knowing that cue-induced t-SP and drug seeking requires activation of NAcore matrix metalloproteinases (MMPs), we sought to determine whether a stress-CS also activates MMPs. We first evaluated the effect of an acute stress on MMP-2,9 activity. For this purpose, rats were microinjected with FITC-quenched gelatin into the NAcore immediately before 30 min of acute restraint stress or 30 min in the home cage. We found that an acute stress increased the MMP-2,9 activity in the NAcore. Then, to evaluate the role of a stress-CS on the behavior and MMP-2,9 activity, rats were restraint stressed for 2h and simultaneously exposed to an odor that became the stress-CS. Control rats were exposed to the same odor in the home cage. 3 weeks after the stress, FITC-quenched gelatin was injected into the NAcore and the effect of the CS or a novel stimulus (NS) was tested in a defensive burying task for 15 min. The burying and immobility behaviors, as well as MMP-2,9 activity were quantified. The stress-CS induced burying behavior and elevated MMP-2,9 activity compared to the sham control. However, there is no difference between stressed rats exposed to the CS and the NS. To determine if the stress-CS induced burying is mediated by MMP-2,9, we pretreated rats with MMP-2 or -9 inhibitors. Both MMP-2 and -9 inhibitors prevented the burying behavior without affecting the immobility. Finally, we quantified MMP-2,9 activity in a cell specific manner. To this end, we used an AAV cre-dependent mCherry virus to transfect medium spiny neurons (MSN) in D1 and D2 cre-dependent rats. The stress-CS significantly increased MMP-2,9 specifically around D1 MSNs. These findings contribute to a growing literature suggesting that PTSD and SUDs share common neural substrates and offer new targets for treating both disorders.

Disclosures: R. Hodebourg: None. **C. Garcia-Keller:** None. **P.W. Kalivas:** None.

Poster

154. Cognitive Factors Affecting Learning and Memory

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 154.01

Topic: H.04. Executive Functions

Title: Within-trial sensory feedback during instrumental learning enables rapid and efficient task acquisition

Authors: *A. RANGANATH, D. HÄHNKE, S. N. JACOB;
Translational Neurotechnology Laboratory, Dept. of Neurosurgery, Klinikum rechts der Isar, Tech. Univ. of Munich, Munich, Germany

Abstract: The process of instrumental learning is time consuming, requiring several hundreds to thousands of trials in which a subject has to link the required response to a preceding sensory cue by exploring all available motor alternatives. Typically, the correctness of response is reported to the subject only at the end of a given trial. In such a scenario, a subject is unable to determine the correctness of the response within the trial to make necessary changes. Here, we investigated whether providing intra-trial sensory feedback aids the process of instrumental learning. We trained 3 cohorts of head-fixed mice (761 sessions) on a two-alternative forced-choice task in which animals indicated their responses to a sensory cue (auditory and/or visual) by rotating a wheel to the left or to the right. The wheel's position could be continuously monitored to track the animals' decision states and to provide closed-loop feedback. The first cohort (n = 9) received no feedback about their responses during a given trial, i.e. wheel movements were not coupled to changes of the auditory cue. The second cohort (n = 10) received unimodal auditory feedback, i.e. wheel movements were coupled to changes of the auditory cue. The third cohort (n = 4) received multimodal auditory and visual feedback, i.e. wheel movements were coupled to changes of both auditory and visual cues. We grouped the performance of animals into novice (0-50%), intermediate (50-70%) and expert (70-90%) stages. We found that animals without feedback took significantly longer to reach the expert stage than animals with unimodal or multimodal feedback (median number of trials 7329 vs. 4918 vs. 3186, Kruskal Wallis test and Dunn's post-hoc test, $p<0.05$). The analysis of wheel movements revealed that animals with multimodal and unimodal feedback performed more exploratory movements before crossing the trained threshold compared to animals with no feedback (16% vs. 10% vs. 8%, expert stage; Kruskal Wallis test and Dunn's post-hoc test, $p<0.001$). Further, the accuracy of trials involving exploratory movements was significantly higher in animals with multimodal and unimodal feedback compared to animals with no feedback (77% vs. 68% vs. 64%, expert stage; Kruskal Wallis test and Dunn's post-hoc test, $p<0.001$). Taken together, these results indicate that providing within-trial, closed-loop sensory feedback expedites the process of instrumental learning by allowing the animals to explore and monitor their actions' sensory consequences. Our findings have implications for how animal training procedures should be designed to achieve efficient and high-throughput training regimes.

Disclosures: A. Ranganath: None. **D. Hähnke:** None. **S.N. Jacob:** None.

Poster

154. Cognitive Factors Affecting Learning and Memory

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 154.02

Topic: H.04. Executive Functions

Support: Puerto Rico IDeA Network of Biomedical Research Excellence 5P20GM103475-18

Title: Postnatal exposure to particulate matter induces neuroinflammation and cognitive deficits in juvenile mice

Authors: H. J. ROSA, D. L. MENENDEZ, N. A. PAGAN, K. M. CASILLAS, ***L. B. MENDEZ**;
Sci. & Technol., Univ. Ana G. Mendez, Carolina, PR

Abstract: Epidemiological studies have reported associations between exposure to ambient particulate matter (PM) and neurocognitive impairments. Children are particularly vulnerable to the effects of ambient PM since their CNS is still in development, especially in regions related to executive functions. Toxicological studies have reported oxidative stress and neuroinflammatory responses in mice exposed to different types of PM. However, most studies have focused on prenatal, perinatal, and adult PM exposures. The goal of this study was to assess if PM exposure impairs the postnatal development of executive function. We hypothesized that PM exposure will impair executive function by inducing inflammatory responses in the CNS. To test this hypothesis, female and male C57BL/6J mice (n=14/group) were exposed intranasally to either saline or increasing doses of diesel exhaust particles (DEP) during postnatal days (PND) 25 to 33. Behavioral and cognitive outcomes were assessed on PND 36 to 38. Mice locomotor activity and exploratory behaviors were evaluated with Open Field Test; and . problem-solving skills, short- and long-term memory with the Puzzle Box paradigm. Mice were euthanized on PND 39 and brain tissue was collected to measure the concentration of proinflammatory cytokines and chemokines. Mice exposed to DEP exhibited hyperactive behaviors and deficits in problem-solving and short-term memory tasks when compared to controls. DEP induced the secretion of IL-1, IL-6 and TNFα; in brain tissue, which persisted 6 days after the last exposure. Analysis of cytokines and chemokines expression suggest that microglia/macrophages were polarized to a M1 phenotype. No sex differences were observed for the measured endpoints. Results suggest that DEP induced pro-inflammatory responses might be associated with impairment of cognitive processes related to executive function, which can have implications in specific learning disabilities and school achievement in children.

Disclosures: H.J. Rosa: None. **D.L. Menendez:** None. **N.A. Pagan:** None. **K.M. Casillas:** None. **L.B. Mendez:** None.

Poster

154. Cognitive Factors Affecting Learning and Memory

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 154.03

Topic: H.04. Executive Functions

Title: Greater Insulin Resistance is Linked to Inhibited Memory Performance in Younger Adults: An Electrophysiological Investigation

Authors: *B. A. LARSEN[1], B. KLINEDINST[3], A. A. WILLETTE[2];
[1]Biomed. Sci., [2]Food Sci. and Human Nutr., Iowa State Univ., Ames, IA; [3]Univ. of Washington, Seattle, WA

Abstract: INTRODUCTION: Global rates of obesity have nearly tripled over four decades, with 13.6% of adults aged ≥20 years (671 million) considered obese in 2016 compared with 4.8% of adults (100 million) in 1975. Obesity induces insulin resistance, and although some studies have found an inverse association between both these risk factors and cognitive performance, the body of literature has been largely inconsistent about such associations. Moreover, studies have predominantly focused on functional magnetic resonance imaging to investigate such associations rather than encephalography (EEG). The primary aim of this study was to investigate via EEG how adiposity and insulin resistance were related to neural activity underlying cognitive performance in tasks measuring learning and memory, social cognition, and executive function abilities in younger adults. METHODS: Using an observational, cross-sectional design, we recruited a convenience sample of 40 participants (18-40 years, 57.5% female) and examined real-time neural electrophysiology using electroencephalography (EEG) on 17 lean participants (mean body mass index (BMI)=21.8±1.7) and 23 participants with obesity (mean BMI=34±6.4) while they completed four cognitive tasks that measured inhibitory control (Stroop task), working memory (Operation Span task, O-Span), emotion regulation (International Affective Picture System, IAPS), and episodic memory (Visual Association Test, VAT). Height, weight, and serum proteomics were collected, and glycemic control was quantified from glycated hemoglobin serum measures. We directly assessed body composition via dual-energy X-ray absorptiometry. Structural equation modeling was utilized in to probe associations between adiposity, insulin resistance, neural activity, and cognition. RESULTS: After controlling for age, sex, and physical activity levels, we found that higher levels of insulin resistance was associated with significantly reduced neural activity and prolonged peak latencies during the VAT task (β=-0.87, $p<0.001$; β=0.69, $p=0.023$), which were, in turn, linked to poorer performance (β=-0.77, $p=0.007$; β=0.73, $p=0.011$). Higher insulin resistance was linked to reduced neural activity and prolonged peak latencies during the O-Span task (β=-0.82, $p=0.017$; β=0.72, $p=0.019$), which were, in turn, linked to poorer performance (β=-0.66, $p=0.035$; β=0.7, $p=0.022$). No differences were observed by body fat or insulin resistance for the IAPS or Stroop tasks. CONCLUSION: Young adults with greater insulin resistance was linked to decreased working memory and episodic memory capacities compared to insulin sensitive counterparts.

Disclosures: B.A. Larsen: None. **B. Klinedinst:** None. **A.A. Willette:** None.

Poster

154. Cognitive Factors Affecting Learning and Memory

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 154.04

Topic: H.04. Executive Functions

Support: PAPIIT Support IN213718

Title: Long-term artificial or natural non-nutritive sweeteners consumption effects on short-term memory and gut microbiota in rats

Authors: *M. RAMOS GARCÍA[1], J. BLE CASTILLO[1], A. GENIS MENDOZA[3], C. GARCÍA-VÁZQUEZ[1], J. MARTÍNEZ MAGAÑA[3], C. ALVAREZ VILLAGOMEZ[2]; [1]División Académica de Ciencias de la Salud, Univ. Juárez Autónoma de Tabasco, Villahermosa, Mexico; [2]División Académica de Ciencias Biológicas, Univ. Juárez Autónoma de Tabasco, Villhermosa, Mexico; [3]Lab. Genómica de Enfermedades Psiquiátricas y Neurodegenerativas, Inst. Nacional de Medicina Genómica, Ciudad de México, Mexico

Abstract: Non-nutritive sweeteners (NNS) have been introduced as an alternative to reduce the caloric content of foods and beverages. Recent research has reported that sucralose induced metabolic impairment via gut microbiota modulation. Nevertheless, the effects of natural NNS such as rebaudioside A (reb A), a stevia-derived glycoside, on gut microbiota have barely been evaluated. Besides, it is not well known whether NNS intake leads to cognitive impairment associated with gut microbiota shifts. We aimed to evaluate the effects of long-term artificial or natural non-nutritive sweeteners on short-term memory and gut microbiota in rats under two different dietary conditions. Male Wistar rats (150-200 g) on a normal diet (ND) or a high-fat diet (HFD) were randomized to receive commercial NNS (sucralose, reb A) or nutritive sweeteners as controls (glucose, sucrose) (n = 8 each per group) for 8 weeks. The NNS were administered in drinking water at doses equivalent to the human acceptable daily intake. Following 8-weeks, the Novel Object Recognition (NOR) task was performed to evaluate memory retention calculated by recognition index (IR). The differences in gut microbiota were determined by 16S rRNA gene sequencing. The media differences in the microbiota composition were compared using the Kruskal-Wallis test. The association between microbiota and NOR performance was analyzed with Spearman´s correlation. In ND-fed rats, sucrose consumption displayed an increase in the abundance of Bacteroidetes compared to glucose (p = 0.006), but reb A exhibited a lower RI and poor performance during the NOR task relative to glucose ($p < 0.05$) without alterations in the microbiota. Meanwhile, in HFD-fed rats, rebaudioside A exposure exhibited a decrease in the proportions of Firmicutes in comparison with glucose (p = 0.003). In this latter dietary group, reb A showed the highest RI of the NOR task respected to glucose ($p < 0.05$). Also, we found a significant negative correlation for Firmicutes with NOR for reb A in the ND group (r = -0.92, p = 0.024). Our results reveal that long-term consumption of reb A exerts differential effects on memory performance and gut microbiota depending on the feeding regimen. Consuming reb A in combination with HFD led to attenuate alterations in memory and microbiota but these results were opposite with a ND. The growing popularity and demand for natural NNS require further research examining their prolonged exposure on cognition processes linked to gut microbiota alterations considering the potential mechanisms implicated.

Disclosures: **M. Ramos García:** None. **J. Ble Castillo:** None. **A. Genis Mendoza:** None. **C. García-Vázquez:** None. **J. Martínez Magaña:** None. **C. Alvarez Villagomez:** None.

Poster

154. Cognitive Factors Affecting Learning and Memory

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 154.05

Topic: H.04. Executive Functions

Support: NIMH Grant R00MH118422
NARSAD Young Investigator Award to V.M.K.N

Title: An open-source behavior controller for associative learning and memory (B-CALM)

Authors: *M. ZHOU, B. WU, V. K. NAMBOODIRI;
Neurol., Univ. of California, San Francisco, San Francisco, CA

Abstract: The study of associative learning and memory is a cornerstone of psychology and behavioral neuroscience. Hence, the neural mechanisms underlying these processes are extensively studied using behavioral tasks in laboratory animals. Traditionally, these tasks have been controlled using commercial hardware and software, which limits scalability and accessibility due to their cost. More recently, due to the revolution in microcontrollers or microcomputers, several general-purpose and open-source solutions have been advanced for controlling neuroscientific behavioral tasks. While these solutions have great strength because of their flexibility and general-purpose nature, for the same reasons, they suffer from some disadvantages including the need for considerable programming expertise, limited online visualization, or slower than optimal response latencies. Here, to mitigate these concerns, we present an open-source behavior controller for associative learning and memory (B-CALM). B-CALM uses a low-cost Arduino Mega 2560 microcontroller interfacing with a MATLAB Graphical User Interface. B-CALM provides an integrated suite that can control a host of associative learning and memory behaviors. To demonstrate its functionality, we trained head-fixed mice of both sexes to successfully perform five standard associative learning procedures including Pavlovian conditioning, operant conditioning, cue-action reward task, two-option choice task, and peak interval procedure. These can be run directly from a user-friendly Graphical User Interface (GUI) written in MATLAB that controls many independently running Arduino Mega microcontrollers in parallel (one per behavior box). We demonstrated that the timing accuracy and response latency of our system is on the order of tens of microseconds. Moreover, our setup can be customized to interface and synchronize with external data acquisition hardware (e.g., fiber photometry system). The GUI also enables real-time data visualization of animal behavior. Our system has some current limitations as we do not directly allow the control of arbitrary hardware such as live video streaming or integration of multiple separate microcontrollers for the same task with online feedback control. However, we believe that expert programmers can use our general programming logic since all codes are open-source. In sum, B-CALM will enable researchers to execute a wide variety of associative learning and memory tasks in a scalable, accurate, and user-friendly manner. Hence, we believe that it is a valuable addition to the open-source toolkit available to behavioral neuroscientists.

Disclosures: **M. Zhou:** None. **B. Wu:** None. **V.K. Namboodiri:** None.

Poster

154. Cognitive Factors Affecting Learning and Memory

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 154.06

Topic: H.04. Executive Functions

Title: Effects of serotonin 6 receptor agonist treatment on probabilistic reversal learning.

Authors: *B. ALVAREZ[1], S. LOPEZ[2], C. CAVAZOS[2], C. MORALES[2], A. GUTIERREZ[2], J. ROBINSON[2], D. AMODEO[2];
[1]The Ohio State Univ. Neurosci. Grad. Program, Columbus, OH; [2]California State Univ. San Bernardino, San Bernardino, CA

Abstract: Serotonin 6 receptors (5-HT6) have recently shown promise as a novel therapeutic for various neuropsychiatric disorders. Previous studies have found that 5-HT6 receptor blockade can enhance performance on reversal learning tasks. Reversal learning is often utilized to gage behavioral inflexibility, a symptom present in several neuropsychiatric disorders. These studies do not focus on potential sex differences nor do they employ probabilistic reinforcement schedules. Our previous study found that EMD386088, a 5-HT6 receptor agonist, impaired probabilistic reversal performance and working memory in male C57BL/6J mice. We have also previously shown that 5-HT6 modulation differently impacts locomotor activity in male and female C57BL/6J mice as well. The current study aimed to examine the reproducibility of our 5-HT6 receptor modulation findings in the spatial T-maze in mouse operant chambers. We also examined the potential sex differences that EMD386088 has on probabilistic reversal learning. In addition, the current study utilized repeated drug administration compared to the single acute treatments used in our spatial tests. We predicted that the operant chamber results will parallel results from the spatial tests, inducing behavioral inflexibility in both males and females after EMD386088 treatment. Mice were tested in operant discrimination task using an 80/20 probabilistic reinforcement procedure. Mice were tested on a two-choice operant task, each mouse was tested on acquisition and then reversal learning across several days. Mice learned to obtain a sucrose pellet reinforcement from the magazine once a “correct” nose poke was made (reinforced on 80% of trials) compared with the “incorrect” nose poke (reinforced on 20% of trials). During each reversal day, mice received an intraperitoneal injection of either 0, 1.0, or 5.0 mg/kg of EMD386088 10 minutes prior to each session. Unlike our previous experiments, no sex differences were observed during initial probabilistic discrimination in C57BL/6J mice. Both males and females displayed increased trials and days to reach learning criterion for reversal learning. The vehicle treated female C57BL/6J mice required more days and trials to reach criterion during reversal compared to vehicle treated male C57BL/6J mice. Female mice treated with 1.0 and 5.0 mg/kg of EMD386088 displayed greater behavioral flexibility compared to vehicle treated female mice, which was not predicted. Male mice that received 1.0 mg/kg EMD386088 displayed comparable reversal learning performance while 5.0 mg/kg impaired reversal learning performance.

Disclosures: **B. Alvarez:** None. **S. Lopez:** None. **C. Cavazos:** None. **C. Morales:** None. **A. Gutierrez:** None. **J. Robinson:** None. **D. Amodeo:** None.

Poster

154. Cognitive Factors Affecting Learning and Memory

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 154.07

Topic: H.04. Executive Functions

Support: Colby College
Maine INBRE

Title: Fear factor: Does adolescent choline supplementation boost or attenuate fear learning?

Authors: *C. EVANGELISTA, J. HERSH, M. MACOMBER, A. DOAK, M. J. GLENN; Colby Col., Waterville, ME

Abstract: The prevalence of fear-related disorders continues to be widespread while our understanding of them remains limited. The development and maintenance of such disorders can be investigated using associative learning. Learning to fear certain stimuli can occur by experiencing a traumatic event directly or indirectly. Direct experience of a traumatic event (e.g., getting bitten by a dog) is called first-order conditioning (FOC). Stimuli present during that traumatic event (e.g., the sound and sight of a dog barking) become primary fear triggers. Encountering primary fear triggers with other harmless stimuli (e.g., friends, dog parks) can spread fear learning by leading those people and places to acquire fear-eliciting properties. These secondary fear triggers are acquired through indirect fear learning, which is called second-order conditioning (SOC). In the present study, we investigate these fear learning processes and how certain factors may impact that learning. One such dietary factor that has been shown to influence learning and memory is an essential nutrient called choline, which is a precursor to the neurotransmitter acetylcholine and is found in foods such as eggs, broccoli, and liver. Choline supplementation has been demonstrated to boost learning and protect against several neural insults. However, the effect of choline on fear learning remains unclear. Will choline enhance or attenuate fear learning? To study this, male and female Long-Evans rats were fed standard or choline-supplemented diets starting from adolescence. Later in adulthood, they underwent FOC and SOC procedures. In FOC, cue A was paired with a mild shock. In SOC, cue B was paired with cue A—no shock was delivered. The days following FOC and SOC, tests were conducted to assess fear to the secondary and primary fear triggers. Startle responses were measured as an indicator of fear. The results showed a significant sex difference in fear response: Females showed greater startle responses compared to males. Although there were no effects of diet, trends suggest that adolescent choline may enhance fear learning and also improve extinction of fear memories. These preliminary findings could help us better understand the formation and maintenance of direct and indirect fear learning. Dietary choline supplementation may have both

harmful and beneficial effects on fear conditioning: It may boost fear learning while also facilitating extinction learning.

Disclosures: C. Evangelista: None. **J. Hersh:** None. **M. Macomber:** None. **A. Doak:** None. **M.J. Glenn:** None.

Poster

154. Cognitive Factors Affecting Learning and Memory

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 154.08

Topic: H.04. Executive Functions

Title: Suvn-i7016031: a novel m1-receptor positive allosteric modulator (m1-pam) for the treatment of dementia associated with neurodegenerative disorders

Authors: *V. BENADE, V. PALACHARLA, V. GOYAL, R. BADANGE, K. BOJJA, A. SHINDE, S. PETLU, R. SUBRAMANIAN, P. JAYARAJAN, R. NIROGI;
Suven Life Sci. Ltd, Suven Life Sci. Ltd, Hyderabad, India

Abstract: SUVN-I7016031 is a novel and selective positive allosteric modulator (PAM) of the M1 subtype of the muscarinic acetylcholine receptors (mAChRs). SUVN-I7016031 has produced significant increases in striatal inositol 1-phosphate (IP-1) levels in rats indicating the activation of M1 receptors. SUVN-I7016031 did not show any agonist like effect when tested alone in acute hippocampal slices as reflected by lack of increase in neuronal spike rate relative to basal up to the tested concentrations of 10 µM. SUVN-I7016031 showed allosteric potency at M1 receptors with improved neuronal firing, when tested in combination with EC_{20} of carbachol. SUVN-I7016031 has excellent pharmacokinetics when tested in rodents and non-rodents. SUVN-I7016031 was tested in various animal models to evaluate its potential for the treatment of cognitive deficits associated with various neurodegenerative disorders like Alzheimer's disease and Parkinson's disease. In the object recognition task (ORT) model, SUVN-I7016031 reversed the time delay and scopolamine-induced amnesia in rats. SUVN-I7016031 significantly increased the duration of freezing in scopolamine challenged adult rats in the contextual fear conditioning task, reflecting the retention of associative memory. In social recognition task, rats treated with SUVN-I7016031 remembered their respective conspecific familiar juvenile males. Further, SUVN-I7016031 potentiated the effects of donepezil on elicited theta power, indicating an enhancement of hippocampal cholinergic neuronal activity. Treatment with SUVN-I7016031 produced significant increase in cortical levels of soluble amyloid precursor protein alpha (sAPPα) in rats, indicating neuroprotective and neurotrophic properties of SUVN-I7016031. SUVN-I7016031 also attenuated haloperidol-induced amnesia in rats in a social recognition task, reflecting the potential for PD dementia. Inferences from efficacy observed in various animal models suggest that SUVN-I7016031 may have potential in the treatment of dementia associated with various neurodegenerative disorders.

Disclosures: **V. Benade:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **V. Palacharla:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **V. Goyal:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **R. Badange:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **K. Bojja:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **A. Shinde:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **S. Petlu:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **R. Subramanian:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **P. Jayarajan:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **R. Nirogi:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd..

Poster

154. Cognitive Factors Affecting Learning and Memory

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 154.09

Topic: H.04. Executive Functions

Title: Neurodevelopmental risk associated to PAH-particulate matter maternal exposure in newborns from Puebla, Mexico

Authors: *L. RAMOS-CHÁVEZ[1], K. RODRÍGUEZ-ÁLVAREZ[2], J. RAMÍREZ-MÉNDEZ[2], P. PETROSYAN[3], M. GONSEBATT[3,4], W. GARCÍA-SUÁSTEGUI[2], O. LÓPEZ-AYALA[3,5], L. PADILLA-MARTÍNEZ[4];
[1]Inst. Nacional de Psiquiatría Ramón De La Fuente Muñiz, Cd. de México, Mexico; [2]Lab. de Toxicología Molecular, Dept. de Biología y Toxicología de la Reproducción, Inst. de Ciencias, Benemérita Univ. Autónoma de Puebla, Puebla, Mexico; [3]Medicina Genómica y Toxicología Ambiental, Inst. de Investigaciones Biomédicas-UNAM, Cd de México, Mexico; [4]Hosp. de la Mujer Puebla, Puebla, Mexico; [5]Hosp. de la Mujer-SSA, Puebla, Mexico

Abstract: Polycyclic aromatic hydrocarbons (PAHs) are ubiquitous carcinogenic and neurotoxic compounds. They are mainly present in the air of industrialized cities in the micrometric particulate matter particle (PM 2.5-10 µm). Puebla is one of the metropolises in Mexico with an important population density that has natural and anthropogenic sources of PM2.5-10. The City has an automatic air quality monitoring system which gives daily reports of PM2.5-10 levels. According to this system a severe problem of air quality is present. Further the PM2.5-10 levels change during each season; from winter to spring these levels are increased. Children older people, and pregnant women are more vulnerable to the exposure risk and its deleterious effects. In this work we evaluated maternal exposure to environmental PAHs through the urinary marker 1-hydroxypyrene (1-OHP) and assessed the neurodevelopment disorders in their newborns. The participant mothers lived during the complete gestational period in Puebla without a smoking history and at optimal reproductive age (25-35 years old). In this study 85 mothers were included, from different zones of the City (North, South, West, and East). We observed that in the dry season the PM2.5-10 exposure is increased in all the City areas. The commercial

(downtown) area presented higher PM2.5-10 levels and women that live in this area have higher (increased) urinary 1-OHP levels. We found a correlation between the PM2.5 and PM10 concentrations and the urinary 1-OHP levels (R2=0.29 P=0.0096; R2=0.22 P=0.048 respectively). No apparent neurodevelopmental damage was observed in the newborns however many effects could happen later in life. It is important to evaluate this vulnerable population to determine the long-term effects of the gestational exposure to PAHs-PM2.5-10 associated with intelligence and memory skills.

Disclosures: **L. Ramos-Chávez:** None. **K. Rodríguez-Álvarez:** None. **J. Ramírez-Méndez:** None. **P. Petrosyan:** None. **M. Gonsebatt:** None. **W. García-Suástegui:** None. **O. López-Ayala:** None. **L. Padilla-Martínez:** None.

Poster

154. Cognitive Factors Affecting Learning and Memory

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 154.10

Topic: H.04. Executive Functions

Support: : Consejo Nacional de Ciencia y Tecnología (CONACyT grants No. 792201 and INFR-281265).
Secretaria de Educación Pública de México-Apoyo para el fortalecimiento de los Cuerpos Académicos

Title: Effects of training of related and unrelated behavioral repertoires and the presence or absence of reward on solving a detour task in CD1 mice

Authors: *B. NUMPAQUE[1], A. LONGÁN[1], T. CAMPOS-ORDOÑEZ[1,2], J. BURITICÁ[1];
[1]Lab. of Cognition and Comparative Learning, Univ. de Guadalajara, Guadalajara, Mexico;
[2]Lab. of Neurosci., Univ. de Colima, Colima city, Mexico

Abstract: The ability to solve problems offered by animal species is a trait on which the survival of many of them depends. Evolution of some brain structures has been linked to the need of species to solve numerous problems in its environment, just as brain size has been linked to problem-solving ability. Traditionally, the way in which problem solving occurs has been understood in two ways: on one hand, problem solving is acquired through trial and error; on the other hand, solution appears in a direct, spontaneous, and sudden way, called insight. Other factors contributing to problem solving are the animals' previous experience with similar objects, other behavioral repertoires acquired in the same or different contexts, or the experience with different motivational conditions. The Detour task has played a central role in the study of problem solving and has been used among numerous species; however, its use is not limited to problem solving but extends to study inhibitory control, navigation, cognitive/motor development, and social learning, among others. In the case of mice, detour task had been used primarily to assess inhibitory control and decision making, however, to date it has not been used

to assess the effects of training in related or non-related repertoires to solve the task and assess the effect of prior experience with different motivational conditions: absence and presence of reward. Herein, in an improved detour test, we assessed the effects of training and prior experience using four groups (CD1 strain, males, 10 subjects each): two groups with a related-to-task training, varying among them the prior experience with the task (four sessions, 15 minutes each, with reward, followed by four sessions with absence of reward) and other two groups with a non-related-to-task training, also varying among them the prior experience. Effects were measured in terms of number of solutions and latency to first solution. Preliminary results showed a strong effect of training of behavioral repertoires in the frequency of resolution, but there was no strong effect of the order of exposure to apparatus with or without reward. Those results are consistent with literature in the case of effects of training and shows there's little or no effect related to intrinsic/extrinsic motivational conditions on the number of resolutions given by animals.

Disclosures: B. Numpaque: None. **A. Longán:** None. **T. Campos-Ordoñez:** None. **J. Buriticá:** None.

Poster

154. Cognitive Factors Affecting Learning and Memory

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 154.11

Topic: H.04. Executive Functions

Title: Test Anxiety is Associated with Reduced Error- and Feedback-Related Negativity on a Go/No-Go Task

Authors: *H. MATKINS, E. A. BOURASSA;
Mississippi Col., Clinton, MS

Abstract: On electroencephalography (EEG), an incorrect motor response is followed by a sharp negative deflection in the frontal and central cortices. This error-related negativity (ERN) is believed to be elicited from the anterior cingulate cortex, functioning as an error-detection system. Interestingly, an ERN can be elicited even when the participant is consciously unaware that an error was made. Previous work has shown that the ERN is more prominent in patients with a variety of anxiety disorders as well as non-clinical populations that rate highly on anxiety scales. The hypothesis of this study was that participants with high test anxiety (HTA) would have a larger ERN than those with low test anxiety (LTA). Participants were screened for test anxiety using the blue-box stress test; those identified as HTA and LTA then performed a Go/No-Go task while EEG was recorded. Unexpectedly, HTA participants had a smaller ERN compared to LTA. It was then hypothesized that the expected effect may not be present unless negative performance feedback was provided, so the experiment was repeated with the modification that all participants were given negative performance feedback throughout the Go/No-Go task. As with the first experiment, HTA had a smaller ERN than LTA. While this

study was not designed to measure the feedback-related negativity (FRN), it appeared that the FRN was absent from HTA but not LTA participants. Event-related spectral perturbation (ERSP) analysis showed no differences between HTA and LTA on correct trials while receiving negative feedback, but HTA had significantly higher theta/alpha power than LTA on error trials. Without negative feedback, ERSP analysis showed that HTA had higher theta and lower beta power on both correct and error trials. These results suggest that an underlying deficit in students with HTA may be a failure to identify errors and respond to feedback. Because the identification of an error and ability to respond to feedback are required for learning to occur, it is possible that test anxiety has features in common with learning disabilities.

Disclosures: H. Matkins: None. **E.A. Bourassa:** None.

Poster

154. Cognitive Factors Affecting Learning and Memory

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 154.12

Topic: H.04. Executive Functions

Title: Test Anxiety is Associated with Reduced Feedback-Related Negativity but Increased Error-Related Negativity on a Time Estimation Task

Authors: L. LANDRY[1], H. MATKINS[2], *E. A. BOURASSA[3];
[1]Biol. Sci., [3]Mississippi Col., [2]Mississippi Col., Clinton, MS

Abstract: Recent work in our lab has shown that participants with high test anxiety (HTA) have a smaller error-related negativity (ERN) and feedback-related negativity (FRN) compared to low test anxious (LTA) participants in a Go/No-Go task. One possible interpretation of those results is that test anxiety is associated with a reduced ability to detect and correct errors and therefore may have features in common with learning disabilities. To test this hypothesis, participants were screened for test anxiety using the blue-box stress test; those identified as HTA and LTA then performed a time estimation task while EEG was recorded. During the first half of the task, participants learned to press the space bar 1700 ms after a cue within 100 ms (1600-1800 ms). On some blocks of trials, participants were given no feedback, on other blocks they were told their time after each trial, and on other blocks they were given contrived feedback (50% correct, 50% incorrect). In the second half of the task, participants were to perform the task again but there were no blocks where they were told their time. It was hypothesized that HTA would be slower to learn the task and would have poorer performance during the recall phase of the task than LTA. It was hypothesized that HTA would have smaller ERNs and FRNs. Unexpectedly, HTA learned the task just as well as LTA and performed better during the recall phase of the task. Interestingly, LTA had a significant decrease in task accuracy in the recall phase on blocks without feedback, which improved when given contrived feedback; this effect was not seen in HTA. Similar to our previous results in the Go/No-Go task, HTA did not have an FRN; however, HTA did have an ERN during both the learning and recall phases of the task and these ERNs

were larger than the ERNs in LTA. Event-related spectral perturbation analysis showed a variety of differences between groups; the most common difference seen was a decrease in beta power in HTA compared to LTA. Compared to our recent work with the Go/No-Go task, this experiment was consistent with respect to the lack of FRN in HTA; however, HTA had a robust ERN unlike in the Go/No-Go task. The distinction between this task and the Go/No-Go task that leads to the difference in the ERN effect requires further research.

Disclosures: L. Landry: None. **H. Matkins:** None. **E.A. Bourassa:** None.

Poster

155. Long-Term Memory: Consolidation and Reconsolidation: Behavior

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 155.01

Topic: H.07. Long-Term Memory

Support: Sao Paulo State Research Foundation (FAPESP) Grant 2016/18039-9 to S.M.C
Coordenação de Aperfeiçoamento de Pessoal de Nível Superior-Brasil (CAPES)—Finance Code 001

Title: Building bridges to make memories last: integration between events shapes long-term memory formation

Authors: *A. SOLIANI, S. M. CERUTTI;
Federal Univ. of Sao Paulo, Diadema, Brazil

Abstract: In an ever-changing environment, a key challenge of a memory system is a trade-off between transience and persistence since events may gain or lose significance over time. Given that episodic memory is temporally organized and the role of time in linking memories, one intuitive hypothesis is that events across time interact to modulate long-term memory formation via memory integration. To test this, we trained male rats (3-6 months old) in a weak contextual fear conditioning task which was insufficient to generate a long-term fear memory (event A). We then exposed animals to a modified context (event B, no shock) within a short time window (30 min) after event A. As predicted, we found that a weak contextual fear memory (event A) can be transformed into long-term memory if this experience is integrated or linked to a second contextual memory (event B) in close temporal proximity, as shown by the generalization of fear across events. Additionally, we also found that memory integration and subsequent long-term memory formation for these two events depend on temporal and spatial factors and the type of event experienced by the subject, such as the degree of novelty encountered by the subject during event B. In contrast with the younger animals, middle-aged rats (16-18 months old) were unable to form a long-term memory by integrating related events across time. Together, our data suggest that the brain's ability to integrate new information with a pre-existing memory has implications for long-term memory formation and may contribute to our understanding of how we create an episodic timeline, a process impaired by normal aging.

Disclosures: **A. Soliani:** None. **S.M. Cerutti:** None.

Poster

155. Long-Term Memory: Consolidation and Reconsolidation: Behavior

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 155.02

Topic: H.07. Long-Term Memory

Support: NSERC Discovery Grant

Title: Activation of M_1 cholinergic receptors or exposure to contextual novelty during memory reactivation enables spatial memory destabilization in aged mice

Authors: ***A. E. HUFF**[1], K. H. JARDINE[1], W. S. MESSER, Jr.[2], B. D. WINTERS[1];
[1]Psychology and Collaborative Neurosci. Program, Univ. of Guelph, Guelph, ON, Canada;
[2]Pharmacol. and Exptl. Therapeut., Univ. of Toledo, Toledo, OH

Abstract: Previously consolidated memories can be reactivated by exposure to reminder cues associated with the original learning event. This can destabilize memories, enabling weakening, strengthening, or information integration. Following this, memories need to be reconsolidated. The age and strength of a memory can affect its likelihood to destabilize, and exposure to novelty or activation of M_1 muscarinic cholinergic receptors (mAChRs) at the time of reactivation can promote spatial memory destabilization. However, aged mice do not display reactivation-dependent memory updating. It is possible that this is a result of the destabilization process becoming dysfunctional, as the cholinergic system deteriorates with aging and this co-occurs with spatial memory deficits and cognitive inflexibility in aged humans and rodents. We hypothesized that object location (OL) memory destabilization would be impaired in aged mice but could be promoted by enhancing activity at mAChRs. Here, we show that in young male C57BL/6 mice, strongly encoded OL memories do not readily destabilize, but destabilization can be initiated by exposure to contextual novelty during memory reactivation. Moreover, both destabilization of relatively weak OL memories, and novelty-induced destabilization of strong OL memories are prevented by mAChR antagonism with systemic scopolamine (0.3 mg/kg). In addition, activation of M_1 mAChRs with systemic CDD-0102A (0.3 mg/kg) facilitated destabilization of strongly encoded OL memories without the presence of explicit contextual novelty during memory reactivation. Interestingly, unlike in younger mice, weakly encoded OL memories did not readily destabilize in nine-month-old male C57BL/6 mice, but destabilization could be promoted by exposure to novelty or stimulation of M_1 mAChRs during memory reactivation. This research enhances our understanding of the role of acetylcholine in long-term memory dynamics and suggests implications for the understanding and treatment of cognitive inflexibility that can occur in the normal aging process as well as dementia.

Disclosures: **A.E. Huff:** None. **K.H. Jardine:** None. **W.S. Messer:** None. **B.D. Winters:** None.

Poster

155. Long-Term Memory: Consolidation and Reconsolidation: Behavior

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 155.03

Topic: H.07. Long-Term Memory

Support: P031S160068

Title: Behavioral and Molecular Characterization of a Mouse Gulf War Illness Model Allows for the Search for Therapeutics

Authors: *J. MARRERO-VALENTÍN, L.[1], D. PEREZ[1], P. A. FERCHMIN[2], N. SABEVA[1]; [1]Univ. Central Del Caribe, Bayamon, PR; [2]Neuroprotection for Life, Carmel, IN

Abstract: Gulf War Illness (GWI) is a chronic multiorgan condition that prominently involves the brain. It is characterized by a cognitive deficit associated with neuroinflammation and neuronal loss. GWI causative factors are the simultaneous exposure to pyridostigmine bromide (PB, administered for prophylactic purposes against nerve agents), permethrin (PER), and N, N-diethyl-meta-toluamide (DEET) for insect control along with traces of Sarin. Here, we report an improved murine GWI model and the testing on this model of a therapeutically promising nicotinic α7nAChR ligand, the 4R-cembranotrienes-diol (4R). To recreate GW conditions, we enhanced an established mouse GWI model (10 days PB + PER) with DEET, traces of DFP (a Sarin surrogate), and moderate stress. After exposure to the GW agents, behavioral testing is being conducted every 30 days for three months. We assessed the learning abilities using the Barnes maze, where control and GWI mice showed the same ability to learn to locate the escape box during the three days training period. Latency and visits to the target escape box were evaluated after removing the rewarding escape box. GWI mice showed steady nose-poke and time spent at the escape hole during testing (Day 30, 4.5±0.6 and Day 60, 4.05±0.6). Conversely, control animals showed intense interest (Day 30, 6.7±0.8), followed by a 50 % decline on Day 60 (3.4±0.9). Thus, controls demonstrated that, contrary to GWI mice, they retain the capability to extinguish obsolete spatial information. Additionally, Light Dark Chamber testing 30 days post-exposure demonstrated that GWI mice had decreased exploratory behavior (Rears/5 min) compared to controls (Day 30, 24.3 ± 3.6 vs. 15.8 ± 2.1), suggesting the early onset of anxiety. Similar, the latency to light increased in the GWI mice while it declined with time to control (Latency to Light (s): Day 30, 24.2 ± 3.7 vs. 38.6 ± 9.1 and Day 60, 13.9±2.8 vs. 45.5±11.9). These results were not related to alterations in motor function since the number of transitions between the two compartments remained similar among the groups, along with velocity and distance covered. We will be testing whether 4R restores extinction and anxiety in GWI mice by applying 4R five times a week for three weeks (6mg/kg i.p.) 100 days after exposure to GW agents. Molecular analysis for neuronal inflammation and synaptic integrity and behavioral testing for cognition and anxiety will be conducted to evaluate the proposed treatment's efficacy. The present work contributes to the understanding of GWI. It will test a promising candidate drug for treating GWI veterans and future victims of similar civilian or military adverse events.

Disclosures: **J. Marrero-Valentín:** None. **D. Perez:** None. **P.A. Ferchmin:** None. **N. Sabeva:** None.

Poster

155. Long-Term Memory: Consolidation and Reconsolidation: Behavior

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 155.04

Topic: H.07. Long-Term Memory

Support: PRONACES-CONACYT Grant 194171
VIEP-BUAP 2021-2022 (BUAP-CA-288)
LD PhD CONACYT Grant No. 850282

Title: Propranolol affects differentially spatial learning and memory of resilient and anxious rats.

Authors: *L. DÍAZ[1], A. UGARTE[1], C. CORTES[1], J. R. EGUIBAR[2];
[2]Intl. Office, [1]Benemérita Univ. Autónoma De Puebla, Heroica Puebla de Zaragoza, Mexico

Abstract: High emotional events tend to consolidate as a long-term memory, this process ismediated by stress hormones like noradrenaline and glucocorticoids in brain areassuch as hippocampus and the basolateral amygdala. Furthermore, the level of stressis important, in different animal models middle stress responses alter their spatialtasks performance. We had two inbreeding sublines from Sprague-Dawley (SD) rats,the first with a high-spontaneous yawning (HY) with a mean of 20 yawns/h, and thesecond with a low-yawning (LY) frequency with just 2 yawns/h. LY rats had higherstress responses with respect to HY when tested in the open-field arena becausethey ambulated less and had more fecal bolus. Previously, we obtained that LYmales had long-term memory deficits in the Barnes maze with respect to HY. Basedon the above, the aim of this study was to determine the effect of a β adrenergicantagonist on the spatial learning and memory of both sublines. We use LY and HYmale rats (6 rats/group), they maintained under standard animal room conditions. Allexperiments done between 1000 to 1300 h using a Barnes maze, 30 minutes beforetraining the subjects (Ss) received 0.5, 1.0 or 2.0 mg/Kg of propranolol hydrochloride(Sigma-Aldrich, USA) by subcutaneous injection in the dorsal neck region. Trainingconsisted in eight trials in one day, in each trial Ss learned a fixed position of theescape box. Short-term memory (STM) evaluated 24 hours later, and long-termmemory (LTM) seven days later. The escape latency and number of errorsmeasured. Our results shown that 0.5 and 1.0 mg of propranolol increased thenumber of errors in LTM of LY subline with respect to HY ($P<0.05$). In this last grouponly the 2.0 mg dose impact their early learning in HY ($P<0.05$). The escape latencyof male HY Ss only increased with the highest dose used of 2.0 mg/Kg ($P<0.01$). Weconcluded that memory deficits shown in the high-innate anxiety of LY males aredependent on noradrenergic transmission. However, the proficient spatialperformance of HY males and their stress-resilience could be associated to a higherexpression of β adrenergic receptors.

Disclosures: **L. Díaz:** None. **A. Ugarte:** None. **C. Cortes:** None. **J.R. Eguibar:** None.

Poster

155. Long-Term Memory: Consolidation and Reconsolidation: Behavior

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 155.05

Topic: H.07. Long-Term Memory

Support: Endowed Scholar Program
Brain Research Foundation
STAR Program
Brain & Behavior Research Foundation
Whitehall Foundation
JSPS KAKENHI

Title: Social transmission of new knowledge without firsthand experience in mice

Authors: *R. KIM[1,2], H. BITO[1], T. KITAMURA[2,3];
[1]Dept. of Neurochemistry, Grad. Sch. of Medicine, The Univ. of Tokyo, Tokyo, Japan; [2]Dept. of Psychiatry, [3]Dept. of Neurosci., Univ. of Texas Southwestern Med. Ctr., Dallas, TX

Abstract: In order to survive in nature, animals use prior knowledge to determine whether the places and objects in front of them are safe or dangerous. Animals can acquire new knowledge via two types of learning: by firsthand experiences (such as during classical conditioning) or by secondhand experiences through observing and listening to another animal's experiences (social learning). The mechanism of the former has been well studied, while that of the latter is not well understood. The social transmission of food preference (STFP) task in rodents is considered as a behavioral model for social learning. In this task, an animal (observer) learns that an odor is safe by smelling another animal (demonstrator) that has safely eaten a food associated with this unknown odor. Once learned, the observer shows a "preference" to a food with this familiar odor (smelled from a demonstrator) than the same food with a novel odor in a test session. STFP, however, requires habituating the observer with a food-filled cup, thus providing the observer with a firsthand experience that a food is in the cup. Furthermore, an odor itself is sufficient to generate a preference to a food with the same odor, without any need to interact with a demonstrator animal to establish STFP. These issues make it challenging to disambiguate, based on animal's behavior, whether the observer has *socially* acquired "a new knowledge" from the demonstrator. We here established a new experimental model for social learning in mice, social transmission of food finding (STFF), by a modification of STFP task, and tested whether an animal can acquire a new knowledge from another. In STFF, we excluded the habituation session from the protocol, and we evaluated whether the observer acquired a knowledge about an unknown odor associated with the food, by measuring the latency of the animal to eat the food in the cup. We found that when the observer smelled an unknown odor from the demonstrator, the latency to eat a food with this associated odor was significantly shorter than that of a control

observer animal that was not exposed to the smell. To induce this behavior, it was necessary to smell an unknown odor directly from the demonstrator, indicating that mice can socially learn an association of an unknow odor related a food from the demonstrator mice. In addition, we found that mice recognized not only positive but also negative valence about an unknown odor in a manner dependent to the demonstrator's state (painful or dying, or healthy). The hippocampus was necessary for acquisition but not for recall of STFF. These findings suggest that STFF is a robust task for a social learning in which mice learn new knowledge without any firsthand experience.

Disclosures: R. Kim: None. **H. Bito:** None. **T. Kitamura:** None.

Poster

155. Long-Term Memory: Consolidation and Reconsolidation: Behavior

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 155.06

Topic: H.07. Long-Term Memory

Support: NSERC

Title: Investigating the Role of Nicotinic Receptors in Object Memory Destabilization

Authors: *E. P. MINARD[1], C. E. WIDEMAN[2], B. D. WINTERS[2];
[1]Psychology, [2]Univ. of Guelph, Univ. of Guelph, Guelph, ON, Canada

Abstract: Consolidated memories can be updated through a process of memory destabilization and subsequent reconsolidation. Previous research indicates that acetylcholine (ACh) release is necessary for object memory destabilization through the activation of its muscarinic receptors (mAChRs). Remote memories are resistant to destabilization but can be reliably destabilized when novel information is present at the time of reactivation, likely due to ACh release in response to novel information. However, this research has yet to extend to nicotinic acetylcholine receptors (nAChRs). Accordingly, we investigated the role of nAChRs in object memory destabilization in standard and remote memory conditions. We hypothesized that, like mAChRs, nAChRs would be necessary for standard and remote object memory destabilization. To test this, we used male C57BL/6 mice and injected a systemic nAChR antagonist, mecamylamine, 30 minutes before memory reactivation. Mecamylamine blocked reactivation-induced memory destabilization in standard conditions but not remote conditions. Rather, mecamylamine seemed to block reconsolidation in remote conditions. Upon further investigation, we found that mecamylamine blocked reconsolidation in both standard and remote conditions when injected immediately before reactivation. These findings signify a potential functional differentiation of mAChRs and nAChRs and thus expand on the current understanding of cholinergic regulation of object memory destabilization, an essential process for long-term memory storage and adaptive updating.

Disclosures: E.P. Minard: None. **C.E. Wideman:** None. **B.D. Winters:** None.

Poster

155. Long-Term Memory: Consolidation and Reconsolidation: Behavior

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 155.07

Topic: H.07. Long-Term Memory

Support: Brazilian government agency CNPq (Universal 2018 – 405100/2018-3)

Title: The role of hippocampal IP_3R on contextual fear memory

Authors: *P. S. LUNARDI[1], H. S. FERNANDES[2], B. POPIK[2], L. O. ALVARES[3];
[1]UFMG, Belo Horizonte, Brazil; [3]Federal Univ. Rio Grande do Sul, [2]Federal Univ. Rio Grande do Sul, Porto Alegre, Brazil

Abstract: Intracellular calcium stores (ICS) play a dynamic role in neuronal calcium (Ca^{2+}) homeostasis both by buffering Ca^{2+} excess in the cytoplasm or providing an additional source of Ca^{2+} when concentration increase is needed. However, in spite of the large body of evidence showing Ca^{2+} as an essential second messenger in many signalling cascades underlying synaptic plasticity, the direct involvement of the intracellular Ca^{2+}-release channels (ICRCs) in memory processing has been highly overlooked. Here we investigated the role of the ICRC inositol 1,4,5-trisphosphate receptor (IP_3R) activity during different memory phases using pharmacological inhibition in the dorsal hippocampus during contextual fear conditioning. We first found that post-training administration of the IP_3R antagonist 2-aminoethyl diphenylborinate (2-APB) impaired memory consolidation in a dose and time dependent manner. Inhibiting IP_3Rs also disrupted memory retrieval. Contextual fear memory reconsolidation or extinction, however, were not sensitive to IP_3R blockade. Taken together, our results indicate that hippocampal IP_3Rs play an important role in contextual fear memory consolidation and retrieval.

Disclosures: P.S. Lunardi: None. **H.S. Fernandes:** None. **B. Popik:** None. **L.O. Alvares:** None.

Poster

155. Long-Term Memory: Consolidation and Reconsolidation: Behavior

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 155.08

Topic: H.07. Long-Term Memory

Title: Differential effects of memory reconsolidation on episodic details versus subjective feelings.

Authors: *G. SHIN[1], S. DUBROW[2], V. P. MURTY[3];
[1]Psychology, [2]Dept. of Psychology, Univ. of Oregon, Eugene, OR; [3]Psychology, Temple Univ., Philadelphia, PA

Abstract: Memory becomes prone to reconstruction during restorage after retrieval. While mainly studied in rodent models, clinical neuroscience has begun to capture the role of reconsolidation in humans. Given that episodic memory and subjective feelings are represented in discrete neural substrates (i.e., hippocampus vs. striatum), this field often limits investigations to one form of emotional memory leaving open questions regarding their putative interactions. To provide a more comprehensive understanding of the downstream consequences of reconsolidation, it is essential to characterize their interactions. Here, we conducted a study that examines how both episodic details and feelings change with biased re-exposure during reconsolidation. Human participants (n=24) performed a reconsolidation experiment over three days. On Day 1, they learned positive and negative attributes of novel faces. On Day 2, within the reconsolidation window, faces were re-exposed with previous positive attribute (Update+), negative attribute (Update-), or were not updated (Control). On the last day, we characterized face recognition, face-attribute associative memory, and subjective valence ratings. Face recognition was greater in the Update+ and Update- versus Control condition (all $p < .001$), with no significant differences between Update+ and Update- ($p = .991$). While associative memory was above chance in all conditions (50%; all $p < .001$), there were no significant differences across conditions, suggesting that reconsolidation did not influence associative memory. However, faces in the Update- condition had lower subjective valence ratings compared to the Control condition ($p = .006$), and were marginally lower compared to the Update+ condition ($p = .059$). In general, these findings show that re-exposure during reconsolidation increases face recognition but surprisingly does not influence associative memory. Further, there were valence-specific effects where negative but not positive updates influenced later subjective feelings. These findings support a model in which episodic memory and subjective feelings may be independently influenced via reconsolidation. We hope to extend these findings by probing the underlying neural mechanisms to provide new insights into how to increase the effectiveness of targeting and editing unique traumatic memories during the reconsolidation window in the clinic.

Disclosures: G. Shin: None. **S. Dubrow:** None. **V.P. Murty:** None.

Poster

155. Long-Term Memory: Consolidation and Reconsolidation: Behavior

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 155.09

Topic: H.07. Long-Term Memory

Support: NIA R00 AG049090
R01 AG070094
FL DOH 20A09

NIAAA R01 AA029700
NSF DMR-1644779

Title: Longitudinal characterization of resting state fMRI, DTI, and action-place spatial learning in the TgF344-AD rat reveals impaired action-place learning emerging at 5-months

Authors: *J. OGG[1], J. RADOVICH[2,3], J. HARTZOG[2,3], J. BHAGU[2,3], C. SIMMONS[1], A. BREA GUERRERO[1], A. LE[1], S. MOSELEY[1], B. CLARK[4], A. WILBER[1], S. GRANT[2,3]; [1]Dept. of Psychology, [2]Dept. of Chem. & Biomed. Engineering, FAMU-FSU Col. of Engin., Florida State Univ., Tallahassee, FL; [3]CIMAR, Natl. High Magnetic Field Laboratory, Florida State Univ., Tallahassee, FL; [4]Dept. of Psychology, Univ. of New Mexico, Albuquerque, FL

Abstract: A hallmark of preclinical Alzheimer's Disease (AD) is spatial disorientation, such as getting lost in new locations. One potential cause is disrupted exchange between egocentric and allocentric reference frames. Both the parietal (PC) and restrosplenial cortex (RSC) have garnered attention for their roles in encoding and transforming information between these reference frames. The RSC and PC also are earlier sites of dysfunction in humans with AD and rodents modeling aspects of AD. This study aimed to examine resting-state functional MRI (rsfMRI) and the relationship with coordination between reference frames in an AD rat model. We hypothesized that pathology development in transgenic AD rats leads to brain network dysfunction, which causes impaired coordination between reference frames. In TgF344-AD rats and littermate controls, reference frame coordination was assessed with an action-oriented spatial navigation task. Rats were required to associate actions (left or right turn) with locations. Around a central starting point, four arms of equal length were positioned 90 degrees from the next. From a central starting point, the rat exited one arm at a time in a pseudorandom order. To receive a reward, the rat must exit the arm and displace the correct object covering one of two wells on the left or right side. East and west arms had the correct object on the left, while north and south arms had the correct objects on the right. Correct, incorrect or no response was tallied. Upon removal of the object, the rat returned to the center. Days to criterion and side bias, head scanning, and procedural errors, were assessed at 3, 5 & 8.5 mos. Graph theory was applied to longitudinal MRI data acquired *in vivo* at 21.1T to assess functional and structural connectivity alterations by rsfMRI and structural diffusion tensor imaging (DTI) for assessing, respectively. Under light anesthesia (1-2% isoflurane), full brain rsfMRI datasets were acquired at 250x250x1500-µm using 300 repetitions without stimulation followed by acquisition of an 18-direction DTI dataset. Thus, we assessed relationships between reference frame coordination and rsfMRI/DTI at 2, 4, 6, 10, 12, 16 & 18 mos.Our data suggest that both age and genotype lead to declines in action-orientation performance, with differences in genotype emerging at 5 months of age and increasing at older timepoints. These alterations were reflected in the functional and structural networks in at least the PC, with more profound changes developing longitudinally. These findings highlight a new focus for understanding cognitive deficits in AD by using allocentric and egocentric coordination as a novel predictor of early declines in AD.

Disclosures: J. Ogg: None. **J. Radovich:** None. **J. Hartzog:** None. **J. Bhagu:** None. **C. Simmons:** None. **A. Brea Guerrero:** None. **A. Le:** None. **S. Moseley:** None. **B. Clark:** None. **A. Wilber:** None. **S. Grant:** None.

Poster

155. Long-Term Memory: Consolidation and Reconsolidation: Behavior

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 155.10

Topic: H.07. Long-Term Memory

Support: NSERC RGPIN/04795-2020

Title: The hippocampus promotes long-term memory formation by preventing sensory interference

Authors: *I. GROVES[1], D. E. ARKELL[2], E. R. WOOD[3], O. HARDT[1];
[1]McGill Univ., Montreal, QC, Canada; [2]The Ctr. for Cognitive and Neural Systems, The Univ. of Edinburgh, Edinburgh, United Kingdom; [3]Univ. of Edinburgh, Edinburgh, United Kingdom

Abstract: Damage to the hippocampus leads to anterograde amnesia for declarative memories, but it remains unresolved how this deficit arises. Active decay theory proposes that a protective index within the hippocampus shields newly acquired memory-content representations in extra-hippocampal areas from continued interference arising from ongoing sensory stimulation that normally occurs after learning. Without a functioning hippocampus, interfering stimulation disrupts memory consolidation in these areas, resulting in anterograde amnesia. We tested this this hypothesis in rats with an object recognition task, an accepted model for human declarative memory. We found that inactivating the hippocampus prior to object learning with intrahippocampal injections of GABAA and -B agonists (muscimol+baclofen) impaired novel object recognition tested 24 h after learning. Reducing sensory stimulation immediately after, but not 1 h later rescued this memory deficit. Visual sensory stimulation during the time after learning was sufficient to impair object recognition memory in rats with inactivated hippocampi but not in intact animals. Furthermore, blocking plasticity in hippocampus with the NMDA receptor antagonist AP5 before object learning, but not thereafter, also led to amnesia for objects, which also was rescued by reducing sensory stimulation after learning. Taken together, our findings suggest that a memory representation in the hippocampus protects object representations in other brain regions from sensory interference after learning, thereby promoting their stabilization and long-term retention in memory.

Disclosures: I. Groves: None. **D.E. Arkell:** None. **E.R. Wood:** None. **O. Hardt:** None.

Poster

155. Long-Term Memory: Consolidation and Reconsolidation: Behavior

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 155.11

Topic: H.07. Long-Term Memory

Support: AMED (JP22zf0127005,JP22km0908001)
JSPS KAKENHI (16H06280, 20H03552, 21H05674)
MEXT World Premier, International Research Center Initiative
JST CREST
Takeda Science Foundation
Uehara Memorial Foundation
Goho fellowship

Title: Transient recruitment of adult-born neurons for fear memory consolidation in REM sleep

Authors: *S. SRINIVASAN[1], I. KOYANAGI[1,2], P. VERGARA[1], Y. WANG[1,2], J. YU[1,2], T. NAOI[1], K. E. VOGT[1], Y. CHERASSE[1], T. SAKURAI[1,2,3], N. KUTSUMRURA[1], T. TEZUKA[1,4], M. SAKAGUCHI[1,2,3];
[1]Intl. Inst. for Integrative Sleep Med., [2]Doctoral Program in Neuroscience, Grad. Sch. of Comprehensive Human Sci., [3]Fac. of Med., [4]Fac. of Engineering, Information and Systems, Univ. of Tsukuba, Ibaraki, Japan

Abstract: Memory replay during rapid-eye-movement (REM) sleep is suggested to contribute to memory consolidation (Skaggs & McNaughton, Science). The dentate gyrus (DG) in the hippocampus hosts contextual fear memory trace (Liu et al., Nature) and adult-neurogenesis (Akers et al, Stem cells). Recently, we provided evidence that the activity of ABNs during REM sleep is necessary for contextual fear memory consolidation (Kumar et al., Neuron). However, the mechanism is not clear. Therefore, we hypothesize that re-activation of the ABNs, which represent the context to be associated with fear, during REM sleep is necessary for fear memory consolidation (Koyanagi et al., Neur Regen Res). In this study, we silenced the ABN activities representing the context during retrieval which did not impair the memory. However, silencing the ABNs during REM sleep impaired the memory. We also found a distinct dynamics of the ABN activity during REM sleep. Taken altogether, we propose that contextual fear memory consolidation relies on the transient recruitment of ABNs representing a specific context.

Disclosures: S. Srinivasan: None. **I. Koyanagi:** None. **P. Vergara:** None. **Y. Wang:** None. **J. Yu:** None. **T. Naoi:** None. **K.E. Vogt:** None. **Y. Cherasse:** None. **T. Sakurai:** None. **N. Kutsumrura:** None. **T. Tezuka:** None. **M. Sakaguchi:** None.

Poster

155. Long-Term Memory: Consolidation and Reconsolidation: Behavior

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 155.12

Topic: H.07. Long-Term Memory

Support: NSERC Grants to HL

Title: Tracing the limits: distributed learning parameters that make a context fear memory resistant to lesions of the hippocampus in the rat

Authors: *D. MCCALLUM, K. ROBERTS, S. SMITH, K. PANGANIBAN, M. LOWRIE, N. M. FOURNIER, M. G. REYNOLDS, H. LEHMANN;
Trent Univ., Peterborough, ON, Canada

Abstract: Damage to the hippocampus (HPC) results in retrograde amnesia for certain types of memories, often termed declarative and/or episodic. There are instances, however, in which these types of memories are seemingly unaffected by HPC damage, such as when the memory is acquired through distributed learning. This has been demonstrated in several non-human animal studies, most extensively using contextual fear conditioning. Specifically, distributing the contextual fear conditioning across multiple sessions, rather than one massed session, can make the context memory less vulnerable to HPC damage. This suggests that distributed conditioning establishes a greater or stronger memory trace in non-HPC memory systems that becomes less dependent on the HPC. The following experiments examined the number of distributed sessions and temporal parameters that determine how resistant a context fear memory is to HPC lesions. In each experiment rats received multiple conditioning sessions. Each session lasted 3 minutes and involved one context-shock (1.0 mA) pairing. Three to 5 days after their final conditioning session, they received sham or neurotoxic lesions of the HPC. Following recovery from surgery the rats were returned to the condition context for a retention test. In Experiment 1, the rats received 2 to 10 conditioning sessions (2 per day). The HPC rats that received 6 sessions or more showed as much freezing during retention testing as their respective control groups, whereas the freezing was significantly lower in HPC rats that received fewer than 6 sessions. These findings suggest that a context fear memory trace resistant to HPC damage can be established with as few as 6 distributed single-shock conditioning sessions. In Experiment 2, we examined whether distributing these 6 sessions within a single day (1-hour intervals) would create a memory equally resistant to HPC damage as when acquired over 3 days. The 1-hour interval was selected because it is known to be sufficiently long to enable the activation of a new cellular consolidation bout between each conditioning event. We found, even with the single-day distribution, that the memory was resistant to HPC lesions. In Experiment 3, the interval between the separate single-day conditioning sessions was reduced from 1hr to 5-min, limiting the opportunity for multiple cellular consolidation bouts over the course distributed conditioning. In this instance, the HPC rats from the 5-min interval group suffered from retrograde amnesia. Therefore, a context memory trace resistant to HPC damage can be created over 6 conditioning sessions in a single day but requires the opportunity for multiple cellular consolidation bouts.

Disclosures: D. McCallum: None. **K. Roberts:** None. **S. Smith:** None. **K. Panganiban:** None. **M. Lowrie:** None. **N.M. Fournier:** None. **M.G. Reynolds:** None. **H. Lehmann:** None.

Poster

155. Long-Term Memory: Consolidation and Reconsolidation: Behavior

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 155.13

Topic: H.07. Long-Term Memory

Support: NSERC CGS-D to IB
NSERC Discovery Grant to KPO
NSERC Discovery Grant to MK

Title: Lipopolysaccharide-induced impairment of memory acquisition and consolidation processes in a rodent model of lithium chloride-induced anticipatory nausea

Authors: *I. BISHNOI, K.-P. OSSENKOPP, M. KAVALIERS;
Psychology, Western Univ., London, ON, Canada

Abstract: Introduction. Up to 45% of patients who undergo chemotherapy experience a type of classical conditioning called anticipatory nausea (AN). Here, cues from the hospital context become paired with the nauseating chemotherapy occurring within the context. Once paired, returning to the hospital elicits nausea and/or vomiting even in the absence of chemotherapy. In rodents, this can be modeled by pairing a context with a nauseating stimulus, like lithium chloride (LiCl), which leads to conditioned disgust behaviours (e.g., gaping) when exposed to the context alone. Current antiemetic treatments are unsatisfactory for AN. New evidence suggests that selective immune activation may be used to treat AN.
Methods. Acquisition. Over 4 conditioning days (1, 4, 7 & 10), 32 adult male Long Evans rats were intraperitoneally (ip) injected with LPS (200 μg/kg) or NaCl 90 mins before LiCl (ip, 127 mg/kg) or NaCl and placed into a distinct context for 30 mins (creating 4 groups: NaCl-NaCl, LPS-NaCl, LPS-LiCl, NaCl-LiCl). Consolidation. Over 4 conditioning days, 48 distinct adult male Long Evans rats were ip injected with LiCl or NaCl and placed into a distinct context for 30 mins. After this, rats were ip injected with LPS or NaCl (creating 4 groups: NaCl-NaCl, NaCl-LPS, LiCl-LPS, LiCl-NaCl). Delayed Consolidation. Thus far, over 4 conditioning days, 16 adult male Long Evans rats were ip injected with LiCl or NaCl and placed into a distinct context for 30 mins. Rats were ip injected with LPS or NaCl 24 hours after each conditioning day (creating 4 groups: NaCl-NaCl24, NaCl-LPS24, LiCl-LPS24, LiCl-NaCl24). Extinction. Conditioning days were followed by 4 no injection test days (13, 16, 18 & 22).
Results. LiCl induced conditioned gaping in rats on conditioning day 10 and test day 13 across experiments (ps<.01). On these days, LPS given 90 mins before the LiCl-induced AN paradigm impaired the acquisition of AN (ps<.01). Additionally, LPS given immediately after this paradigm impaired the consolidation of AN (ps<.05). Further, LPS impaired the delayed consolidation of AN when given 24 hours after the paradigm (ps<.05). A rapid extinction of conditioned gaping was found in LiCl treated rats in all experiments after test day 13.
Implications. Conditioned disgust responses and a rapid extinction once a context is no longer paired with a nauseating stimulus are hallmarks of AN, suggesting that the LiCl-induced AN paradigm can be used to model AN. Immune activation with LPS significantly impairs both the acquisition and consolidation of LiCl-induced AN, confirming the impairing effects of LPS on learning and memory. Further studies are being conducted to understand the time course of these effects.

Disclosures: I. Bishnoi: None. **K. Ossenkopp:** None. **M. Kavaliers:** None.

Poster

155. Long-Term Memory: Consolidation and Reconsolidation: Behavior

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 155.14

Topic: H.07. Long-Term Memory

Support: Healthy Brains, Healthy Lives

Title: The relationship between sleep spindles and overnight declarative memory consolidation in Parkinson's disease

Authors: *S. LAHLOU[1], M. KAMINSKA[2], J. DOYON[3], J. CARRIER[4], M. SHARP[1]; [1]Montreal Neurolog. Inst., Montreal, QC, Canada; [2]McGill Univ. Hlth. Ctr., Montreal, QC, Canada; [3]McConnell Brain Imaging Ctr., Montreal, QC, Canada; [4]Psychology, Hôpital Du Sacré-Coeur De Montréal, Montreal, QC, Canada

Abstract: Healthy sleep is required for successful memory consolidation, i.e., the transformation of newly acquired learning into long-term memory. Sleep spindles, EEG oscillations occurring during non-REM sleep, are thought to promote the brain plasticity processes that underlie consolidation. In Parkinson's patients, sleep spindle abnormalities have been associated with the subsequent development of dementia, but the mechanism underlying this association is unknown. The goal of this study is to investigate the relationship between sleep spindle abnormalities and declarative memory consolidation in Parkinson's patients.

To address this goal, we recorded overnight polysomnography and measured memory before and after sleep in 32 PD patients free of dementia (mean age 65 years, 34% female). The memory task consisted of an initial encoding phase where participants learned 50 word pairs. Recall for one half of the word pairs was tested before sleep by cueing with one word of the pair, and asking them to verbally recall its associate. Recall for the remaining half was tested in the morning. Consolidation was measured as the relative difference between the pre- and post-sleep performance. Mean recall accuracy was 55.8% at night and 34.1% in the morning. The mean relative difference in recall accuracy comparing pre- and post-sleep was -39.1%.

We found an association between worse overnight memory consolidation and lower spindle density on frontal derivations ($r=0.46$, $p=0.01$). This association was only found for spindles occurring during non-REM Stage 3 (i.e. slow-wave sleep), and not during non-REM Stage 2 (spindle density: $r=-03$, $p=0.09$). We also explored the temporal clustering of spindles into 'trains', i.e., when multiple spindles happen in rapid succession, given previous work suggesting that this may play a role in consolidation. We found that patients with a lower proportion of clustered spindles as opposed to isolated spindles exhibited worse declarative memory consolidation ($r=0.46$, $p=0.009$). We will conduct additional analyses on the coupling between sleep spindles and slow-waves.

Our results demonstrate that abnormalities in sleep micro-structure in Parkinson's patients are associated with impairments in sleep-dependent cognitive processes, and that these might further interact with non-REM Stage 3 (i.e., slow-wave sleep).

Disclosures: S. Lahlou: None. **M. Kaminska:** None. **J. Doyon:** None. **J. Carrier:** None. **M. Sharp:** None.

Poster

155. Long-Term Memory: Consolidation and Reconsolidation: Behavior

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 155.15

Topic: H.07. Long-Term Memory

Support: NIA R00 AG049090
R01 AG070094
FL DOH 20A09
NIAAA R01 AA029700

Title: The role of an anterior thalamo-parietal cortex network in an action-orientation task

Authors: *C. SIMMONS[1], J. OGG[1], B. J. CLARK[2], A. A. WILBER[1];
[1]Psychology, Florida State Univ., Tallahassee, FL; [2]Psychology Dept., Univ. of New Mexico, Albuquerque, NM

Abstract: The anterior thalamus (ATN) is known to contain head direction cells that are responsible for signaling the directional orientation of an animal within an environment. These cells have direct and indirect connections with the parietal cortex (PC), an area hypothesized to play a role in coordinating viewer-dependent and viewer-independent spatial reference frames. This coordination between reference frames would allow an individual to translate movements toward a desired location from memory. Functional connectivity between the ATN and PC would thus be critical for orienting and moving toward remembered locations. This hypothesis was tested by running rats through an action-orientation task that required the rats to associate an appropriate action (left or right turn) with a directional heading. In this task, there are four arms of equal length positioned around a central starting point. Each arm is offset from the next by 90 degrees and has a unique allocentric direction (north, south, east, or west) in the room. A trial begins with the rat in the central starting point. A pseudorandom selection determined the arm order (i.e., random without repeats). After exiting an arm, the rat had to turn and then displace the correct object covering one of two feeding stations located to the left and the right in order to receive a reward. For a pair of arms facing opposite directions (i.e., east and west), the reward was located on the left, and for the other pair, the reward was located on the right. Thus, each of the four reward locations were associated with a different combination of allocentric heading direction and egocentric action. Removal of an object was scored as correct or incorrect. Trials in which the rat did not displace any objects were scored as ‘no response’ trials. After an object was removed, the rat returned to the center starting position and the maze was reset for the next trial. To investigate the role of the PC, ATN, and the ATN-PC network, muscimol (GABAa agonist) inactivation infusions targeted bilateral PC, bilateral ATN, ATN-PC network (Left ATN-Right PC or Right ATN-Left PC), or network control (unilateral inactivation). Muscimol sessions were counterbalanced and compared to saline sessions within the same animal. Inactivations resulted in decreased accuracy for all conditions. Only bilateral PC inactivation resulted in increased no response trials. Thus, while there are some differences between the inactivation conditions, the

overall similarity between individual brain regions and network inactivation suggest that the ATN-PC network is critical for linking an action with a spatial orientation for successful navigation.

Disclosures: **C. Simmons:** None. **J. Ogg:** None. **B.J. Clark:** None. **A.A. Wilber:** None.

Poster

155. Long-Term Memory: Consolidation and Reconsolidation: Behavior

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 155.16

Topic: H.07. Long-Term Memory

Support: ICMR SRF Grant: 3/1/2/136/Neuro/2020-NCD-I
DST Cognitive Science Research Initiative Grant: DST/CSRI/2017/150[G]
DST FIST Grant: SR/FST/LS-I/2017/05[C]
DST PURSE Grant: SR/PURSE Phase 2/39[C]

Title: Environment Enrichment Modulated Behavioral Tagging in Novel Object Recognition Long-Term Memory

Authors: *M. KAUSHIK[1], S. D. JOSHI[2], S. PARVEZ[1];
[1]Toxicology, Jamia Hamdard, New Delhi, India; [2]Electrical Engin., Indian Inst. of Technol. Delhi, New Delhi, India

Abstract: Acquisition and retention of information for different time intervals is the most crucial and fundamental brain process, also referred as learning and memory. Increasing burden of neurodegenerative disorders indirectly increases the burden of memory decline in the society, making it essential to decipher the cascade of learning and memory. The Behavioral Tagging (BT) model is the most suitable neurobehavioral model for learning and memory. The concept of BT underlies the experience of novel environment in order to establish the learning tag and *de novo* synthesis of plasticity related proteins (PRPs). The novel environment could be provided in number of ways, either through a novel task in between a regular behavioral task or through enriching the housing conditions of the animals under investigation. The aim of the present study was to explore the role of Environment Enrichment (EE) as the novelty in the BT model of learning and memory via PRPs induction. The male wistar rats were subjected to Novel Object Recognition (NOR) task with ten minutes of EE as the novel task within the 1-1.5h of NOR training session. NOR test was performed 24h after training and rat brain was excised immediately after the test session for molecular analysis of PRPs. It was found that EE modulated BT established memory consolidation, however, it was non-significant in comparison to than other type of novel task such as open field task. PRPs such as PKM-ζ, BDNF, CaMKII etc. are significantly expressed after the EE modulated BT. Taken together, our results are the first to demonstrate the role of EE modulated BT in memory consolidation.

Disclosures: **M. Kaushik:** None. **S.D. Joshi:** None. **S. Parvez:** None.

Poster

155. Long-Term Memory: Consolidation and Reconsolidation: Behavior

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 155.17

Topic: H.07. Long-Term Memory

Support: NSERC Grant 400176

Title: Object memory updating deficits in aging male mice can be rescued by pharmacological activation of M1 muscarinic acetylcholine receptors

Authors: *K. JARDINE, H. EDWARDS, C. WIDEMAN, B. WINTERS;
Univ. of Guelph, Guelph, ON, Canada

Abstract: Long-term declarative memories must be modifiable to maintain relevance in changing environments. Aging individuals often show declarative memory updating impairments, and the neural basis of this specific cognitive deficit remains unclear. Cholinergic system dysfunction in the aging brain disrupts many aspects of cognition, but its part in memory updating deficits has not been investigated. However, in young rats, there is evidence that the cholinergic system is important for object memory modifications. Specifically, activation of the M1 subtype of muscarinic acetylcholine receptors (mAChR) in perirhinal cortex (PRh) is required for reactivation-based object memory updating in young rats. Therefore, we hypothesize that cholinergic system dysfunction contributes to object memory updating deficits in the aging brain and that increasing M1 mAChR activation specifically can restore these deficits. To test this, we used a post-reactivation object memory modification (PROMM) task for mice, in which a reactivated object memory is updated with new contextual information in a memory updating session. Using this task, we characterized object memory updating abilities in male mice at different ages; 3-month-old mice showed intact object memory updating, while 12-month-old mice were impaired. In young mice, systemic administration of the M1 mAChR antagonist dicyclomine (16 mg/kg) prior to the memory updating session prevented the contextual update to the reactivated object memory. In aged mice that initially showed a PROMM task impairment, systemic administration of the M1 mAChR agonist CDD0102A (0.3 mg/kg) during the memory updating session restored object memory updating. Interestingly, despite impaired PROMM task performance in the aging mice, western blot analysis revealed a trending increase in M1 mAChR expression in PRh in aged mice compared to young mice. However, greater M1 mAChR levels in PRh were correlated with better PROMM task performance in young mice only. Together, these results indicate that M1 mAChR signaling is critical for object memory updating in mice, that activation of these receptors can ameliorate object memory updating deficits in aging mice, and that age-related decline in endogenous cholinergic transmission, rather than reduced M1 mAChR expression, contributes to memory inflexibility in the aging brain.

Disclosures: **K. Jardine:** None. **H. Edwards:** None. **C. Wideman:** None. **B. Winters:** None.

Poster

155. Long-Term Memory: Consolidation and Reconsolidation: Behavior

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 155.18

Topic: H.07. Long-Term Memory

Support: PAPIIT IN205222

Title: Blockade of protein kinase C prevents memory facilitation produced by microinjection of CORT:BSA into the dorsal hippocampus

Authors: *A. C. MEDINA, P. C. BELLO-MEDINA, M. MARTÍNEZ-DEGOLLADO, G. L. QUIRARTE, R. A. PRADO-ALCALÁ;
Neurobiología Conductual y Cognitiva, Inst. de Neurobiología, UNAM, Querétaro, Mexico

Abstract: It is known that learning generated by highly aversive experiences protects memory from amnestic treatments administered into the dorsal hippocampus (DH), such as protein synthesis inhibitors; intense learning also induces morphological changes in dendritic spines in DH. On the other hand, it has been shown that BSA conjugated corticosterone (CORT:BSA) facilitates memory when administered into DH, which has led to the assumption that a non-genomic pathway is part of the mechanisms involved in memory formation. The aim of this work was to determine if blockade of the genomic pathway allows the facilitation of memory induced by the activation of membrane glucocorticoid receptors and if this facilitation is blocked by the administration of a protein kinase C inhibitor. This kinase has been related to changes in the neuronal cytoskeleton, phosphorylation of glutamate receptors, structural changes, and the consolidation of memory of aversive tasks. In the first experiment, groups of rats were treated with anisomycin (ANI, 62.5 µg/0.5 µL) or vehicle, twenty minutes before inhibitory avoidance (IA) training using a moderate (1.0 mA) foot-shock, and immediately after training were administrated CORT:BSA (10, 20, or 30 ng/0.5 µL) or vehicle, bilaterally into DH. In a second experiment, we evaluated if cheleritryne (CHEL, a drug that blocks alpha, delta, and epsilon isoforms of PKC) and RU-38486 (antagonist to glucocorticoid receptors) block memory facilitation induced by CORT:BSA (20 ng). Groups of rats were microinjected with ANI or vehicle; five minutes later, the rats received CHEL (7.86 µg/0.5 µL), RU-38486 (10 ng/0.5 µL), or vehicle; and immediately after training the rats were administrated CORT:BSA (20 ng/0.5 µL) or vehicle. In a third experiment, groups of rats received ANI, CHEL, or RU-38486 before training and before the retention session, to control for state dependence. Long-term memory was tested 48 h later. We found that ANI produced amnesia, which was reversed by CORT:BSA; CHEL and RU-38486 blocked the effect of CORT:BSA, and no state dependency was found. These results suggest that the activation of a non-genomic pathway by CORT:BSA related to protein kinase C, are part of the mechanisms involved in memory consolidation. We thank the technical support of B. Osorio, N. Serafín, M. García, A. Castillo, M. A. Carbajo, M. E. Rosas, and R. Martínez. Supported by PAPIIT IN205222.

Disclosures: **A.C. Medina:** None. **P.C. Bello-Medina:** None. **M. Martínez-Degollado:** None. **G.L. Quirarte:** None. **R.A. Prado-Alcalá:** None.

Poster

155. Long-Term Memory: Consolidation and Reconsolidation: Behavior

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 155.19

Topic: H.07. Long-Term Memory

Support: PAPIIT IN205222
CONACYT Grant 473131

Title: Effects of dorsomedial striatum blockade by tetrodotoxin on memory consolidation in the rat

Authors: *M. MARTÍNEZ-DEGOLLADO, A. C. MEDINA, P. C. BELLO-MEDINA, G. L. QUIRARTE, R. A. PRADO-ALCALÁ;
Neurobiología Conductual y Cognitiva, Inst. de Neurobiología, UNAM, Querétaro, Mexico

Abstract: Reversible lesions allow the identification of brain areas involved memory. Voltage-dependent sodium channels blockers, such as tetrodotoxin (TTX), produce amnesia of moderate training of inhibitory avoidance (IA); however, when training intensity is increased, memory deficits are not observed. One structure of interest is the striatum, which has been differentiated into dorsomedial (DMS) and dorsolateral striatum, which process information about spatial navigation and procedural memory, respectively. To find out if infusion of TTX (2.5 ng) into the DMS interferes with memory consolidation of IA, we carried out three experiments, using 1.0 mA for training, and animals received bilateral infusions into the DMS 30 min before training. In the first experiment, two groups of rats received vehicle solution (VEH) or TTX; 24 h later retention of the task was measured. A significant deficiency was produced by TTX ($p < 0.0001$). As TTX was administered 30 min before training, the second experiment investigated if the retention deficit was due to state-dependency. One group received TTX and another one received VEH, both before training and before the 24-h retention test. The VEH group had optimal retention whereas the TTX group showed amnesia ($p < 0.01$ vs. VEH). The third experiment evaluated whether TTX induced a learning deficit rather than a memory consolidation deficit. One group received VEH, and another group received TTX before training; learning was measured 30 min later, and retention was evaluated 24 h after training. At the 30-min test, both groups showed optimal retention scores; at the 24-h test, the VEH group maintained the previous score while the TTX group was amnestic ($p < 0.01$ vs. VEH). We then investigated whether intense training would impede the amnestic effect of TTX, as when it has been administered to the hippocampus, amygdala, and prefrontal cortex. During training 0.0. 0.5, 1.0, or 3.0 mA were administered; for each intensity, one group of rats received VEH, and another group received TTX; 24 h later retention of the task was measured. The two 0.0 mA groups displayed very low retention scores. TTX produced a significant amnestic state when 0.5 and 1.0 mA were used ($p <$

0.01 vs. VEH). By contrast, the TTX group showed optimal retention when 3.0 mA was used for training. These results showed that DMS normal activity plays an important role in memory consolidation of IA and confirms that intense training protects against the amnestic effect of treatments that disrupt neuronal functions. We thank the technical support of N. Serafín, N. Aranda, M. García, A. Castilla, O. González, M.E. Rosas and R. Martínez. Funded by PAPIIT (IN205222) and CONACYT (473131).

Disclosures: M. Martínez-Degollado: None. **A.C. Medina:** None. **P.C. Bello-Medina:** None. **G.L. Quirarte:** None. **R.A. Prado-Alcalá:** None.

Poster

156. Episodic and Episodic-Like Memory

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 156.01

Topic: H.07. Long-Term Memory

Title: Testing pattern separation in refractory epilepsy patients

Authors: *N. GEIGEL, S. LONG, A. GUNDUZ;
J. Crayton Pruitt Family Dept. of Biomed. Engin., Univ. of Florida, Gainesville, FL

Abstract: Studying episodic memory and pattern separation in epilepsy patients with seizure zones near the hippocampus allows us to understand how the disease affects memory related structures. We used a previously developed task known as the Mnemonic Similarity Task to tax pattern separation in medical refractory epilepsy patients. The 5 patients recruited for the study were implanted with intracranial electrodes to localize the seizure onset zone for resection. We used BCI2000 to code the Mnemonic Similarity task to record behavioral data while also recording the neurological signal from deep brain locations. The task asked subjects to first classify images as indoor and outdoor. Afterwards, they were presented with a surprise memory test where they had to classify images as repeated, similar (lures), or new (foils) images they had not previously seen. From the behavioral data we were able to calculate the percent responses for each trial type. For repeated images, the patients responded correctly 84% of the time, responding similar 12% and new 4% of the time. For similar (lure) images, they responded correctly 40% of the time, responding repeated 49% and new 10% of the time. For new images, they responded correctly 76% of the time while responding repeated 2.8% and similar 21% of the time. We can conclude that the task can be extrapolated to our population and accurately tax pattern separation. Next steps will be to look at the subjects with worse performance in the task to determine if interictal epileptiform discharges in the hippocampus during the encoding of images caused interference leading to impaired pattern separation.

Disclosures: N. Geigel: None. **S. Long:** None. **A. Gunduz:** None.

Poster

156. Episodic and Episodic-Like Memory

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 156.02

Topic: H.07. Long-Term Memory

Title: Look closely! - Viewing behavior is associated with long-term memory of naturalistic episodes

Authors: *H. BERNHARD[1,2], A. GAIDOSCH[3], S. GEISS[3], C. PAULUS[3], R. P. W. ROUHL[5], V. H. J. M. VAN KRANEN-MASTENBROEK[6], B. M. JANSMA[4], P. DE WEERD[4], M. J. ROBERTS[4], J. REITHLER[4];
[1]Dept. of Cognitive Neurosci., [2]Ctr. for Integrative Neurosci., [4]Maastricht Brain Imaging Ctr., [3]Maastricht Univ., Maastricht, Netherlands; [5]Dept. of Neurol., [6]Dept. of Clin. Neurophysiol., Maastricht Univ. Med. Ctr., Maastricht, Netherlands

Abstract: Memory encoding of naturalistic stimuli, such as movies, requires binding perceptual, spatial and temporal elements into coherent representations. In these temporally evolving stimuli, only a subset of information can be sampled. Consequently, perceptual sampling behavior, such as eye movements, should shape the formation of episodic memories. Previous research using static images has shown that the number of fixations predicts recognition memory performance. However, it is unclear how visual sampling affects memory performance of dynamic stimuli. Here, we investigated the role of visual sampling on the encoding of naturalistic episodes. We hypothesized that denser sampling behavior (saccades, fixations and smooth pursuits) could allow binding of elements within an episode, leading to better memory performance. Participants (n=20) viewed 100 unique movie clips while their gaze positions were tracked. Each movie contained a short narrative, requiring temporal integration of its constituent events for subsequent memory recall. Memory performance was measured after 24 hours in a cued and free recall task, and assessed by three independent raters. Eye movement events were classified algorithmically based on gaze data velocity thresholds. Preliminary analyses (n=16) suggest that viewing behavior is related to subsequent memory recall in the cued but not the free recall task. More saccades ($t(15) = 2.912$; $p = 0.011$) and fixations ($t(15) = 2.946$; $p = 0.01$) but not smooth pursuits ($t(15) = 0.13$; $p = 0.899$) were related to successful cued memory recall. These findings suggest that viewing behavior during encoding of dynamic stimuli affects long-term memory performance. The denser sampling of temporally evolving information during naturalistic episodes may contribute to stronger binding between the constituent elements, thereby strengthening episodic memory traces.

Disclosures: H. Bernhard: None. **A. Gaidosch:** None. **S. Geiss:** None. **C. Paulus:** None. **R.P.W. Rouhl:** None. **V.H.J.M. van Kranen-Mastenbroek:** None. **B.M. Jansma:** None. **P. de Weerd:** None. **M.J. Roberts:** None. **J. Reithler:** None.

Poster

156. Episodic and Episodic-Like Memory

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 156.03

Topic: H.07. Long-Term Memory

Title: Memory for narrative events linked to gaze behavior, semantic features, and event segmentation

Authors: *A. M. GREENE, M. NAU, C. I. BAKER;
Lab. of Brain and Cognition, Natl. Inst. of Mental Hlth., Bethesda, MD

Abstract: Gaze behavior determines what aspects of the world are sampled, shaping both our visual experience as well as our memories of it later. While our experience is continuous, our episodic memories are segmented into discrete events. Prior work examined intensively how the brain performs this event segmentation, but its relationship to gaze behavior still remains poorly understood. Movies are useful naturalistic stimuli that enable us to test how continuous narratives are segmented into events. Here, we test whether the event structure of a movie is reflected in viewing gaze behavior, how viewing gaze behavior predicts later recollection of events, and how both interact with the semantic content of each movie scene. We investigated this by collecting eye-tracking and verbal-description data from twenty-two participants. They watched and then recalled a 50-minute clip of the BBC show Sherlock, which has been used extensively in prior neuroimaging work. We found that gaze patterns were indeed distinct across events and consistent across participants. Moreover, we tested whether event boundaries trigger systematic changes in gaze behavior, and characterized how similar different events were in terms of gaze, but also in terms of verbally recalled semantic features. We specifically test whether eye movements predict the semantic similarity between remembered events. By doing so, we aim to uncover whether and how gaze reflects narrative event segmentation, which will help elucidate how episodic memories are formed and recalled.

Disclosures: A.M. Greene: None. **M. Nau:** None. **C.I. Baker:** None.

Poster

156. Episodic and Episodic-Like Memory

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 156.04

Topic: H.07. Long-Term Memory

Support: ONR MURI Grant N00014-19-1-2373

Title: Evolving Memory: From Simple Foraging Associations to Cognitive Map Construction with Homeostatic Plasticity

Authors: *E. GRIBKOVA[1,2], R. GILLETTE[1,3];
[1]Neurosci. Program, [2]Coordinated Sci. Lab., [3]Dept. of Mol. and Integrative Physiol., Univ. of Illinois at Urbana-Champaign, Urbana, IL

Abstract: Cognitive mapping builds internal representations of the world and is essential to episodic memory and mental imagery. Here we show how circuitry of basic foraging decision can be straightforwardly expanded for affective valuation and cognitive map construction in the agent-based foraging simulation, ASIMOV, reproducing likely evolutionary pathways.
Behavioral choice in foraging is governed by reward learning and motivation, which interact to assign subjective value to sensory stimuli. These qualities characterize foraging generalists that hunt in variable environments and are precursors to more complex memory systems. ASIMOV's core decision network is based on neuronal circuitry of cost-benefit decision in the predatory sea-slug *Pleurobranchaea californica*. ASIMOV's virtual forager affectively integrates sensation, motivation (hunger), and learning to make cost-benefit decisions for approach or avoidance of prey, providing reward and nutrition upon consumption. Olfaction is used for both odorant discrimination and spatial navigation.
We developed a Feature Association Matrix (FAM) with reward learning and hippocampus-like sequence learning to map and establish relations. It does the basic tasks as most models of hippocampal function, but with much less computational demand. The FAM uses some of the simplest hippocampal-like associative architectures and learning rules for establishing pair-wise associations between sensory inputs and reward inputs. The FAM chains pairwise associations to memorize a sequence and assigns reward values along the chain. It shows how higher-order conditioning mechanisms and sequence memorization gives rise to cognitive mapping, through encoding additional contexts into pair-wise associations. Spatial learning for distant landmarks in terms of direction and distance is enabled by a simple path integration system. Homeostatic plasticity mechanisms further enable more complex spatial mapping, including obstacle avoidance learning, by down-sampling complex spatial paths into simplified sequences of navigation vectors.
Addition of the FAM's spatial and episodic memory to ASIMOV's forager shows how the neuronal circuitry of foraging decision may have served as the framework for cognitive mapping in evolution.

Disclosures: E. Gribkova: None. **R. Gillette:** None.

Poster

156. Episodic and Episodic-Like Memory

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 156.05

Topic: H.07. Long-Term Memory

Support: NSF Grant 1633873

Title: Age and retrieval-related scene reinstatement: moderating effects of cortical thickness

Authors: *J. OLIVIER, S. SROKOVA, M. D. RUGG;
Univ. of Texas at Dallas, Richardson, TX

Abstract: Episodic memory retrieval is associated with the reinstatement of patterns of cortical activity that partially overlap those elicited during encoding, a phenomenon termed 'cortical reinstatement'. It has been previously reported that retrieval of visual scene stimuli is associated with cortical reinstatement in scene-selective cortical regions, most notably, the parahippocampal place area (PPA) and the retrosplenial complex (RSC). In addition, scene-related cortical reinstatement has been reported to be weaker in older relative to young adults. Here, we examined whether age differences in the strength of cortical reinstatement in the PPA and RSC are mediated by cortical thickness. To do this, we combined two datasets in which young (total N = 42) and older (total N = 44) adults underwent fMRI as they performed one of two source memory tasks. In both tasks, participants studied words paired with scenes and either with faces (dataset 1) or with scrambled images (dataset 2). At retrieval, participants in both tasks judged whether test words were old and for any word endorsed old, they then indicated which visual stimulus category the word had been paired with (i.e., scene, face, or scrambled). Older age was robustly and negatively associated with a univariate index of scene reinstatement in both the PPA ($r = -.354$, $p < .001$) and RSC ($r = -.367$, $p < .001$). Age group was also strongly negatively associated with global cortical thickness ($r = -.713$, $p < .001$). Mediation analysis revealed that the effects of age on scene reinstatement were fully mediated by cortical thickness in the PPA ($r = -.143$, $p = .190$). By contrast, cortical thickness did not moderate the relationship between age group and scene reinstatement in the RSC ($r = -.302$, $p = .005$). The findings point to a functional dissociation between the two regions in respect of their sensitivity to age differences in brain structure. Moreover, they suggest that, at least in the RSC, increasing age is associated with functional differences that are independent of age-related cortical atrophy.

Disclosures: J. Olivier: None. **S. Srokova:** None. **M.D. Rugg:** None.

Poster

156. Episodic and Episodic-Like Memory

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 156.06

Topic: H.07. Long-Term Memory

Support: Personalized health and related technologies
Swiss National science fundation

Title: Bodily self-consciousness is associated to hippocampal and sensorimotor reinstatement of encoding activity

Authors: *N. H. MEYER[1], B. GAUTHIER[1], J. BOSCHERON[1], E. FRANC[1], F. LANCE[1], J. POTHEEGADOO[1], O. BLANKE[1,2];

[1]LNCO CNP BMI, Swiss Federal Inst. of Technol., Lausanne, Switzerland; [2]Neurol., Univ. Hosp. Geneva, Geneva, Switzerland

Abstract: Episodic memories (EM), are contextual memories of self-related events. Recent work showed that EM strength and vividness decrease with modulation of bodily self-consciousness (BSC; Blanke, 2012; 2015), the pre-reflective component of self-consciousness based on multisensory and sensorimotor perception of bodily signals (Bergouignan et al., 2014; Gauthier et al., 2020, Marcotti and St. Jacques, 2021). EM has been linked to the reinstatement of encoding-related activity of the hippocampus during retrieval; however, the link between BSC and EM at the neural level, events that may make remembered episodes become experienced as belonging to the self, is currently unclear. In this behavioral, virtual reality (VR) and fMRI study, we investigated the neural substrates linking BSC and EM during the incidental encoding of 3D life-like scenic virtual episodes, created in VR.
We merged fully immersive VR with motion tracking and fMRI (Gauthier et al., 2021) to alter BSC using visuomotor and perspectival incongruency during the incidental encoding of three virtual scenes, each associated with a specific experimental condition: first-person synchronous avatar, first-person asynchronous avatar, and third-person asynchronous avatar. We measured participants' BSC by asking them to rate their sense of agency (SoA) for each condition. The recognition memory was assessed one hour after the encoding, with an object recognition task (i.e. Bréchet et al.,2019; Gauthier et al.,2020).
Using searchlight representational similarity analysis (Kriegeskorte et al., 2008) we showed that the activity of the left hippocampus was more similar to its encoding activity under visuomotor and perspectival congruency (first-person synchronous avatar) suggesting that hippocampal reinstatement depends on the sense of self and SoA in particular. The level of similarity of the hippocampal activity between encoding and retrieval was further linked with the memory performance of participants. In a final step, we show that SoA activation in right dorsal premotor cortex and right insula (during encoding), alters functional connectivity with the left hippocampus. To summarize, we show that modulation of BSC during the incidental encoding of virtual scenes modulates later EM retrieval, mediated by linking SoA-related activity to the left hippocampus. These data suggest that naturalistic visuomotor and perspectival congruency during encoding leads to stronger hippocampal reinstatement and is linked to a SoA network, describing a mechanism that may turn remembered episodes into episodes of the remembered self.

Disclosures: **N.H. Meyer:** None. **B. Gauthier:** None. **J. Boscheron:** None. **E. Franc:** None. **F. Lance:** None. **J. Potheegadoo:** None. **O. Blanke:** None.

Poster

156. Episodic and Episodic-Like Memory

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 156.07

Topic: H.07. Long-Term Memory

Support: Start up funds

Title: Behavioral evidence of independent mechanisms for memory system cooperation and competition.

Authors: *C. REBMANN, M. FREEDBERG;
Univ. of Texas, Univ. of Texas - Austin, SAN MARCOS, TX

Abstract: Behavioral and neuroscientific studies reveal that multiple memory types, and their associated networks, interact during learning. Episodic memories are verbally accessible and related to facts, events, or objects, whereas procedural memories include skills and habits. Recent studies show evidence for both competitive and cooperative interactions when participants perform these tasks in series. However, learning in the real world likely involves the parallel use of both memory types, and thus, these studies may not accurately portray how these memory types interact. Acquiring both in close temporal proximity should cause memory interference if they compete. Alternatively, simultaneously acquiring information from both memory types should be possible if these systems cooperate. Our objective was to examine behavioral interactions using a task where both episodic and procedural task demands were present, allowing us to measure the simultaneous acquisition of episodic and procedural contingencies. Episodic tasks involved learning deterministic information, like learning facts. Procedural tasks involved gradually learning probabilistic information, like learning skills. Participants acquired associations with deterministically (episodic) and probabilistically (procedural) linked stimulus-to-response (S-R) mappings. Additionally, participants learned combinations that included both types of information (mixed). Thirty-two participants performed each combination type in a pseudo-random order for six blocks. Counterbalancing minimized stimulus, order, and response-related effects. Learning was measured during a final testing block by comparing the performance of combinations practiced during training to combinations introduced during testing. Learning episodic combinations was negatively correlated with procedural learning. Paradoxically, we found evidence of significant learning for the mixed combinations, which involved simultaneously learning both types of information. The learning was unrelated to episodic and procedural learning, suggesting that integrating information from both systems (cooperation) is supported by an independent mechanism from the one that causes competition. Awareness of combination types was not associated with learning, ruling out attentional effects. These results reconcile the disparate findings in the literature by showing that competitive and cooperative interactions are supported by independent mechanisms, suggesting a new model for memory network dynamics.

Disclosures: C. Rebmann: None. **M. Freedberg:** None.

Poster

156. Episodic and Episodic-Like Memory

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 156.08

Topic: H.07. Long-Term Memory

Support: ERC Advanced Grant
THINK@Ruhr

Title: Neural correlates of novel object recognition in pigeons

Authors: *F. OKSUZ[1], M. FLAIM[2], O. GUNTURKUN[2];
[1]Biopsychology, Rub Res. Sch., Bochum, Germany; [2]Biopsychology, Ruhr-Universitat Bochum, Bochum, Germany

Abstract: Distinguishing between a novel and familiar stimulus is a fundamental ability in all learning and memory processes. This ability has been extensively investigated in mammals using the spontaneous object recognition (SOR) task, which takes place in an open field environment. The first phase of the SOR presents two identical objects and allows the subject to explore them for a predetermined amount of time. Then there is a retention interval, where the subject does not see any objects, which can last anywhere from 30 seconds to 24 hours. Finally, the last phase presents one object from the first phase and a novel object. Mammals will spend significantly more time exploring the novel object, even though neither object has biological significance. A variety of methods has shown that the perirhinal cortex is crucial for this behavior. Despite the universal usefulness of novelty detection, the SOR task has only been recently modified for pigeons. Like mammals, pigeons also spend significantly more time exploring the novel object. However, in this experiment with pigeons, there was large amount of variability and only one retention interval was used. Further, it is completely unknown what brain region supports this behavior in pigeons, partially because of the differences between mammalian and avian brain organization. Our experiment will expand the procedure and enhance the power of the SOR task in pigeons with a within-subjects design. We will administer a 4 trial SOR task (n = 16), where each trial will have a different retention interval. The retention intervals will be 1, 5, 20, or 60 minutes. Then we can determine the most effective retention interval for revealing exploratory behavior and reduce variability in the results. Further, we will also investigate the underlying neural correlates of novel object recognition by using immediate early gene staining techniques. This experiment would help identify the brain regions involved in object recognition and novelty, potentially identifying the avian equivalent to the perirhinal cortex.

Disclosures: **F. Oksuz:** None. **M. Flaim:** None. **O. Gunturkun:** None.

Poster

156. Episodic and Episodic-Like Memory

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 156.09

Topic: H.07. Long-Term Memory

Support: NS110863

Title: Progesterone Receptors Regulate Declarative Memories in Male Mice

Authors: *S. JOSHI, J. KAPUR;
Univ. of Virgina, Univ. of Virgina, Charlottesville, VA

Abstract: Progesterone is present in the male brain; it antagonizes the actions of androgens to suppress mating behavior and male aggression. These effects depend on the expression of progesterone receptors (PRs), as their deletion alters these behaviors. In contrast, extra-hypothalamic PR expression and function in males remain underexplored. We first evaluated whether PRs are expressed in the hippocampus and entorhinal cortex (Ent) of male mice and regulated the activity of neurons in this circuit. Then, we evaluated whether PRs regulated mnemonic processes depending on the hippocampus-Ent activity in males. We found PR mRNA expression in the hippocampi and Ent of adult male mice. A strong PR expression was seen in the neurons of Ent, dentate hilus, and CA1 and subiculum. In contrast, the PR expression was weak in the hippocampal DGCs and CA3 neurons. Most of the PR-expressing neurons also expressed CamKII but not interneuronal markers parvalbumin (PV) and somatostatin (Som). In the dentate hilus, PR-expressing neurons expressed GluA2 subunits, a maker of mossy cells, and lacked the expression of PV and Som. This indicated that PRs were primarily expressed in the excitatory neurons of the hippocampus and Ent. We evaluated the effect of PR activation on neuronal activation in these regions using TRAP mice. More neurons were TRAPed in the mice treated with PR agonist Nestorone in the home cages compared to vehicle-treated mice. Nestorone treatment increased the number of active CA1+subicular and Ent neurons 2-3 fold compared to that in vehicle-treated mice. The number of active DGCs doubled following Nestorone treatment. Mice with a brain-specific PR deletion (PRKO) were impaired in novel object recognition tested 8 hr after familiarization (% time with novel object 44 ± 7 in PRKO, n=10 vs 60 ± 8, n=7 in WT, $p<0.005$, student's t-test). A similar impairment was also seen when the testing was done 1 hr later. This impairment was not associated with altered brain progesterone levels or impacted locomotor and exploratory activity in these mice. Treatment of animals with anti-progestin Ru-486 for a week also affected novel object recognition (Ru-486 43 ± 15, n=7 vs vehicle 62 ± 13, n=9, $p<0.05$). The PRKO male mice were also impaired in recognizing a change in an object's place and also were unable to recognize the novel arm in a Y maze forced-alternation task. The Ent-specific deletion of PRs also affected novel object recognition (PRKO 39 ± 13, n=12 vs 54 ± 15, n=8, $p<0.05$). These studies have uncovered a critical role of progesterone-PR signaling in regulating declarative memories in males.

Disclosures: S. Joshi: None. **J. Kapur:** None.

Poster

156. Episodic and Episodic-Like Memory

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 156.10

Topic: H.07. Long-Term Memory

Title: Spiking sequence fidelity in the human anterior temporal lobe predicts successful memory encoding and and retrieval

Authors: *J. ZHANG[1,2], J. H. WITTIG, Jr.[1], S. INATI[1], T. E. BEHRENS[2], K. ZAGHLOUL[1]; [1]NINDS, Bethesda, MD; [2]Univ. of Oxford, Oxford, United Kingdom

Abstract: Bursts of single unit spiking activity are observed in the human anterior temporal lobe (ATL) during resting and task-related states. These bursts are sequences of spiking neurons that uniquely represent individual categories and items. Sequences are coupled with sharp wave ripples in the medial temporal lobe (MTL) and recapitulate when associated memory is cued and retrieved. However, their precise role in memory remains unclear. Here we show that sequence fidelity predicts successful memory encoding and retrieval. In single cell data from subjects who completed a recognition recall task, we found that burst sequences during trials of subsequently recalled stimuli reliably represented category-level information about the stimuli and were consistent with sequences during recall. Additionally, better recognition performance is correlated with better recall performance, and correctly recognized and recalled trials have stronger sequence fidelity. Similarly, image stimuli, which had significantly better recognition accuracy and recall rate than text stimuli, had sequences that reliably represented semantic information while text stimuli did not. These results suggest that the fidelity of sequences in the ATL for representing semantic information about stimuli input predicts whether such stimuli are successfully encoded in and retrieved from memory. These results reveal an important functional role of bursting activity observed in cortex and enhances our understanding of the mechanism of memory at a cellular level. Our findings could lead to additional studies about the characterization of such sequences, what upstream factors influence their reliability, the generalizability of their functional roles to other cortical regions, and broader questions about information encoding in the brain. Developing a more detailed mechanistic model for memory may improve diagnosis and treatment of dementia, and insights on information encoding in the brain may inspire advancements in artificial intelligence, which has growing applications in our world today.

Disclosures: **J. Zhang:** None. **J.H. Wittig:** None. **S. Inati:** None. **T.E. Behrens:** None. **K. Zaghloul:** None.

Poster

156. Episodic and Episodic-Like Memory

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 156.11

Topic: H.07. Long-Term Memory

Support: Samarbeidsorganet, Helse Midt-Norge RHF
Norwegian National Advisory Unit for functional MRI at Department of Medical Imaging, St. Olav's University Hospital

Title: Revisiting the link between handedness and memory in men and women. A HUNT4 Hjernetrim Study

Authors: *D. R. SOKOLOWSKI[1,2], T. I. HANSEN[1], A. K. HABERG[1,2];
[1]Dept. of Neuromedicine and Movement Sci., NTNU, Trondheim, Norway; [2]Dept. of Radiology and Nuclear Med., St. Olavs Hosp., Trondheim, Norway

Abstract: The effects of handedness on cognition are often ignored in cognitive science. Different types of handedness and their interaction with sex are overlooked, or non-right-handers are excluded from study cohorts altogether. This study aimed to assess the differences in memory performance between familial and non-familial right- and left-handers. We used Memoro, our web-based cognitive test battery, and invited participants from the fourth wave of The Trøndelag Health Study, HUNT4. We focused on 5 memory scores: verbal list learning, visual memory object identity and location (Euclidean map), pattern separation ability, and digit span backwards maximal span. Out of 5615 participants (13 - 97 years old, 57.8% women), 90.4% were familial right-handed (fRH), 4% were familial left-handed (fLH), 3.6% were nonfamilial left-handed (nLH), and 2% had non-standard handedness (familial or nonfamilial ambidextrous or nonfamilial right-handed). There were no significant frequency differences in handedness between men and women. Since the non-standard groups were very heterogeneous and the number of participants low, we focused on comparing fRH, fLH, nLH. We found several memory scores to be differently affected by left-handedness in the familial and nonfamilial groups, and this effect was varied by sex. Most notably, while fLH was associated with advantages in certain abilities and disadvantages in others, nLH was never associated with a cognitive advantage. For verbal memory, fRH women remembered significantly more words than fRH men ($\beta = -0.36$, $p < 0.001$) and fLH women ($\beta = -0.25$, $p < 0.01$), but not fLH men ($\beta = -0.07$, $p = 0.59$). Both nfLH men and women remembered less words than fRH women ($\beta = -0.45$, $p < 0.001$ and $\beta = -0.27$, $p < 0.01$, respectively). For visual memory object identity, fRH women remembered object positions better than fRH men ($\beta = -0.24$, $p < 0.001$) and nfLH men ($\beta = -0.32$, $p < 0.01$), but not other groups. For visual memory location memory measured as Euclidean distances, fRH women were significantly less precise than fRH women ($\beta = 0.23$, $p < 0.05$), but similar to other groups. In pattern separation, we found a statistical trend of fRH women achieving lower scores then fLH men ($\beta = 0.20$, $p = 0.06$), but similar to other groups. For digit span backwards, fRH women had lower span than fRH men ($\beta = 0.21$, $p < 0.001$) and fLH men ($\beta = 0.27$, $p < 0.05$), and similar to other groups. These results show that fLH had profound effects on memory in men but not in women. They also show that ngLH affected cognition very differently from the fLH, confirming that cognitive science studies should always distinguish between the two modes of left-handedness and that handedness is a diversity measure worth including.

Disclosures: D.R. Sokolowski: None. **T.I. Hansen:** None. **A.K. Haberg:** None.

Poster

156. Episodic and Episodic-Like Memory

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 156.12

Topic: H.07. Long-Term Memory

Support: NIA 2RF1AG039103

Title: Transient and sustained fMRI recollection effects are age-invariant

Authors: *M. HOU, M. DE CHASTELAINE, M. D. RUGG;
Univ. of Texas at Dallas, Dallas, TX

Abstract: Findings from prior studies in young adults indicate that recollection-related neural regions dissociate according to the time course of their respective recollection effects: whereas the effects are transient in medial temporal and midline cortical regions, in lateral cortical regions and the striatum they track the period over which recollected content must be maintained. Here, we examined whether this dissociation is also evident in older adults. Young and older participants (N= 24 in each group) encoded a series of word-picture pairs, judging which of the denoted objects was the smaller. In a subsequent scanned test phase, studied and unstudied words were presented. Participants first judged whether a test word was old or new. For items judged old, instructions were to recall the associated picture and hold it in mind across a delay period that varied randomly from 2 to 8 sec. A cue denoted which of three judgments should be made on the retrieved picture. Additional responses were available for words deemed new or when an associate could not be retrieved. Compared to the young group, older adults demonstrated significantly lower recollection estimates. fMRI recollection effects were operationalized as greater neural activity elicited by test words for which the associated picture was successfully retrieved relative to words for which recollection of the associate picture failed. Replicating prior findings, transient recollection effects were identified in posterior hippocampus, parahippocampal cortex and medial prefrontal cortex, while sustained effects were evident in lateral prefrontal cortex, intraparietal sulcus, angular gyrus, inferior temporal gyrus and the striatum. Crucially, neither class of effect differed according to age group in any of the regions where they were identified. These findings add to the evidence that retrieval-related activity in different recollection-sensitive regions can be temporally dissociated. More importantly, the findings suggest that both transient and sustained recollection effects are largely stable across much of the healthy human adult lifespan.

Disclosures: **M. Hou:** None. **M. de Chastelaine:** None. **M.D. Rugg:** None.

Poster

156. Episodic and Episodic-Like Memory

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 156.13

Topic: H.07. Long-Term Memory

Support: CNPq
CAPES
FAPEMIG

Title: Proactive interference between non-overlapping content memories

Authors: *L. M. Z. MANSK, M. C. PASSOS, L. F. JAIMES, G. S. PEREIRA;
Physiol. and Biophysics, UFMG, Belo Horizonte, Brazil

Abstract: Different memory traces can be formed simultaneously and interact with each other in a dynamic process. However, how the hippocampal circuits deal with the concomitant acquisition of memory traces is still an open question. Recently, it was proposed that the integration of adult born neurons may have a role on shaping the hippocampal circuits of memories that overlap in content. Here, we asked whether the formation of hippocampal-dependent memories, that differ in content, may interfere on each other. Male C57BL/6 (8 weeks old) were submitted to behavioral paradigms that yield distinct non-associative declarative-like memories: Social Recognition (SR) and Novel Object Recognition (NOR). To test for retroactive (RI) and proactive (PI) interference, the animals went through SR and NOR, varying the sequence in which the training for each memory occurred. Memory was accessed 24h after the training. As an attempt to increase adult neurogenesis, animals received memantine (25 mg/kg i.p.) (MEM) 7 days prior the behavioral tasks or were housed in enriched environment (EE) during the week before the tasks. Immunohistochemistry assay, using anti-doublecortin (DCX), was performed to quantify newborn neurons on the dentate gyrus. Regardless of the sequence in which the acquisition of NOR and SR occurred, the first one impaired the memory retrieval of the second one, characterizing a PI. No evidences for RI were observed. MEM administered 7 days prior to SR and NOR learning failed to prevent memory interference and to increase the number of DCX+ cells/mm² on hippocampus. As a second attempt to increase adult neurogenesis animals were housed in EE, but it did not prevent the PI to occur. Our findings show that subsequent learning of different hippocampus-dependent memories caused proactive interference, suggesting an interaction between both memory traces. However, adult neurogenesis seems not to be a mechanism mediating such interaction.

Disclosures: L.M.Z. Mansk: None. **M.C. Passos:** None. **L.F. Jaimes:** None. **G.S. Pereira:** None.

Poster

156. Episodic and Episodic-Like Memory

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 156.14

Topic: H.07. Long-Term Memory

Support: DFG (German Research Foundation) Grant 419037518 – FOR 2812, P2

Title: Modeling the function of episodic memory in spatial learning

Authors: *X. ZENG, L. WISKOTT, S. CHENG;
Inst. for neural computation, Dept. of computer science, Ruhr Univ. Bochum, Bochum, Germany

Abstract: Episodic memory, usually defined as memories for specific past events, has been studied extensively in the past few decades. However, most research has focused on examining the contents of episodic memory, its neural substrate as well as the encoding and retrieval mechanisms. By contrast, little is understood about the function of episodic memory in learning and decision-making. In this study, we propose that episodic memory can facilitate learning in two fundamentally different modes: retrieval and replay. We study their properties by comparing three learning paradigms using computational modeling based on visually-driven reinforcement learning. Firstly, episodic memory is retrieved to learn from single experiences (one-shot learning); secondly, episodic memory is replayed to facilitate learning of statistical regularities (replay learning); and, thirdly, learning occurs online as experiences arise with no access to past experiences (online learning). We selected three reinforcement learning algorithms to model the three learning paradigms, respectively, and examined their behaviors in spatial learning tasks in simulations. We found that episodic memory benefits spatial learning in a broad range of conditions, but the performance difference is meaningful only when the task is sufficiently complex and the number of learning trials is limited. Furthermore, the two modes of accessing episodic memory facilitate spatial learning in distinct ways. One-shot learning is initially faster than replay learning, but the latter reaches a better asymptotic performance than the former. Our model also accounts for experimental results where learning is slowed down while hippocampal replay is inhibited, but the hippocampus, and hence episodic memory, is intact during learning. Understanding how episodic memory drives behavior will be an important step towards elucidating the nature of episodic memory.

Disclosures: X. Zeng: None. **L. Wiskott:** None. **S. Cheng:** None.

Poster

156. Episodic and Episodic-Like Memory

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 156.15

Topic: H.07. Long-Term Memory

Title: Individual differences in post-stimulus reaction time at encoding predict subsequent spatial context memory performance

Authors: *G. VELEZ LARGO[1], A. ELSHIEKH[1], S. RAJAGOPAL[4], S. PASVANIS[4], T. HAMAÏDE[2], M. N. RAJAH[3,4];
[1]Integrated Program in Neurosci., [2]Anat. and Cell Biol., [3]Psychiatry, McGill Univ., Montreal, QC, Canada; [4]Douglas Brain Imaging Centre, Douglas Inst., Montreal, QC, Canada

Abstract: Individuals vary widely in their abilities to encode past events in rich spatial contextual detail. We tested the hypothesis that trial-by-trial fluctuations in attention at encoding play an important role in individual differences in spatial context memory, along with other potential contributors such as: education, executive functioning, and levels of mind-wandering. We also hypothesized that individual differences in attentional lapses at encoding would be related to altered brain activity in regions important for encoding. To this end, 39 healthy young adults (mean age = 26.5 ± 4.4, 19 females) participated in a novel *Attention At Encoding Task* fMRI paradigm, which consisted of 4 runs. In each run, participants were asked to encode 48 coloured photographs of common objects and their left/right spatial location, and to subsequently retrieve them (192 encoding trials across all 4 runs). In addition, participants were required to respond as quickly as possible to a central fixation cross that expanded in size at a random duration after each encoding trial. Response times (RTs) to the fixation cross were hypothesized to reflect individuals' attention levels on a trial-by-trial basis during encoding. Using a mixed-effects logistic regression model in R we found that longer post-stimulus RT predicted poorer spatial context memory at the group level. This effect significantly varied across participants and was modulated by their levels of mind-wandering, executive functioning, and baseline memory performance. We performed a parametric modulation analysis using SPM12 to explore how post-stimulus RT was related to brain activation during encoding. Our preliminary whole-brain results indicate that longer post-stimulus RT is related to decreased deactivation in the midline prefrontal cortex, a region implicated in lapses of attention and mind-wandering. The current study highlights how individual differences in mind-wandering and executive functioning moderate the effect of a momentary lapse in attention (longer post-stimulus RT) on subsequent spatial context retrieval and contributes to the growing body of research on individual differences in episodic memory.

Disclosures: G. Velez Largo: None. **A. Elshiekh:** None. **S. Rajagopal:** None. **S. Pasvanis:** None. **T. Hamaïde:** None. **M.N. Rajah:** None.

Poster

156. Episodic and Episodic-Like Memory

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 156.16

Topic: H.07. Long-Term Memory

Title: Neural pattern similarity between naturalistic events at encoding differentially predicts later reinstatement across the cortex

Authors: *M. HEBSCHER, J. L. VOSS;
Univ. of Chicago, Chicago, IL

Abstract: Everyday memory involves high overlap between the actors, locations, and objects of events. Under some circumstances it may be beneficial to distinguish, or differentiate, neural representations of similar events to avoid interference at recall. Under other circumstances,

forming overlapping representations of similar events, or integration, may aid recall by linking new memories to old memories. It is currently unclear how and under which conditions the brain supports these seemingly conflicting functions of differentiation and integration. In the present study, we examined how encoding of highly overlapping naturalistic events affects their later retrieval. Subjects (n=20) performed an episodic memory task in which they encoded and recalled naturalistic video stimuli with high feature overlap in the fMRI scanner. Multivoxel pattern analyses (MVPA) measured across-item similarity of neural representations at encoding, reflecting the degree to which videos are integrated or differentiated, while encoding-retrieval similarity provided a measure of neural reinstatement of videos. We found that across-item similarity at encoding was differentially related to later cortical reinstatement. Parietal and temporal regions showed a positive relationship between across-item similarity at encoding and reinstatement, such that stimuli that were more highly integrated were more likely to be later reinstated. Occipital regions, particularly lower-level visual processing regions, showed the opposite pattern, with greater differentiation of stimuli predicting their later reinstatement. Greater integration at encoding positively predicted later objective and subjective memory performance in parietal, temporal, and occipital regions, but not in lower-level visual processing regions. These findings suggest that integration of overlapping stimuli in higher-level sensory processing regions at encoding is beneficial for later neural reinstatement and memory recall. By contrast, differentiation of overlapping stimuli in lower-level visual processing regions leads to greater neural reinstatement, with no effect on memory performance. Together, these findings demonstrate that stimuli can be simultaneously integrated and differentiated in different populations across the brain.

Disclosures: **M. Hebscher:** None. **J.L. Voss:** None.

Poster

156. Episodic and Episodic-Like Memory

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 156.17

Topic: H.07. Long-Term Memory

Support: NIHM 7R01MH120194-02
NSF GRFP

Title: Direct electrical stimulation of the human amygdala enhances declarative memory over long delays

Authors: *M. K. HOLLEARN[1], L. BLANPAIN[3], J. R. MANNS[5], S. B. HAMANN[5], K. BIJANKI[6], R. E. GROSS[7], D. DRANE[4], J. M. CAMPBELL[2], K. L. WAHLSTROM[1], J. T. WILLIE*[8], C. S. INMAN*[1];
[1]Psychology, [2]Interdepartmental Program in Neurosci., Univ. of Utah, Salt Lake City, UT; [3]Neurosci., [4]Neurol., Emory Sch. of Med., Atlanta, GA; [5]Psychology, Emory Univ., Atlanta, GA;

[6]Neurosurg., Baylor Col. of Med., Huston, TX; [7]Neurosurg., Emory Univ. Sch. of Med., Atlanta, GA; [8]Neurosurg., Washington Univ. Sch. of Med. and Barnes-Jewish Hosp., Saint Louis, MO

Abstract: As we previously demonstrated that brief electrical stimulation to the basolateral amygdala (BLA) reliably enhances declarative memory in humans after a one-day delay without eliciting an emotional response. The present study examines whether human amygdala stimulation enhances declarative memory at longer delay intervals (2-12 days). We recruited 25 drug-resistant epilepsy patients undergoing stereo EEG surgery with depth electrode contacts implanted in BLA, sub-regions of the medial temporal lobe (MTL), and sub-regions outside of the MTL. During continuous intracranial EEG recording, each participant was presented with a series of images of neutral objects. Across patients, we delivered a brief stimulation to the BLA (8 trains of 50-Hz pulses at 0.5 mA) before, during, or after image presentation and at varying stimulation duration (1-3 seconds, $n = 20$) to determine which stimulation parameters might boost memory enhancement one day later. In addition to parameter variations at the one-day delay, we tested participants at longer time delays ($n = 5$) to observe the persistence of memory enhancement over time. Across all conditions, we found previously stimulated trials had higher d' scores compared to previously non-stimulated trials ($t(24) = 2.97$, $p = .007$, $d = .24$). However, this was not observed in high confidence trials ($t(24) = 1.38$, $p = .181$, $d = .12$). This expands our previous findings of memory enhancement due to BLA stimulation with the inclusion of stimulation and delay variations. Memory enhancement due to prior stimulation was the same at longer delays compared to one-day delay ($B = -.08$, $SE_b = .12$, $t(24)= -.68$, $p = .501$, $d = .34$), suggesting that the stimulation enhancement remained over time, up to 12 days. This was also true for high confidence trials ($B = -.02$, $SE_b = .18$, $t(24)= -.10$, $p = .923$, $d = .05$). Initial local field potential analyses suggest that BLA stimulation encodes a marker of prior stimulation in the MTL memory network and other cortical memory-related regions at delays of up to 12 days. The current results indicate that brief electrical stimulation to the human amygdala can enhance item-specific memory for neutral objects even in the absence of awareness of the stimulation for up to 12 days, reflecting a key role of the amygdala in prioritizing experiences for long-term storage in declarative memory. Further inquiry in humans and experimental animals will be required to fully optimize the potential of amygdala-mediated memory enhancement. These studies may reveal the basic mechanisms of endogenous memory prioritization and yield insights into new memory-enhancing therapies.

Disclosures: M.K. Hollearn: None. **L. Blanpain:** None. **J.R. Manns:** None. **S.B. Hamann:** None. **K. Bijanki:** None. **R.E. Gross:** None. **D. Drane:** None. **J.M. Campbell:** None. **K.L. Wahlstrom:** None. **J.T. Willie*:** None. **C.S. Inman*:** None.

Poster

156. Episodic and Episodic-Like Memory

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 156.18

Topic: H.07. Long-Term Memory

Support: NIH R56 AG068149

Title: Age-related neural dedifferentiation at the level of individual stimulus items

Authors: *S. SROKOVA[1], A. N. Z. AKTAS[1], J. D. KOEN[3], M. D. RUGG[2];
[1]Univ. of Texas at Dallas, Univ. of Texas at Dallas, Richardson, TX; [2]Ctr. for Vital Longevity, Univ. of Texas at Dallas, Dallas, TX; [3]Psychology, Univ. of Notre Dame, Notre Dame, IN

Abstract: Cognitive aging is associated with a reduction in selectivity for preferred stimuli in category-selective cortical regions, a phenomenon termed 'age-related neural dedifferentiation'. There is compelling evidence that age-related neural dedifferentiation is detectable at the level of stimulus categories (e.g., visual images of scenes). However, much less is known about age-related neural dedifferentiation at the level of individual stimulus exemplars. To address this question, young and older adults of both sexes underwent fMRI while viewing images of scenes and objects. After their initial presentation, 20% of the items were later repeated, and another 20% were 'repeated' in the form a visually similar 'lure'. It is well established that the repetition of a stimulus exemplar elicits a diminished neural response relative to its first presentation, a phenomenon termed 'repetition suppression'. Here, we employed repetition suppression as a metric of item-level differentiation under the assumption that a more differentiated neural representation will lead to greater repetition suppression when the item is repeated than when it is followed by a similar lure. At the whole brain level, both younger and older adults demonstrated robust repetition suppression effects for exact repeats of scenes in the scene-selective Parahippocampal and Occipital 'Place Areas'. Repetition suppression for objects was evident in the object-selective Lateral Occipital Complex, as well as in the bilateral parahippocampal and occipital cortices, lingual gyrus, inferior frontal gyrus, dorsomedial prefrontal cortex, and the right posterior hippocampus. Object lures were associated with sparser suppression effects which were confined to occipital and parahippocampal regions while suppression effects for scene lures overlapped with the suppression effects elicited by scene repetitions. Of importance, at the whole brain level, none of the aforementioned suppression effects differed reliably between the younger and older age groups. The null effects of age on the suppression effects for repeats and lures suggest that age-related neural dedifferentiation, at least as operationalized by whole-brain univariate fMRI metrics, does not extend to neural representations of individual stimulus items.

Disclosures: S. Srokova: None. **A.N.Z. Aktas:** None. **J.D. Koen:** None. **M.D. Rugg:** None.

Poster

156. Episodic and Episodic-Like Memory

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 156.19

Topic: H.07. Long-Term Memory

Title: Pattern integration and separation: dual process model of human episodic memory

Authors: *H. R. EVENSMOEN[1], L. RIMOL[1], H. RISE[2], T. HANSEN[1], H. NILI[3], A. WINKLER[4], A. HÅBERG[1];
[1]NTNU, Trondheim, Norway; [2]UIO, Oslo, Norway; [3]Univ. of Oxford, Oxford, United Kingdom; [4]NIH, Bethesda, MD

Abstract: We propose that episodic memory relies on two fundamentally opposite processes; pattern integration helps consolidate the relationship between the events that make up an episode, and pattern separation keeps different episodes apart. It is currently unclear whether the brain keeps track of the precise timing of the events within an episode, or indeed the precise timing of the episodes themselves. We showed 101 participants 48 unique 'episodes' consisting of five visual events on a computer screen, and tested subsequent recall of the precise timing as well as the order of events and episodes. Precise timing was preserved within episodes, but it was mainly the 'relative timing' (or the 'temporal pattern') of the events that was preserved. The duration of the entire episode tended to be compressed, and compression within episodes was associated with successful recall of the relative timing of the events. Conversely, participants tended to expand the time between neighboring episodes, and such expansion was associated with successful recall of episode order. Functional MRI in a subgroup of participants demonstrated that the activation patterns of individual episodes became more unique with expansion of time to neighboring episodes, and with more accurate recall of time across episodes. In contrast, event-specific activation patterns within episodes became more similar with temporal compression of the episode and with more accurate recall of the relative timing of the events. These findings are consistent with a dual model of episodic memory where pattern integration takes place within episodes to consolidate memories, and where pattern separation takes place between episodes making the episodes more unique.

Disclosures: H.R. Evensmoen: None. **L. Rimol:** None. **H. Rise:** None. **T. Hansen:** None. **H. Nili:** None. **A. Winkler:** None. **A. Håberg:** None.

Poster

156. Episodic and Episodic-Like Memory

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 156.20

Topic: H.07. Long-Term Memory

Support: NIH/NINDS ZIA NS003144

Title: Neural dynamics underlying successful memory formation and retrieval

Authors: *M. BAUMHAUER[1], J. I. CHAPETON[2], W. XIE[2], K. ZAGHLOUL[3];
[1]Natl. Inst. of Neurolog. Disorders and Stroke, North Bethesda, MD; [2]NIH, [3]NIH, Bethesda, MD

Abstract: The neural dynamics underlying memory formation and retrieval are not yet fully understood. Here, using intracranial electrocorticography data collected from 8 subjects during a paired associate verbal memory task, we examined the time-evolution of brain patterns

underlying successful memory formation and retrieval. Based on dimension reduction, we first examined the trajectories of the recorded neural data as participants tried to encode and recall a pair of words. We then examined the shapes of these neural trajectories and quantified their similarity across trials. We found that the shapes of neural trajectories across trials were similar within memory encoding and retrieval regardless of whether participants had successfully remembered the words or not. Yet, the neural trajectories of correct trials have significantly larger contour areas as compared with that of incorrect trials. However, we observed limited evidence when encoding and retrieval neural trajectories were compared at the trial level. These results suggest that successful memory encoding modulates the neural dynamics that scaffold memory formation and retrieval.

Disclosures: **M. Baumhauer:** None. **J.I. Chapeton:** None. **W. Xie:** None. **K. Zaghloul:** None.

Poster

156. Episodic and Episodic-Like Memory

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 156.21

Topic: H.08. Learning and Memory

Support: Cambridge Commonwealth European and International Trust: Vice Chancellors Award

Title: Memory Suppression Relies on Targeted Representational Control of Individual Memories

Authors: *F. BERGMANN[1], N. KRIEGESKORTE[2], M. C. ANDERSON[1];
[1]MRC Cognition and Brain Sci. Unit, Univ. of Cambridge, Cambridge, United Kingdom;
[2]Columbia Univ., New York City, NY

Abstract: Some memories haunt us. However, prior research has shown that the human brain can learn to control intrusive memories even when faced with reminders. By deliberately suppressing their retrieval, we can make memories less frequent, less vivid and may even forget them. This suggests that memory control depends on the targeted weakening of individual representations of unwanted memories. Here we investigated the mnemonic strength of unwanted memories using fMRI. For this, we used the Think/No-Think task in which people are asked to repeatedly suppress the retrieval of a memory, given a reminder to it. On each trial, we also asked participants to report if they recalled a memory, despite attempts to suppress it. We found that stopping retrieval engaged a fronto-parietal set of regions typical for retrieval suppression, and activation in the hippocampus for intrusive memories - albeit reduced compared to voluntary retrieval. To track the gradual decrease in memory strength, we then correlated activation patterns of each suppression trial with those from a separate visual task that belonged to the same item. This allowed us to quantify the degree to which a specific memory was reinstated. We hypothesized that there should be more evidence for memory reinstatement in the hippocampus and parietal areas on trials with memory intrusions, than on trials without memory

intrusions. However, the overall reinstatement of memory-specific activation should decline over repeated suppression attempts. Therefore the reduction in reinstatement on across intrusion trials might also relate to the ability to control the frequency of involuntary recalls. Hence, each time we push an intrusive memory out of awareness, its mnemonic strength might weaken until its memory trace no longer supports effective remembering.

Disclosures: F. Bergmann: None. **N. Kriegeskorte:** None. **M.C. Anderson:** None.

Poster

156. Episodic and Episodic-Like Memory

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 156.22

Topic: H.07. Long-Term Memory

Support: ONR Grant N00014-17-1-2961
ONR Grant N00014-20-1-2578

Title: Recurrent Inhibitory Dynamics in Entorhinal Layer II Enhances Hippocampal Pattern Separation

Authors: *Y. ZHENG[1], J. W. ANTONY[2], C. RANGANATH[1], R. C. O'REILLY[1];
[1]Dept. of Psychology, Univ. of California, Davis, Davis, CA; [2]Dept. of Psychology & Child Develop., California Polytechnic State Univ., San Luis Obispo, CA

Abstract: The hippocampus plays a critical role in episodic memory and spatial navigation. At the entry of the hippocampus stands the superficial entorhinal cortex (EC), which was traditionally assumed to be solely an information relay station in episodic memory models. More recent models have focused on “grid cells” in superficial MEC, which have been proposed to support generalizable knowledge of spatial or task structure. In contrast to these views, recent neuroanatomy and neurophysiology data suggest that EC plays a more significant role in integrated computations within the hippocampal circuit. EC layer II (“EC2”) has specialized cell types, including MEC stellate cells and LEC fan cells that integrate information from multiple cortical areas and are embedded within networks with strong inhibitory connections. Grid cells in MEC layer 2, for instance, are thought to emerge from a continuous attractor network that integrates visual and motor information (e.g., speed, head direction). In contrast, EC layer 3 (“EC3”) pyramidal cells show more spatial tuning properties and a sparser connectivity profile with cortical inputs, preserving information in a more raw form. Critically, EC2 projects directly to the Dentate Gyrus and CA3 subfields, whereas EC3 projects to CA1. These findings suggest the possibility that computations in EC2 and EC3 contribute to learning within the hippocampal circuit. Incorporating known characteristics of EC2 and EC3 in a biologically plausible computational model of the hippocampus (Zheng et al., 2021), we found that the recurrent inhibitory circuit in EC2 dramatically increases the model’s capability to successfully encode large numbers of overlapping events. Preliminary results indicate that these benefits emerge

because the inhibitory EC2 network adds another layer of binding and pattern separation prior to information encoding in the trisynaptic pathway. Our modeling suggests that, rather than playing a unitary role in generalization of task or spatial structure, EC2 and EC3 play complementary, integrated roles in learning within the hippocampal circuit, enabling the disambiguation of similar events.

Disclosures: **Y. Zheng:** None. **J.W. Antony:** None. **C. Ranganath:** None. **R.C. O'Reilly:** A. Employment/Salary (full or part-time):; Obelisk Lab in the Astera Institute, eCortex.

Poster

156. Episodic and Episodic-Like Memory

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 156.23

Topic: H.07. Long-Term Memory

Support: ONR N00014-17-1-2961
NSERC Postdoctoral Fellowship

Title: Dynamic hippocampal-cortical interactions during event boundaries support retention of complex narrative events

Authors: *A. J. BARNETT[1], M. NGUYEN[2], J. SPARGO[2], R. YADAV[2], B. I. COHN-SHEEHY[2], C. RANGANATH[2];
[1]Psychology, Univ. of Toronto, Toronto, ON, Canada; [2]UC Davis, Davis, CA

Abstract: According to most memory theories, memory encoding involves continuous communication between the hippocampus and neocortex. These theories, and most studies investigating these interactions in humans, have overlooked the temporal dynamics of hippocampal-neocortical interactions. Recent work has shown that we perceive complex events in our lives as dynamic, with relatively distinct starting and stopping points known as event boundaries. Event boundaries may be important for memory, as they are associated with increased activity in the hippocampus, and functionally connected cortical regions (the posterior cingulate cortex, lateral parietal cortex, and parahippocampal cortex) that carry event-specific multivariate patterns. Our objective was to determine how functional connectivity between the hippocampus and neocortical regions during the encoding of naturalistic events (movies) related to subsequent retrieval and retention of those events. Participants encoded two 15-minute cartoon movies during fMRI scanning. After encoding, participants freely recalled one of the movies immediately, and the other after a 2-day delay. We quantified hippocampal-neocortical functional connectivity at time windows around each event onset, middle, and offset, and compared these measures with subsequent recall. These analyses revealed that higher functional connectivity between the hippocampus and posterior medial network (PMN) regions at an event's offset predicted whether that event was subsequently recalled. This finding was limited to event offset; in contrast, mid-event connectivity between the hippocampus and PMN was

marginally associated with poorer memory. Furthermore, hippocampal-PMN connectivity predicted not only whether events were retained in memory, but also the degree to which these events could be recalled in detail after a 2-day delay. These data demonstrate that the relationship between memory encoding and hippocampal-neocortical interaction is more dynamic than suggested by most memory theories, and they converge with recent modeling work suggesting that the event offset is an optimal time for memory encoding.

Disclosures: **A.J. Barnett:** None. **M. Nguyen:** None. **J. Spargo:** None. **R. Yadav:** None. **B.I. Cohn-Sheehy:** None. **C. Ranganath:** None.

Poster

156. Episodic and Episodic-Like Memory

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 156.24

Topic: H.07. Long-Term Memory

Support: ONR Grant N00014-20-1-2758
ONR Grant N00014-17-1-2961
NIH Grant 1R36MH130100-01

Title: Modeling Pattern Completion and Pattern Separation Using Hippocampal-Prefrontal Connections

Authors: *A. B. WILLIAMS, C. RANGANATH, R. O'REILLY;
UC Davis, Davis, CA

Abstract: The hippocampus has been associated with diverse functions, such as mnemonic discrimination (“pattern separation”), recollection-based recognition, and memory integration. Each of these functions has been simulated with computational models of the hippocampus, but all of these actions cannot be accomplished within the same model using the same inputs. Drawing on computational models of the prefrontal cortex (PFC), we investigated the possibility that prefrontal modulation enables the hippocampus to flexibly accomplish these otherwise incompatible goals. We developed a biologically-based model of prefrontal-hippocampal interactions, based on anatomical findings showing that prefrontal inputs target interneurons in entorhinal cortex. First, the model was trained to learn a set of visually- and semantically-similar items. Next, we simulated a retrieval practice phase, requiring fine-grained mnemonic discriminations between similar items. Prefrontal input was used to inhibit representations of overlapping features between items, mimicking the kind of memory monitoring processes proposed to focus processing of the distinctive stimulus features. Prefrontal inhibition during retrieval practice effectively updated hippocampal representations via error-driven learning, reducing the influence of overlapping features, and reducing representational similarity between highly similar items. Effects of prefrontal modulation varied according to the degree of modulatory input and also by subfield. The simulations align with lesion data implicating the

PFC in goal-directed memory retrieval, and they show how top-down modulation can be used to bias hippocampal pattern separation and completion and update episodic memory representations.

Disclosures: A.B. Williams: None. **C. Ranganath:** None. **R. O'Reilly:** A. Employment/Salary (full or part-time):; Obelisk Lab in Astera Institute, eCortex.

Poster

156. Episodic and Episodic-Like Memory

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 156.25

Topic: H.07. Long-Term Memory

Support: NSF GRFP

Title: Multiple approaches towards the modulation of emotional memory in depression

Authors: *M. CASTRO[1], B. HAYES[1], T. PHILLIPS[1], R. VAS[1], A. HARIKUMAR[2], L. FERGUSON[1], S. L. LEAL[1];
[1]Psychological Sci., Rice Univ., Houston, TX; [2]Clin. Psychology, Georgia State Univ., Atlanta, GA

Abstract: The ability to modulate memory is important to either enhance or impair memory for certain types of experiences. The medial temporal lobe (MTL), which includes the hippocampus and surrounding cortical regions, is involved in episodic memory, or memory for events. The MTL is under heavy modulation from neurotransmitters, such as serotonin and norepinephrine. Furthermore, the amygdala is involved in the emotional modulation of memory via its connectivity with the hippocampus. The hippocampus can perform two key computations in support of episodic memory: pattern separation, or the ability to discriminate between representations with similar features, and pattern completion, or the ability to generalize across representations with similar features. We have developed an emotional mnemonic discrimination task that taxes the emotional modulation of hippocampal pattern separation. Our prior work has shown that individuals with depression show a negativity bias, where negative mnemonic discrimination is enhanced while neutral mnemonic discrimination is impaired. We examined performance on the emotional mnemonic discrimination task in individuals with depression under two different modulatory conditions: 1) emotion regulation (psychological distancing) during encoding and 2) antidepressant use. Both of these modulatory influences have shown to impact MTL function. We examined the impact of antidepressant responsiveness and emotion regulation strategy during encoding on the emotional mnemonic discrimination task in two separate studies. We found similar results under both modulatory approaches, where depressed individuals who responded to antidepressants or who applied emotion regulation strategies during encoding showed a reduction in negativity bias as well as enhanced neutral mnemonic discrimination. For those taking antidepressants, we found differential effects in those taking

selective-serotonin reuptake inhibitors (SSRIs) versus other types of antidepressants, where SSRIs selectively reduced the negativity bias while other types of antidepressants selectively enhanced neutral mnemonic discrimination. These results suggest that two very different approaches toward modulating memory in depression can similarly impact cognition. However, the neural mechanisms underlying these effects may be unique and will be important to explore in the future.

Disclosures: **M. Castro:** None. **B. Hayes:** None. **T. Phillips:** None. **R. Vas:** None. **A. Harikumar:** None. **L. Ferguson:** None. **S.L. Leal:** None.

Poster

156. Episodic and Episodic-Like Memory

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 156.26

Topic: H.07. Long-Term Memory

Support: NIH Grant R21 AG061597

Title: Unpacking reappraisal: A systematic review of fMRI studies of psychological distancing and reinterpretation

Authors: *E. E. DICKER[1], B. T. DENNY[1], M. L. JUNGLES[1], P. GOODSON[1], J. CHAVEZ[1], J. S. JONES[1], R. B. LOPEZ[2];
[1]Rice Univ., Houston, TX; [2]Psychological & Cognitive Sci., Worcester Polytechnic Inst., Worcester, MA

Abstract: A substantial and growing volume of work has examined the neural mechanisms of cognitive reappraisal, an emotion regulation strategy that involves changing the way one thinks about a stimulus in order to change its affective impact. Moreover, while reappraisal as a strategy can represent a broad class of cognitive change tactics that may be implemented alone or in tandem, an increasing number of studies have further operationalized reappraisal and have examined the psychological and neural mechanisms of separable reappraisal tactics. Two such tactics of particular interest when using reappraisal to down-regulate negative emotion are psychological distancing and reinterpretation. Psychological distancing may be operationalized as appraising an emotional stimulus as an objective, impartial observer, whereas reinterpretation is frequently operationalized as imagining a better outcome for a situation than what initially seemed apparent. Theoretical frameworks and prior behavioral evidence have suggested that the specific reappraisal tactic one employs may have important differential consequences on behavior. In the current study, we assessed the degree of overlap and differentiation of the neural correlates underlying distancing and reinterpretation by performing a meta-analysis of 32 published functional magnetic resonance imaging (fMRI) studies of distancing (16 total contrasts) and reinterpretation (17 total contrasts) using multilevel kernel density analysis (MKDA). Results showed that distancing and reinterpretation each recruited regions reported by

previous neuroimaging meta-analyses of reappraisal overall, including common engagement of posterior dorsomedial prefrontal cortex, left lateral temporal cortex, and left posterior parietal cortex. However, distancing relative to reinterpretation implementation was uniquely associated with recruitment of right dorsolateral prefrontal cortex and a dorsal region of left posterior parietal cortex, each of which has been associated in prior work with mentalizing and perspective taking as well as selective attention and working memory. Reinterpretation relative to distancing implementation, by contrast, was uniquely associated with recruitment of left ventrolateral prefrontal cortex, associated in prior work with response selection and inhibition. These results are consistent with prior theoretical models for the functional neural architecture of reappraisal via distancing and reinterpretation and suggest potential future applications in region-of-interest specification and neural network analysis in studies focusing on specific reappraisal tactics.

Disclosures: **E.E. Dicker:** None. **B.T. Denny:** None. **M.L. Jungles:** None. **P. Goodson:** None. **J. Chavez:** None. **J.S. Jones:** None. **R.B. Lopez:** None.

Poster

156. Episodic and Episodic-Like Memory

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 156.27

Topic: H.07. Long-Term Memory

Support: NSF Grant SMA-1853936
NSF Grant SMA-1559393

Title: Development of a novel and naturalistic face-name mnemonic discrimination task

Authors: *R. MANNION, A. HARIKUMAR, S. LEAL;
Psychological Sci., Rice Univ., Houston, TX

Abstract: Difficulty remembering faces and the association between faces and names is a common struggle for many people, especially as we age. Subtle changes in appearance, common facial characteristics across individuals, and the overlap of names across individuals contribute to the struggle of remembering face-name associations. Thus, there is great interference across our memories for faces and names. The hippocampus, a region important for memory processing, can perform two key computations to support episodic memory: pattern separation and pattern completion. Pattern separation reduces interference across experiences with overlapping information, whereas pattern completion fills-in incomplete information based on previous experiences. Older adults often show deficits in hippocampal pattern separation, thus tasks that tax this computation may provide more sensitive memory measures of age-related cognitive decline. In the current study, we have developed a novel face-name mnemonic discrimination task that taxes hippocampal pattern separation, where the emotional expression (e.g., positive, negative, and neutral) and similarity (e.g., high and low) of face-name stimuli were varied to examine the effects of emotion and similarity on face-name associative memory across the

lifespan. Twenty-five young adults (all mean age ± *SD*, 23 ± 4; 17 female) and twenty-one older adults (72 ± 7; 17 female) were shown a series of face-name pairs during encoding and were later tested on their memory of the faces and face-name pairs in two separate retrieval tasks. During the retrieval tasks, participants were shown repeated faces/names (targets), new faces/names (foils), or similar but not identical faces/names (lures). Task performance was measured using target recognition (d′), a general memory measure, and lure discrimination (LD), a measure that relies on hippocampal pattern separation, and analyzed using repeated-measures ANOVA. We found that older adults struggled to remember faces and face-name pairs more than young adults across all measures. However, while young adults remembered emotional faces better than neutral faces, older adults selectively remembered positive faces, consistent with the positivity effect in aging. These results suggest that the inclusion of highly interfering stimuli in associative memory tasks may provide a more sensitive measure of age-related changes in memory.

Disclosures: R. Mannion: None. **A. Harikumar:** None. **S. Leal:** None.

Poster

156. Episodic and Episodic-Like Memory

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 156.28

Topic: H.07. Long-Term Memory

Title: Post-encoding music effects on mnemonic discrimination

Authors: *K. R. CLARK, G. C. BOLANOS, S. L. LEAL;
Rice Univ., Rice Univ., Houston, TX

Abstract: Music holds a special place within the realm of memory. Music can act as a cue for memory recall, may provide enriched contexts for memory encoding, and can modulate memory formation. While we are often able to recall music and memories associated with music well into old age, many of our memories are subject to forgetting. Episodic memory (i.e., memory for events) is susceptible to decline in aging populations. As such, music's ability to induce emotional arousal can potentially impact memory processes. The emotional-arousal hypothesis suggests that emotional arousal leads to the release of norepinephrine and cortisol which can then exert their effects on the amygdala, which is involved in the emotional modulation of memory processing in the hippocampus. Episodic memory is supported by hippocampal pattern separation, a neural computation responsible for reducing interference across memories with overlapping content, allowing for the storage of unique events. Mnemonic discrimination is a behavioral correlate of pattern separation requiring participants to differentiate between two similar experiences and is more sensitive to age-related decline compared to standard memory tasks. However, we do not know whether music (via emotional arousal) can modulate mnemonic discrimination. The current study investigates the effect of music-induced emotional arousal during consolidation on mnemonic discrimination by first dividing participants into four

listening groups with two music conditions and two control conditions: 1) high-arousal positively-valenced music, 2) high-arousal negatively-valenced music, 3) low-arousal neutrally-valenced audio, and 4) silence. During encoding, participants view a series of everyday household objects. After a short break, participants either listen to music, audio clips, or silence while completing a menial task (questionnaires). Participants are then tested on their memory for the objects they viewed earlier. Participants view a mix of images that are exact repeats of previous images (targets), completely new images (foils), or are similar to previous images (lures), in which lure items are critical for taxing hippocampal pattern separation. To quantify the effect of music on consolidation, we examined both target recognition (memory for repeated objects) and lure discrimination (correct rejection of lure objects) across the four groups. Our findings serve to inform the understanding of how music could be used as a tool for modulating memory, potentially for music-oriented memory interventions.

Disclosures: K.R. Clark: None. **G.C. Bolanos:** None. **S.L. Leal:** None.

Poster

156. Episodic and Episodic-Like Memory

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 156.29

Topic: H.07. Long-Term Memory

Support: Fulbright

Title: Effects of image memorability on episodic mnemonic discrimination

Authors: *F. MORALES-CALVA, M. SEKILI, A. VELGEKAR, S. L. LEAL;
Psychological Sci., Rice Univ., Houston, TX

Abstract: Although elements like the emotional valence of an experience can help an item be better remembered, some items are consistently better remembered or forgotten by most people. This intrinsic ability of certain elements is known as memorability. Memorability is said to be able to explain up to 70% of the variability in memory performance and appears to be an inherent feature of episodic memory. Computational models suggest that the hippocampus can perform two key computations in support of episodic memory. Pattern separation is the ability to discriminate among similar experiences and allows them to be stored as non-overlapping representations while pattern completion is the ability to accurately generalize when given partial cues. While these computations have been hypothesized to help explain memorability, no study to our knowledge has investigated the interaction between mnemonic discrimination, the behavioral correlate of pattern separation, and memorability. To explore this gap, we set out to examine the impact of image memorability on hippocampal pattern separation. Stimuli were categorized based on memorability and similarity of lure images and were used to develop a memorability-based mnemonic discrimination task that taxes hippocampal pattern separation. Additionally, we ran a memorability-based post-hoc analysis on an emotional mnemonic

discrimination task to account for effects of emotion and memorability on memory performance. We found that high image memorability was an established differentiating factor for immediate target recognition, however, these effects of memorability were not present after a 24-hour delay. When examining lure discrimination measures, which have not yet been examined within a memorability framework, we did not see effects of memorability on lure discrimination either immediately or 24 hours later. However, we observed that memorability interacted with emotion, but only for lure discrimination measures. These results have important implications for how we understand memorability and provide a better understanding of the effects that memorability and emotional content may have on episodic memory.

Disclosures: F. Morales-Calva: None. **M. Sekili:** None. **A. Velgekar:** None. **S.L. Leal:** None.

Poster

156. Episodic and Episodic-Like Memory

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 156.30

Topic: H.07. Long-Term Memory

Support: EU-M-GATE 765549
Foundation Adelis

Title: On the statistics of free memory recall

Authors: *M. TSODYKS[1,2], M. KATKOV[1,2];
[1]Weizmann Inst. of Sci., Rehovot, Israel; [2]Inst. for Advanced Study, Princeton, NJ

Abstract: Free recall of randomly assembled lists of words is widely used to study human memory in laboratory settings. We recently introduced a mathematical model of free recall that reproduced well the average performance of human participants in experiments with randomly assembled lists of words or short sentences for a wide range of list lengths and two presentation speeds. While it is well known that memory recall is highly variable, experiments are usually analyzed in terms of average performance and the distribution of performance around the mean was never systematically studied. Here we propose that calculating the variance of recall performance provides interesting tests for models. To this end, we used our model to predict the statistics of memory recall. When applying our model to experimental data, a crucial assumption was made that upon presentation, a certain fraction of presented items that remain in memory are candidates for recall, and that the number of such items (M) can be estimated with recognition experiments performed by the same group of participants under identical conditions of item presentation as in the recall experiments. It is not clear whether this assumption is valid under different experimental paradigms and with different groups of participants. For example, assuming that M is distributed across participants as a truncated Gaussian, we fitted parameters of this distribution and compared the average M across participants measured in recognition experiments and the one calculated from estimated distribution. We obtained a good match

between two measures, providing an additional support for our crucial assumption. Moreover, the distribution of recall among participants predicted by the model was statistically indistinguishable from the experimentally obtained one. Comparison of model predictions with experimental data on young and old participants indicates that the same recall algorithm is involved in both groups, even though old participants may have fewer candidate memory items for recall after presentation. Overall, using the distribution of recall performance provides stricter tests on the models of free recall. Good match between experimental and theoretical distributions provides an additional support for our model.

Disclosures: **M. Tsodyks:** None. **M. Katkov:** None.

Poster

157. Molecular Mechanisms of Memory

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 157.01

Topic: H.08. Learning and Memory

Support: NIH Grant AG067781
NIH Grant AG045571
NIH Grant AG073153
NIH NIA AG072977

Title: Genome-wide DNA methylation analysis suggests lower CD8+ T cell proportions in SuperAgers

Authors: *I. S. PIRAS[1], M. J. HUENTELMAN[1], A. BONFITTO[1], B. STARK[1], I. A. AYALA[2], S. GUTIERREZ[2], M. M. MESULAM[2], C. GEULA[2], E. J. ROGALSKI[2];
[1]Neurogenomics Division, Translational Genomics Res. Inst., Phoenix, AZ; [2]Mesulam Ctr. for Cognitive Neurol. & Alzheimer's Disease, Northwestern Univ., Chicago, IL

Abstract: SuperAgers (SA) are adults aged 80+ with episodic memory performance that is at least as good as that of average 50-65-year-olds. Understanding the biological determinants of SuperAging may have relevance to preventing age-related cognitive decline and dementia. Here, we conducted a genome-wide DNA methylation (DNAm) analysis of peripheral blood from a cohort of SA and cognitively normal controls (CTL).DNA samples were characterized using the Illumina *MethylationEPIC* array. Preprocessing was conducted using *R-minfi,* and after quality control, we obtained a dataset including 25 SA and 25 CTL for 764,643 CpG sites. Data were quantile normalized and blood cell proportions between SA and CTL were estimated using a published deconvolution method based on a flow-sorted dataset from whole blood (R-*FlowSorted.Blood.EPIC*). Correlation with the top two principal components (PC) was assessed using Pearson's *r*, and the cell proportion comparisons between SA and CTL were conducted using a linear regression model adjusting for age and sex. We detected a significant correlation between cell proportions and DNAm. All blood cell types, with the exception of monocytes,

significantly correlated with at least one of the top two PCs. CD8+ T cells showed a significantly lower proportion in SAs after adjusting for age and sex ($p = 0.017$). CD8+ T cell counts in blood and CSF have been negatively correlated with cognition in Alzheimer's Disease (AD). Functional studies in mice following TBI, reported a positive correlation of CD8+ T cell counts in the injured brain and neurological impairment. Finally, other studies have pointed out the role of CD8+ T cell-mediated mechanisms in the contribution to the neurocognitive impairments in both multiple sclerosis and AD. Lastly, one study has noted opposite results, with better cognitive performance associated with higher numbers of CD8+ T cells in healthy older adults.Our results support the association of lower CD8+ T cells in the SA phenotype. This finding is largely concordant with other independent studies examining CD8+ T cell levels and normative and disease-related cognitive phenotypes. Our results may be explained by the function of CD8+ T cells and their capacity to secrete cytotoxic molecules and proinflammatory cytokines thereby increasing the inflammatory state and consequently negatively affecting cognition. In SAs, the lower proportion of CD8+ T cells might functionally reduce the systemic inflammatory state in those individuals and this could, in turn, be associated with the improved episodic memory that is characteristic of the SA phenotype.

Disclosures: I.S. Piras: None. **M.J. Huentelman:** None. **A. Bonfitto:** None. **B. Stark:** None. **I.A. Ayala:** None. **S. Gutierrez:** None. **M.M. Mesulam:** None. **C. Geula:** None. **E.J. Rogalski:** None.

Poster

157. Molecular Mechanisms of Memory

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 157.02

Topic: C.01. Brain Wellness and Aging

Title: Age-related changes in energy metabolism in peripheral mononuclear blood cells (PBMCs) and the brains of cognitively healthy seniors

Authors: *G. P. ECKERT[1], C. SILAIDOS[1], M. REUTZEL[1], N. LUDIN[2], S. MATURA[3], U. PILATUS[4], E. HATTINGEN[2], J. PANTEL[5];
[1]Inst. of Nutritional Sci., Justus-Liebig-University, Giessen, Germany; [2]Inst. for Neuroradiology, [3]Dept. of Psychiatry, [4]Brain Imaging Ctr., [5]Inst. of Gen. Practice, Goethe-University, Frankfurt, Germany

Abstract: Background: Mitochondrial dysfunction is a hallmark of brain aging and neurodegenerative diseases. For the study of brain aging processes and their possible transition to pathological states, it is of great interest whether mitochondrial function in peripheral cells reflects overall conditions in the brain. In our study we investigated the relationship between mitochondrial function in peripheral blood cells and cerebral energy metabolites in young and older sex-matched, physically and mentally healthy volunteers. **Methods**: Cross-sectional observational study involving 65 young (26.0±0.49 yr.) and 65 older (71.7±0.71 yr.) women and

men. Cognitive health was evaluated using established psychometric methods (MMSE, CERAD, DSM 5 criteria). Blood samples were collected, analyzed, and fresh peripheral blood mononuclear cells (PBMCs) were isolated. Mitochondrial respiratory complex activity, adenosine triphosphate (ATP) levels, and citrate synthase activity (CS) were determined in PBMCs. N-aspartyl-aspartate (tNAA), ATP, creatine (Cr) and phosphocreatine (PCr) were quantified in brains using ^{1}H - and ^{31}P -magnetic resonance spectroscopic imaging (MRSI). Gene expression was quantified using qRT-PCR. **Results**: Activity of mitochondrial respiratory chain complex IV (CIV) and ATP levels were significantly reduced in PBMCs isolated from older participants. Respiratory control ratio and CS activity were unchanged. Expression of genes involved in mitochondrial activity, antioxidant mechanisms, and autophagy were unaffected by age. tNAA levels were reduced, Cr and PCr levels increased, and ATP levels unchanged in the brains of older participants. Markers of energy metabolism in blood cells did not correlate with energy metabolites in the brain. Compared to males, PBMCs isolated from young and older females showed higher CIV activity. tNAA and CR levels were lower in brains of young females compared to young males. **Conclusion:** Age- and sex-related bioenergetic changes were detected in peripheral blood cells and the brains of healthy older people. However, mitochondrial functions in peripheral blood cells do not directly reflect energy related metabolites in the brain. While ATP levels in PBMCs appear to be a valid marker for age-related mitochondrial dysfunction in humans, cerebral ATP in our study remained constant. An anticipated decline in cerebral ATP may be compensated for by hydrolysis of the energy buffer PCr. Our data may also provides important basic data for the early diagnosis of neurodegenerative diseases.

Disclosures: G.P. Eckert: None. **C. Silaidos:** None. **M. Reutzel:** None. **N. Ludin:** None. **S. Matura:** None. **U. Pilatus:** None. **E. Hattingen:** None. **J. Pantel:** None.

Poster

157. Molecular Mechanisms of Memory

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 157.03

Topic: H.08. Learning and Memory

Support: NIA R00AG056596
NIA R21AG068444
Whitehall #2020-05-06
AFAR #A21105

Title: Hippocampal Per1 may contribute to time-of-day effects on memory consolidation

Authors: *L. BELLFY[1], C. W. SMIES[1], K. K. BODINAYAKE[2], A. R. BERNHARDT[1], E. M. STUART[1], D. S. WRIGHT[1], C.-Y. LO[1], H. M. BOYD[1], J. L. KWAPIS[1];
[1]Pennsylvania State Univ., University Park, PA; [2]Univ. of California, Irvine, Irvine, CA

Abstract: Many biological processes are influenced by the circadian system, including memory performance. Behavioral paradigms, such as the dorsal hippocampus (DH)-dependent paradigm Object Location Memory (OLM), typically show that memory is better during the day compared to the night. In this paradigm, mice learn the location of two identical objects during a training session. During the test session 24 hours later, one of the objects is moved to a novel location. Memory is measured as the time the mouse spends investigating the object in the novel location compared to that in the familiar location. We used OLM to answer the outstanding question of what is driving this time-of-day effect on memory performance. We hypothesized that circadian rhythm genes may regulate the consolidation process across the day/night cycle contributing to the time-of-day effect. To test our hypothesis, we first tested long-term memory performance across the day/night cycle and found better memory performance during the day than the night. Next, we tested short-term memory and found that mice were able to acquire the memory at similar levels during the day and the night, suggesting that nighttime acquisition is intact despite the reduced long-term memory. We then assessed memory retrieval across the day/night cycle. Specifically, we trained mice at the peak and trough of memory, ZT5 and ZT17 respectively, but tested them 36 hours later, so mice that were trained during the day were tested at night and vice versa. We found that the time of memory acquisition, rather than the time of retrieval, was the driving factor determining whether memory was intact; mice that were trained during the day were able to retrieve the memory at night whereas the night-trained mice showed poor memory retrieval when tested during either the day or nighttime. Together, these results demonstrate that nighttime memory deficits are likely due to impaired consolidation. As consolidation is known to be transcription-dependent, we performed RNA-sequencing to identify learning-induced gene changes over the day/night cycle. Notably, circadian rhythm genes were commonly upregulated in response to learning during the day but not the night, including the circadian gene, *Period1* (*Per1*). When hippocampal *Per1* expression was assessed, we found that it oscillated in tandem with memory performance, consistent with a potential role in regulating memory across the day/night cycle. In conclusion, memory consolidation oscillates across the 24h day and may be regulated in part by hippocampal *Per1* expression.

Disclosures: L. Bellfy: None. **C.W. Smies:** None. **K.K. Bodinayake:** None. **A.R. Bernhardt:** None. **E.M. Stuart:** None. **D.S. Wright:** None. **C. Lo:** None. **H.M. Boyd:** None. **J.L. Kwapis:** None.

Poster

157. Molecular Mechanisms of Memory

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 157.04

Topic: H.08. Learning and Memory

Support: NIH Grant R00AG056595
NIH Grant R21AG068444
Whitehall Grant 2020-05-06
AFAR Grant A21105

Title: Epigenetic dysregulation of Per1 within the retrosplenial cortex contributes to age-related deficits in spatial memory

Authors: *C. A. BRUNSWICK[1], D. J. BALDWIN[1], K. K. BODINAYAKE[2], L. BELLFY[1], A. R. MCKENNA[1], E. STUART[1], S. MURAKAMI[1], J. L. KWAPIS[1];
[1]Penn State Univ., University Park, PA; [2]Univ. of California, Irvine, Irvine, CA

Abstract: Aging is marked by impairments in memory and disruptions in circadian rhythm. Growing evidence suggests that these changes might both be due to epigenetic dysregulation of clock genes. Although clock genes are best known for their roles in maintaining circadian rhythms in the suprachiasmatic nucleus (SCN), they are also expressed ubiquitously. Prior work from our group suggests that the activity of clock gene *Period1* (*Per1*) within the retrosplenial cortex (RSC) might gate the formation of spatial memory. Here, we investigate the relationship between age, RSC/SCN *Per1* expression, time-of-day, and memory. We trained two cohorts of young (7-weeks) and aging (18-months) C57BL/6J mice in a spatial learning task at six different timepoints (Zeitgeber Times: ZT1, ZT5, ZT9, ZT13, ZT17, ZT21). One cohort was sacrificed 1 hour later to investigate learning-induced *Per1* expression via qPCR while the other was tested 24 hours later to examine memory performance. We found that relative increases in *Per1* expression are induced by learning in both the RSC and the SCN (regardless of animal age), although absolute levels of *Per1* are lower in aging animals. In the RSC, this *Per1* induction fluctuated with time-of-day and was greatest during the day (lights on), which was also when memory performance peaked in young animals, suggesting a link between *Per1* expression and the formation of spatial memory. There was no effect of time-of-day on learning-induced *Per1* expression in the SCN. To investigate a causative role of *Per1* in memory performance, we locally downregulated *Per1* expression in the RSC of young mice and found this impaired memory performance. Likewise, local upregulation of *Per1* in the RSC of aging mice is sufficient to rescue memory formation. Notably, manipulating *Per1* expression in the SCN of young mice does not affect memory performance. In sum, these results suggest that *Per1* expression within the RSC is responsible for linking memory performance to time-of-day. We suggest that brain-wide epigenetic dysregulation of *Per1* associated with aging contributes to both age-related memory deficits and disruptions in circadian rhythm. Local dysregulation of *Per1* within the RSC (and other memory structures, like the dorsal hippocampus) contributes to memory impairments, while dysregulation within the SCN causes circadian disruptions.

Disclosures: C.A. Brunswick: None. **D.J. Baldwin:** None. **K.K. Bodinayake:** None. **L. Bellfy:** None. **A.R. McKenna:** None. **E. Stuart:** None. **S. Murakami:** None. **J.L. Kwapis:** None.

Poster

157. Molecular Mechanisms of Memory

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 157.05

Topic: H.08. Learning and Memory

Support: Swedish Research Council 2018–00660

Title: Hippocampal interleukin-6 affects mnemonic functions and emotionality in a sex-dependent manner

Authors: *F. LONGO[1,2], M. ASKER[1,2], O. A. E. ABUAMRA[1], M. SVENSSON[1], J. RICHARD[1], S. BÖRCHERS[1,2], J.-P. KRIEGER[1], K. P. SKIBICKA[1,2,3];
[1]Univ. of Gothenburg, Gothenburg, Sweden; [2]Wallenberg Ctr. for Mol. and Translational Med., Gothenburg, Sweden; [3]Nutritional Sci., Pennsylvania State Univ., University Park, PA

Abstract: Interleukin (IL)-6, a cytokine, plays a central role in the pathogenesis of inflammatory conditions and has been increasingly recognized as a key contributor to central nervous system (CNS) pathophysiology. IL-6 dysregulation contributes to the pathogenesis of a wide range of neuropsychopathologies including depression, schizophrenia, and cognitive decline. Recently, increased CNS IL-6 levels were linked to the long-term effects of COVID-19 infection including sleeping difficulties, memory performance, depression, and anxiety. To date, the specific brain regions and downstream molecular mechanisms through which central IL-6 modulates emotional and cognitive function remain poorly understood. The ventral hippocampus (vHPC) represents a critical brain region for the control of memory processes and regulation of emotional/affective behaviors. We found that IL-6 is expressed in the vHPC and, surprisingly neurons represent the major IL-6 source cell in the VHPC. Also, IL-6 receptors are expressed in the hippocampus, potentially indicating that locally-produced hippocampal IL-6 can affect hippocampal function. To test whether hippocampal IL-6 contributes to emotional and cognitive behavior control through its action within the vHPC we used both neuropharmacological and virogenetic manipulations to alter IL-6 levels in the vHPC of male and female rats. Microinjections of IL-6 into the vHPC impaired memory acquisition and memory retrieval in female but not male rats, as indicated by reduced novel object exploration in the novel object recognition (NOR) test and reduced ability to locate the platform in Morris water maze (MWM) test. Conversely, viral knockdown of the hippocampal IL-6 by infusion of the adeno-associated virus (AAV)-siRNA-IL-6 into the vHPC resulted in facilitation of learning and memory process in the NOR and MWM test in female rats. In male rats, however, reduced vHPC IL-6 expression improved anxiety-like and depression-like behaviors. Taken together, these results indicate that vHPC IL-6 modulates hippocampus-dependent mnemonic process and affective behaviors, and does so in a sex divergent manner.

Disclosures: F. Longo: None. **M. Asker:** None. **O.A.E. Abuamra:** None. **M. Svensson:** None. **J. Richard:** None. **S. Börchers:** None. **J. Krieger:** None. **K.P. Skibicka:** None.

Poster

157. Molecular Mechanisms of Memory

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 157.06

Topic: H.08. Learning and Memory

Support: NIA R00AG056596
NIA R21AG068444
Whitehall #2020-05-06
AFAR #A21105

Title: Epigenetic mechanisms underlying competition in reconsolidation-based memory updating

Authors: *C. W. SMIES, L. BELLFY, D. S. WRIGHT, M. W. URBAN, C. A. BRUNSWICK, J. L. KWAPIS;
Penn State, Pennsylvania State Univ. - Univ. Park, State College, PA

Abstract: Memories are plastic to allow for modification of recorded experiences. Memories are labile during consolidation and again following retrieval, particularly when new information is presented that needs to be incorporated into existing memory. Although the mechanisms underlying memory consolidation have been heavily explored, the unique mechanisms supporting reconsolidation-dependent memory updating are not as well understood. One potential mechanism that may be important for both consolidation and updating is epigenetic modifications, which change gene expression by modulating chromatin structure. Histone acetylation, a major epigenetic modifier that helps establish a permissive chromatin structure, is modified via the competing actions of histone acetyltransferases (HATs) and histone deacetylases (HDACs). HDAC3, an enzyme that blocks acetylation, functions as a molecular brake pad during memory formation (McQuown et al., 2012); HDAC3 inhibition during memory formation can transform a subthreshold learning event into one that produces robust and persistent long-term memory (McQuown et al., 2012 & Kwapis et al., 2018). However, the role of HDAC3 in reconsolidation-dependent memory updating is unknown. Here we show that systemic administration of the HDAC3 inhibitor RGFP966 improves aging-induced impairments in spatial memory updating in the Objects in Updated Locations paradigm (OUL; reviewed in Wright et al., 2020). Surprisingly, we found that when young animals are systemically administered RGFP966 following an update session, an impairment for the original memory emerges, suggesting that the original and updated information compete for behavioral expression and strengthening the updated memory occurred at the expense of the original information. Next, we used RGFP966 to systemically inhibit HDAC3 immediately after different phases of OUL to test whether strengthening or weakening of the original or updated memory can affect this competition process. Together, the current studies demonstrate that HDAC3 plays a key role in both memory formation and reconsolidation-memory updating and suggest that the original and updated information compete for behavioral expression.

Disclosures: C.W. Smies: None. **L. Bellfy:** None. **D.S. Wright:** None. **M.W. Urban:** None. **C.A. Brunswick:** None. **J.L. Kwapis:** None.

Poster

157. Molecular Mechanisms of Memory

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 157.07

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

Support: Supported by Project "PI20/00153", funded by Instituto de Salud Carlos III and co-funded by the European Union (ERDF "A way to make Europe").
Technical and human support was provided by the General Research Services SGIker [University of the Basque Country (UPV/EHU)].
J.M.-G. is the recipient of Margarita Salas fellowship funded by the European Union-Next Generation EU.

Title: Improvement of recognition memory by CB_1 receptor agonist WIN 55,212-2 in a rat lesion model of cholinergic impairment

Authors: *I. BENGOETXEA DE TENA[1], M. MORENO-RODRÍGUEZ[1], G. PEREIRA-CASTELO[1], J. MARTINEZ-GARDEAZABAL[1,2], I. MANUEL[1,2], L. GIMÉNEZ-LLORT[3], R. RODRÍGUEZ-PUERTAS[1,2];
[1]Pharmacol., Univ. of the Basque Country (UPV-EHU), Leioa, Spain; [2]Neurodegenerative Diseases, BioCruces Bizkaia Hlth. Res. Inst., Barakaldo, Spain; [3]Dept. Psychiatry and Forensic Medicine, Sch. of Med. & Inst. of Neuroscience, Autonomous Univ. of Barcelona (UAB), Barcelona, Spain

Abstract: The impairment of basal forebrain cholinergic neurons (BFCN) is key to developing Alzheimer's disease (AD). The endocannabinoid (eCB) system modulates these pathways, but the overall effect of cannabinoid compounds on memory remains unclear, since their dual neuroprotective-neurotoxic profile depends on factors such as dose and age of the subjects. In this study, we first evaluated the reaction of naïve Sprague-Dawley male rats to a learning and memory task under fear conditions following different behavioral paradigms, studying fear response and its extinction, as well as the correlates between behavior and the activity of cholinergic and cannabinoid receptors. Then, learning and memory were evaluated by novel object recognition task (NORT) using a cholinergic lesion model of dementia specifically targeting BFCN, treated with either 0.05 mg/kg or 0.5 mg/kg of cannabinoid agonist WIN 55,212-2 for 5 days. The same treatment was used to assess cognitive function with an additional animal model of dementia, 3xTg-AD mice, in this case using Barnes maze (BM). Finally, CB_1 receptor activity following the treatment was analyzed by functional [^{35}S]GTPγS autoradiography in both models. Results show a modulation of the cholinergic and cannabinoid receptors activity in untreated naïve Sprague-Dawley male rats following behavioral paradigms including both novelty-seeking and recognition memory (NORT) and aversive stimuli (passive avoidance, PA). Hence, for the studies performed with the rodent models of dementia, we used a single test in each case. In NORT test, rats with a specific lesion of BFCN showed impaired recognition memory in the long-term (24h post-learning), but not the short-term (5h post-learning). When treated with 0.5 mg/kg of WIN 55,212-2, memory was restored in lesioned rats, but impaired in controls. Conversely, the lower dose of 0.05 mg/kg did not affect controls while also restoring recognition memory for lesioned rats. Using the genetic model of dementia, 6-month old 3xTg-AD mice showed delayed learning in BM, and a treatment with 0.1 mg/kg of WIN 55,212-2 (equivalent to 0.5 mg/kg in rats) showed no effect. Interestingly, on the probe day, spatial memory was preserved regardless of phenotype and treatment.
Overall, these results suggest an involvement of the eCB system in modulating learning and

memory paradigms including aversive stimuli, novelty-seeking and recognition and spatial components. Given this cholinergic-cannabinoid crosstalk, in memory impairment derived from BFCN degeneration, as is the case in AD patients, we propose that low doses of cannabinoid agonists might be beneficial.

Disclosures: **I. Bengoetxea de Tena:** None. **M. Moreno-Rodríguez:** None. **G. Pereira-Castelo:** None. **J. Martinez-Gardeazabal:** None. **I. Manuel:** None. **L. Giménez-Llort:** None. **R. Rodríguez-Puertas:** None.

Poster

157. Molecular Mechanisms of Memory

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 157.08

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

Support: Supported by Project "PI20/00153", funded by Instituto de Salud Carlos III and co-funded by the European Union (ERDF "A way to make Europe").
Technical and human support was provided by the General Research Services SGIker [University of the Basque Country (UPV/EHU)
J.M.-G. is the recipient of Margarita Salas fellowship funded by the European Union-Next Generation EU.

Title: Pharmacological cannabinoid system modulation of lipid homeostasis in a rat cholinergic lesion model of dementia

Authors: *J. MARTÍNEZ GARDEAZABAL[1], M. MORENO-RODRIGUEZ[3], I. BENGOETXEA DE TENA[3], G. PEREIRA-CASTELO[2], I. MANUEL[2], R. RODRIGUEZ-PUERTAS[4];
[2]Pharmacol., [1]Univ. of Basque Country UPV/EHU, Leioa, Spain; [3]Pharmacol., Univ. of the Basque Country (UPV/EHU), Leioa, Spain; [4]Pharmacol., Univ. of the Basque Country UPV/EHU, Leioa, Spain

Abstract: Selective vulnerability of the basal forebrain cholinergic neurons (BFCN) is responsible for most of the clinical alterations in Alzheimer's disease (AD). The BFCN-lesioned rats mimic the selective cholinergic vulnerability in AD, showing memory impairment and increase on cortical endocannabinoid (eCB) activity. Since the eCB are neurolipids, this study is aimed to evaluate modifications of specific brain lipids after pharmacological modulation of eCB receptors in the above-mentioned rat model using mass spectrometry imaging (MSI).The results were analyzed in 9 different groups of treatment (CB1 receptor agonist: WIN55,212-2 (low (0.5 mg/kg) and high doses (3 mg/kg) and antagonist: SR141716A (0.5 mg/kg)): control group (aCSF), lesion group (192IgG-SAP), treated control groups with 2 doses of WIN55,212-2 and SR141716A (aCSF+W0.5, aCSF+W3, aCSF+SR) and treated lesion groups (192IgG-SAP+W0.5, 192IgG-SAP+W3, 192IgG-SAP+W+SR, 192IgG-SAP+SR). The lipidomic analysis

in cortex, showed that low doses of WIN55,212-2 treatment increased specific sphingolipid composition related to myelin, such as sulfatides (ST(d18:1/18:0)$^-$, ST(d18:1/24:0)$^-$, ST(d18:1/24:1)$^-$), long chain ceramides (Cer 40:2;O2+H-H_2O and Cer 42:2;O2+H-H_2O), galactosylceramides (GalCer 42:2;O2+K^+) and phosphatidylethanolamines (PE 36:0+K^+ and PE 34:0+K^+). Conversely, C18:0 sphingomyelins (SM (d18:0/18:1) +K^+, SM (d18:0/18:2) +K^+, SM (d18:0/20:0) +K^+, SM (d18:0/20:1) +K^+), that are mainly distributed in grey matter, were decreased. This cannabinoid treatment increased lipids that act as intracellular messenger including lysophospholipids (LPC 18:0 +K^+, LPC 16:0 +K^+, LPC 18:1 +K^+ and LPA 18:1 +K^+), and phosphatidic acid (PA 38:5+K^+ and PA 38:4+K^+). WIN55,212-2 increased DHA (docosahexaenoic acid) enriched phosphatidylcholines (PC 18:1/22:6 +K^+ and PC 18:0/22:6 +K^+) and decreased arachidonic acid (AA) enriched phosphatidylcholines (PC 18:1/20:4 +K^+ and PC 16:0/20:4 +K^+), which are involved in immune and inflammatory processes. We also focused on the BFCN lesion area (aCSF, 192IgG-SAP, aCSF+W, 192IgG-SAP+W), showing that both lesion and treatment increased linoleoylcarnitine (CAR 18:2), oleoylcarnitine (CAR 18:1) and palmitoylcarnitine (CAR 16:0), lipids related to mitochondria metabolism. Lipid homeostasis is essential for functioning of cells to avoid dementia. Pharmacological modulation of eCB system alters specific lipids with important roles in cellular signalling. Proper lipid homeostasis restauration by the activation of the eCB system could be a promising therapy for neurodegenerative disorders that cause dementia.

Disclosures: J. Martínez Gardeazabal: None. **M. Moreno-Rodriguez:** None. **I. Bengoetxea de Tena:** None. **G. Pereira-Castelo:** None. **I. Manuel:** None. **R. Rodriguez-Puertas:** None.

Poster

157. Molecular Mechanisms of Memory

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 157.09

Topic: B.09. Glial Mechanisms

Title: Valproate-adjuvant cognitive behavioral therapy for bipolar disorder and comorbid panic disorder

Authors: *M. JIN[1,2,3], T. SUN[1], D. KIM[1,2], K.-Y. CHOI[1,4];
[1]Dept. of Med. Sci., Chungnam Natl. Univ., Daejeon, Korea, Republic of; [2]Dept. of Anat. and Cell Biol., Chungnam Natl. Univ. Col. of Medicine, Brain Res. Inst., Daejeon, Korea, Republic of; [3]Brain Korea 21 PLUS Project for Med. Sci., Chungnam Natl. Univ. Col. of Med., Daejeon, Korea, Republic of; [4]Dept. of Psychiatry, Chungnam Natl. Univ. Hosp., Daejeon, Korea, Republic of

Abstract: Anxiety disorders are the most common comorbid psychiatric disorders in patients with bipolar disorder. However, managing anxiety symptoms in comorbid conditions is challenging and has received little research interest. Studies of fear conditioning, an animal model of anxiety disorder, have suggested that memory reconsolidation-update (exposure-based

therapy) combined with valproate might facilitate the amelioration of fear memory in preclinical research. To the best of our knowledge, this is the first attempt to combine cognitive-behavioral therapy with valproates in patients with panic disorder, agoraphobia, and comorbid bipolar disorder. We describe case series of successful amelioration of agoraphobia and panic symptoms in patients who failed to respond to 2-3 consecutive standard pharmacotherapy trials over the course of several years. Additionally, we summarize the background of this combination therapy based on the reconsolidation-updating mechanism, critical period reopening and valproate, clinically available histone deacetylase 2 (HDAC2) inhibitor, in preclinical research.

Disclosures: M. Jin: None. **T. Sun:** None. **D. Kim:** None. **K. Choi:** None.

Poster

157. Molecular Mechanisms of Memory

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 157.10

Topic: H.08. Learning and Memory

Support: NJ Governor's Council for Medical Research and Treatment of Autism (CAUT17BSP022)
NSF/IOS 1556968
NSF/IOS 2034864

Title: Spatiotemporal specificity of Neuropilin-2 functions in cortical neuron dendritic spine morphogenesis, maintenance, and learning

Authors: C. EISENBERG[1], C. NEAR[2], J. STRONG[2], J. DELUCIA[1], ***M. W. SHIFLETT**[2], T. S. TRAN[1];
[1]Biol. Sci., [2]Psychology, Rutgers Univ. Newark, Newark, NJ

Abstract: The proper development of neuronal morphologies is critical for patterning of synaptic connections and transmission, which affect circuit activity, and ultimately impact behavior and mental function. A member of the class 3 semaphorins, Sema3F, acting through its Neuropilin-2/plexin-A3 (Nrp2/PlexA3) holoreceptor complex signals *in vivo* during postnatal development to restrain apical dendritic spine morphogenesis of cortical pyramidal neurons and hippocampal neurons, and mediates synaptic transmission in mature brain circuits. Previously, we showed that *Nrp2-/-* null mice exhibit sensorimotor, social, and learning deficits. However, it is not known how loss of Nrp2 in select neuronal populations at specific developmental time points contributes to the dendritic spine and behavior phenotype observed in global Nrp2-deficient mice. Here, we conditionally deleted Nrp2 in cortical layer 5 (L5) pyramidal neurons by using the *Nrp2* flox mouse (*Nrp2*$^{tm1.1Mom}$) and crossed it with the inducible *Etv1*$^{tm1.1(cre/ERT2)Zjh}$ line, where Cre expression can be induced with tamoxifen treatment (+TM), specifically in L5 pyramidal neurons. We induced Nrp2 deletion with +TM at early postnatal (P7-8) and mature (4-6 month old) time points in *Nrp2f/f;Etv1+/Cre* mice and control (Nrp2+/+;Etv1+/Cre or

Nrp2f/f;Etv1+/+ (no cre) animals. Compared to age-matched controls, both postnatal and adult *Nrp2f/f;Etv1+/Cre* deleted mice showed significant increases in spine density on the apical dendrites of L5 pyramidal neurons. We observed motor coordination and sensorimotor learning deficits in the rotarod test in both postnatal and adult *Nrp2f/f;Etv1+/Cre* deleted mice. In unbiased observations, we detected impairments in novel object recognition memory and preference for social novelty only in postnatal *Nrp2f/f;Etv1+/Cre* deleted, but not adult deleted mice. These findings provide novel insights into the spatiotemporal specificity for Nrp2 function in controlling dendritic spine morphogenesis during development and spine maintenance in the adult animal. Additionally, we have dissected the distinct spatiotemporal requirement of Nrp2 for the operation of specific learning, motor, and motivational behaviors that when impaired may contribute to neurodevelopmental disorders. Taken together, our results shed new light on the diverse roles of guidance receptors in wiring the mammalian nervous system leading to complex functions.

Disclosures: C. Eisenberg: None. **C. Near:** None. **J. Strong:** None. **J. DeLucia:** None. **M.W. Shiflett:** None. **T.S. Tran:** None.

Poster

157. Molecular Mechanisms of Memory

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 157.11

Topic: H.08. Learning and Memory

Support: NIH Grant MH 087463
NIH Grant AG 068306

Title: Protein Folding in the Endoplasmic Reticulum is Critical in Long-Term Memory Consolidation.

Authors: *U. MUKHERJEE[1,2], S. CHATTERJEE[1,2], E. BAHL[1], K. GIESE[3], J. MICHAELSON[1,4], T. ABEL[1,2];
[1]Univ. of Iowa, Iowa City, IA; [2]Iowa Neurosci. Inst., Iowa city, IA; [3]King's Col. London, London, United Kingdom; [4]Iowa Inst. of Human Genet., Iowa city, IA

Abstract: Consolidation of newly acquired experiences into persistent long-term memories relies on transcriptional events in a precise spatiotemporal fashion within the hippocampus. Contemporary studies had identified a set of transcriptional regulatory proteins belonging to the nuclear receptor 4a (Nr4a) family as molecular regulators of memory consolidation, whereby the learning-induced expression of Nr4a genes has been shown to facilitate long-term memory and synaptic plasticity. Here, we performed unbiased transcriptomic analyses of the rodent hippocampus following spatial learning to demonstrate that Nr4a regulates the transcription of a discrete set of genes that encode for chaperone proteins localized at the endoplasmic reticulum (ER). Our study showed that Nr4a-driven expression of these chaperone genes is essential for

long-term memory consolidation, as well as for the efficient activity-dependent surface trafficking of key receptor proteins critical in synaptic plasticity. The functional relevance of ER chaperones in memory consolidation was further established in our recent findings that showed a significant enhancement in long-term spatial memory upon overexpressing the chaperone protein Pdia6. Impairment in hippocampus-dependent declarative memory is a defining feature of Alzheimer's Disease and Related Dementias (ADRD), and our analysis of transcriptomic data obtained from human ADRD patients revealed that progression of ADRD pathology and disease burden significantly correlated with the downregulation of Nr4a in the hippocampus. Furthermore, in a tau-based mouse model that mimics the neurodegenerative phenotypes of ADRD-affected individuals, we found that hippocampal levels of the Nr4a family, and the ER chaperone genes downstream of Nr4a, were significantly reduced. Importantly, overexpressing Nr4a1 or the ER chaperone Hspa5 ameliorated such hippocampus-dependent long-term memory deficits associated with these mice. Thus, our findings provide unprecedented molecular insights into the mechanistic basis of cognitive deficits, and establish the ER chaperones, and the protein folding pathways that they regulate, as critical substrates of long-term memory. This transcriptional control on the protein folding machinery becomes compromised in ADRD, pointing us towards novel therapeutic interventions to combat cognitive decline in neurodegenerative disorders.

Disclosures: U. Mukherjee: None. **S. Chatterjee:** None. **E. Bahl:** None. **K. Giese:** None. **J. Michaelson:** None. **T. Abel:** None.

Poster

157. Molecular Mechanisms of Memory

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 157.12

Topic: H.08. Learning and Memory

Support: Walter Benjamin project 468470832
SPP 1665 220176618
SFB 936 178316478
SFB 1328 335447717
FOR 2419 278170285

Title: The bimodal relationship between neuronal activity and cFos expression in the hippocampus

Authors: *M. ANISIMOVA[1,2], P. LAMOTHE-MOLINA[2], T. G. OERTNER[2], C. E. GEE[2]; [1]Univ. of California Davis, Univ. of California Davis, Davis, CA; [2]Inst. for Synaptic Physiol., Ctr. for Mol. Neurobio. Hamburg (ZMNH), Hamburg, Germany

Abstract: Expression of cFos (*FOS*) is widely used as a marker for highly active neurons. It has been proposed that cFos-positive neurons represent the "engram" and that plasticity in these

neurons is the neural substrate of learning. Neuronal spiking is associated with calcium influx through voltage-gated calcium channels, activation of kinases such as MEK and CaMKII, and phosphorylation of CREB, which triggers the rapid production of cFos. These signaling pathways are also considered essential for activity-dependent plasticity. Given the popularity of cFos as an activity marker, surprisingly little is known about the neuronal firing patterns that trigger cFos expression. Here, we investigated the relationship between neuronal spiking and cFos expression in rat hippocampal slice cultures. Global expression of the channelrhodopsin ChrimsonR allowed us to induce action potential trains at different frequencies with millisecond precision while AMPA, NMDA and $GABA_A$ receptors were blocked to prevent fast synaptic transmission. We found strong cFos induction after high-frequency firing (50 Hz), but not at frequencies between 1 and 10 Hz. Surprisingly, 0.1 Hz stimulation was most effective in driving cFos, resulting in a bimodal frequency response curve. The remarkably high efficacy of 0.1 Hz stimulation was confirmed in anesthetized mice, suggesting that it is not an artifact of organotypic slice cultures. Thus, cFos expression is not a simple indicator of the most active neurons, rather it is upregulated in both highly active and slowly firing neurons by different mechanisms. Pharmacological block of CREB, MEK-ERK and calcineurin pathways completely abolished cFos induction at 50 Hz, but had little effect on cFos induction at 0.1 Hz. On the other hand, blocking metabotropic glutamate receptors prevented cFos induction at all tested frequencies. Our results strongly suggest that cFos expression is not triggered in a cell-autonomous fashion by action potentials, but instead through synchronous glutamate release from many neurons via metabotropic signaling cascades.

Disclosures: M. Anisimova: None. **P. Lamothe-Molina:** None. **T.G. Oertner:** None. **C.E. Gee:** None.

Poster

157. Molecular Mechanisms of Memory

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 157.13

Topic: H.08. Learning and Memory

Support: NIH Grant AG062398

Title: Sleep loss impairs spatial memory and differentially affects mTOR signaling depending on sex and brain region

Authors: L. C. GIVVINES, O. SKWIERAWSKI, M. COSTIN, M. E. DECARLO, C. R. PETRUCONIS, E. N. WASH, J. M. MCCARTHY, J. G. GRANA, N. A. BURKERT, I. K. SUCCI, L. S. NARAYANAM, ***J. C. TUDOR**;
St. Joseph's Univ., Philadelphia, PA

Abstract: Sleep is a critical function during which memories are formed. Memory formation requires protein synthesis, which is dependent on several signal transduction pathways, such as

the mammalian target of rapamycin complex 1 (mTORC1) pathway. Sleep deprivation has been found to attenuate mTORC1-mediated signaling in the hippocampus of male mice, causing a decrease in protein synthesis and spatial memory deficits. Using 2- to 4-month-old intact female mice, we determined that fluctuating levels of estradiol did not affect mTOR activity under control conditions. However, five hours of acute sleep deprivation significantly reduced mTOR activity and protein synthesis in the hippocampus and prefrontal cortex of female mice, which differs from findings in males. We also found that spatial memory, as measured in the object place recognition task, is significantly impaired in both sexes following 5 hours of acute sleep deprivation by gentle handling. Interestingly, a chronic sleep restriction of 20 hours of REM sleep loss per day for 7 consecutive days did not affect mTOR activity in female mice but significantly reduced mTOR activity in male mice. Our results show that sleep loss differentially affects mTOR activity based on sex and that not all brain regions are impacted similarly. Our research underscores the need for continued research using females given the differences in the effects of sleep loss and estradiol on mTOR signaling.

Disclosures: L.C. Givvines: None. **O. Skwierawski:** None. **M. Costin:** None. **M.E. DeCarlo:** None. **C.R. Petruconis:** None. **E.N. Wash:** None. **J.M. McCarthy:** None. **J.G. Grana:** None. **N.A. Burkert:** None. **I.K. Succi:** None. **L.S. Narayanam:** None. **J.C. Tudor:** None.

Poster

157. Molecular Mechanisms of Memory

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 157.14

Title: WITHDRAWN.

Poster

157. Molecular Mechanisms of Memory

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 157.15

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

Support: AG067473
VA Grant RX003865
NS114221

Title: Preventive memantine treatment for the comorbidity of ischemic stroke and Alzheimer’s disease

Authors: *S. P. YU[1,4], X. GU[2], M. Q. JIANG[1], T. LIN[2], N. SHAH[2], L. WEI[3];
[1]Emory Univ., Atlanta, GA; [2]Emory Univ., ATLANTA, GA; [3]Dept. of Anesthesiol., Emory Univ., Atlanta, GA; [4]Atlanta VA Med. Ctr., Atlanta, GA

Abstract: Alzheimer's disease (AD) and ischemic stroke are risk factors for each other. The comorbidity of these two neurological disorders in the same patients represents an eminent gap in basic and clinical research. With different time courses of disease processes, AD and stroke share common pathophysiological mechanisms such as NMDA receptor (NMDAR) hyperactivity and Ca^{2+}-associated excitotoxicity. We identified that deficiency of the NMDAR GluN3A subunit is a novel pathogenic mechanism of sporadic AD. Memantine (MEM) is a selective antagonist at extrasynaptic NMDARs associated with excitotoxicity. We test the hypothesis that early treatment of MEM is a disease-modifying therapy for preventing AD progression and simultaneously increasing the tolerance against ischemic attack that occurs in ≥50% of AD patients. MEM effects were tested in two AD mouse models before and after a focal ischemic insult. Cellular, molecular and functional assessments were performed in brain sections and aging animals. In the GluN3A knockout mouse and 5XFAD mouse, oral MEM (10 mg/kg/day in drinking water) for 3 months during the early stages of AD attenuated cognitive decline and showed reduced infarct volume and cell death after focal ischemic stroke. MEM daily treatments before and after stroke improved sensorimotor and psychological functions, and suppressed inflammatory factors while increased Bcl-2 in the AD brain. The chronic MEM treatment was safe while age-dependent memory loss was significantly ameliorated in AD mice. This investigation demonstrates the dual benefits of the clinical drug MEM in AD mouse models before and after ischemic stroke. Further studies will provide more inside information on the mechanism of MEM induced preconditioning effects and justify a clinical trial of the early MEM preventive therapy for people susceptible to AD/related dementia and stroke.

Disclosures: S.P. Yu: None. **X. Gu:** None. **M.Q. Jiang:** None. **T. Lin:** None. **N. Shah:** None. **L. Wei:** None.

Poster

157. Molecular Mechanisms of Memory

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 157.16

Topic: H.08. Learning and Memory

Support: NIDCD R01 DC-018561

Title: HDAC3 inhibition amplifies the magnitude of transcriptional changes induced by auditory associative learning

Authors: *G.-E. GRAHAM[1,2], M. S. CHIMENTI[4], K. KNUDTSON[4], D. GRENARD[2], L. CO[2], K. M. BIESZCZAD[1,2,3,5];
[1]Neurosci. Grad. Program, [2]Behavioral and Systems Neuroscience, Dept. of Psychology,

[3]Rutgers Ctr. for Cognitive Sci. (RuCCS), Rutgers Univ., Piscataway, NJ; [4]Iowa Inst. of Human Genet., Univ. of Iowa Carver Col. of Med., Iowa City, IA; [5]Dept. of Otolaryngology - Head and Neck Surgery, Rutgers Robert Wood Johnson Med. Sch., New Brunswick, NJ

Abstract: Forming memories that last a lifetime requires experience-dependent neurophysiological plasticity. Gene expression, a molecular basis for memory consolidation, enables lasting functional changes to neural processing. We present the first evidence of large transcriptomic changes in the auditory cortex (ACx) induced by auditory associative learning which we further probe with an epigenetic manipulation. Epigenetic regulators such as histone acetyltransferases (HAT) and deacetylases (HDAC) are powerful molecular regulators that work in an activity-dependent manner, control long-lasting effects on neuronal function, and may strengthen learned behaviors. Histone deacetylase 3 (HDAC3) often works with transcriptional machinery to enable activity-dependent *de novo* DNA transcription. Here, we systemically inhibit HDAC3 (HDAC3i) in ACx. Systemic HDAC3i promotes cue-specific forms of neurophysiological plasticity and enable precise memory formation in ACx (Shang & Bieszczad, 2022). However, genes implicated in learning-induced ACx plasticity, memory, and sound-cued behavior are unknown. In our study, bulk RNA-sequencing was performed to determine genome-wide effects of systemic HDAC3i in rats trained to associate a sound cue with reward. We report that HDAC3i amplifies vast changes in learning-dependent transcription by further up- or down-regulating unique subsets of induced genes (relative to vehicle and naïve groups). Interestingly, there are few unique *differentially* expressed genes (vs. vehicle), e.g. *Adamts13, Cabin1,* and *Rexo4*. As HDAC3i primarily further affected learning-induced genes, bioinformatic analysis in iPathway Guide™ determined molecular pathways more strongly activated via HDAC3i vs. training alone. This analysis identified proteins involved with cholinergic & glutamatergic synapses and key regulators of synaptic plasticity & memory. qRT-PCR verified effects in identified genes of interest (GOIs). Single molecule fluorescent *in situ* hybridization (smFISH) visualized GOIs within ACx anatomy. Combining bulk RNA-seq with more sensitive and cell-type specific smFISH reveals broad (genome-wide) and subtle (GOI) learning-induced transcription events. Together, these results characterize the regulatory role of HDAC3 on genetic targets that may be key for neurophysiological plasticity events to support highly precise and lasting associative memories.

Disclosures: G. Graham: None. **M.S. Chimenti:** None. **K. Knudtson:** None. **D. Grenard:** None. **L. Co:** None. **K.M. Bieszczad:** None.

Poster

157. Molecular Mechanisms of Memory

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 157.17

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

Support: KHIDI grant HI18C1801

Title: Inhibition of MEK1/2 promotes endogenous neurogenesis and improves cognitive deficits in models of Alzheimer's disease

Authors: *M.-Y. KIM[1], M. KIM[1], C. LEE[2], H. KIM[1], S. KIM[3], J. SEO[2], K.-J. YOON[4], S. HAN[1];
[1]Genuv Inc., Genuv Inc., Seoul, Korea, Republic of; [2]Daegu Gyeongbuk Inst. of Sci. and Technol. (DGIST), Daegu, Korea, Republic of; [3]Hanyang Univ. ERICA, Ansan-si, Korea, Republic of; [4]Korea Advanced Inst. of Sci. and Technol. (KAIST), Daejeon, Korea, Republic of

Abstract: The potential benefit of enhancing the neurogenic process lies in improved brain cognition and neuronal plasticity, particularly in the context of neuronal injury and neurodegenerative disorders. Alzheimer's Disease (AD) is a neurodegenerative disorder characterized by dementia due to synaptic loss and neuronal death, among many other factors. Adult neurogenesis in the subventricular zone (SVZ) and the hippocampal dentate gyrus (DG) is disrupted in AD. Enhancing adult neurogenesis from endogenous neural stem cells (NSCs) in patient's brain has been suggested as a potential therapeutic intervention for AD. Here, we report that trametinib has the potential to become a therapeutic for AD by activating adult neurogenesis to replenish damaged neurons in the AD-model mice 5XFAD. Using an adult neural stem cell (NSC)-based phenotypic screening platform (ATRIVIEW®), we identified that SNR1611 (trametinib, Mekinist®; a selective MEK1/2 inhibitor) was the most potent hit among the small molecule drugs approved by US FDA. Trametinib rescued AD pathologies of 5XFAD mice including neuronal loss, disruption of the neural network, and cognitive impairment. We also examined the potential of trametinib in AD treatment via enhancing endogenous neurogenesis at a severe stage in a mouse model of AD (5XFAD mouse). Orally administered trametinib not only recovered impaired neurogenesis in the DG and SVZ of the AD model mice 5XFAD but also enhanced cortical neurogenesis. In order to confirm whether these results were caused by inhibition of hyperactivated MEK/ERK signaling in AD, we demonstrated that inhibition of MEK/ERK signaling by MEK1/2 inhibitors or shRNA on NSCs from 5XFAD mice induced neuronal differentiation. Finally, we present human relevance for the therapeutic potential of trametinib by confirming its neurogenic differentiation effect in NSCs derived from AD patient-induced pluripotent stem cells. Overall, these data suggest that trametinib enhances adult neurogenesis and replenishes neurons in brain areas where neurodegeneration most affects AD and that further evaluation of activating neurogenesis as a potent treatment for AD and other neurodegenerative diseases is warranted.

Disclosures: **M. Kim:** A. Employment/Salary (full or part-time):; Genuv Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Genuv Inc. **M. Kim:** A. Employment/Salary (full or part-time):; Genuv Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Genuv Inc.. **C. Lee:** None. **H. Kim:** A. Employment/Salary (full or part-time):; Genuv Inc.. **S. Kim:** None. **J. Seo:** None. **K. Yoon:** None. **S. Han:** A. Employment/Salary (full or part-time):; Genuv Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Genuv Inc..

Poster

157. Molecular Mechanisms of Memory

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 157.18

Topic: H.08. Learning and Memory

Support: NIH Grant 5R01MH117149-03
NIH Grant 1F99NS120543-01

Title: Adaptation of hippocampal and cortical circuit dynamics to novel experience requires the memory associated gene KIBRA

Authors: *L. D. QUIGLEY, R. PENDRY, M. MENDOZA, B. E. PFEIFFER, L. J. VOLK; Neurosci., UT Southwestern Med. Ctr., Dallas, TX

Abstract: Revealing how molecular interactions within neurons contribute to experience-dependent changes in neural activity across large-scale brain networks is a major challenge in neuroscience. The postsynaptic scaffolding protein KIBRA regulates both synaptic plasticity and AMPA receptor trafficking. KIBRA gene variants are linked to normal variation in human memory performance, and mice lacking Kibra show substantial impairment in learning and memory. In addition, KIBRA and the protein complexes it organizes are associated with multiple neuropsychiatric disorders known to have synaptic/circuit etiologies. However, the role of KIBRA in regulating circuit dynamics is unknown. Particularly relevant for the study of network-level memory processes are hippocampal sharp-wave/ripple(SWR) events, a key mechanism that supports memory consolidation/retrieval in rodents. To determine whether KIBRA-dependent plasticity mechanisms regulate behaviorally-relevant hippocampal and cortical network dynamics, we monitored neural activity in the hippocampus(HC) and frontal cortex(ACC) of mice with forebrain-specific deletion of KIBRA (KIBRA cKO) using *in vivo* electrophysiology before and after a novel experience. While baseline features of SWRs and other markers of hippocampal network function were normal in mice lacking KIBRA, experience-dependent alterations in SWR features consistent with information updating were absent. Further, we demonstrate that KIBRA regulates intra-hippocampal(CA3-CA1) communication, implying a role for KIBRA in early network mechanisms of memory formation. Finally, we see that coordinated hippocampal-cortical communication during sleep SWRs was disrupted in KIBRA cKO mice indicating that KIBRA-dependent plasticity mechanisms contribute to systems-level memory consolidation. These findings provide insight into molecular mechanisms that underlie network-level memory formation and consolidation.

Disclosures: L.D. Quigley: None. **R. Pendry:** None. **M. Mendoza:** None. **B.E. Pfeiffer:** None. **L.J. Volk:** None.

Poster

157. Molecular Mechanisms of Memory

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 157.19

Topic: H.08. Learning and Memory

Support: 20RHCOR04

Title: Enhancement of recognition memory by vagus nerve stimulation: proteomic analysis in the hippocampus

Authors: *S. JUNG, L. OLSEN, R. MOORE, S. HARSHMAN, C. HATCHER-SOLIS;
Air Force Res. Laboratory/Applied Neurosci. Br., U.S. Air Force Res. Lab., Wright-Patterson AFB, OH

Abstract: Recognition memory can decline from stress, ageing, or neurodegenerative disease. Vagus nerve stimulation (VNS) is a neuromodulation therapy with the potential to improve cognition. This study investigated the effectiveness of VNS paired with training to enhance recognition memory and the associated global changes in protein regulation in the rodent hippocampus. This study was reviewed and approved by the Wright-Patterson Air Force Base IACUC. Using bottom-up LC-MS/MS -based proteomics, roughly 3,000 proteins from rat hippocampal synaptosomes were analyzed. Protein-protein interaction (PPI) enrichment analysis found differentially expressed proteins related to synaptic signaling and neurotransmitter pathways, including pathways of glutamatergic synapse, dopaminergic synapse, long-term potentiation (LTP), activation of AMPA receptors, etc. PPI network clustering algorithm clustered subgraphs and identified unique protein clusters, including a cluster of synaptic signaling related pathways. This statistically significant cluster included proteins related to LTP, glutamatergic synapses, and dopaminergic synapses, and all molecules in this cluster were positively associated with the rodents' performance in the novel object recognition memory task. Ingenuity pathway analysis identified LTP and branching of neurites to be enhanced by VNS. VNS also increased the number of molecules related to LTP, neuritogenesis, memory, learning and cognition. Rapamycin-insensitive companion of mTOR was identified as an upstream regulator of synaptosome changes due to VNS paired with training. Moreover, using machine learning algorithms, we created neural network algorithm models to predict memory performance (training $r^2 = 0.986$, validating $r^2 = 0.991$) and VNS treatment (training $r^2 = 0.998$, validating $r^2 = 0.995$). Based on the results, it is proposed that VNS paired with cognitive training may enhance recognition memory via increases in glutamatergic signaling and early LTP during the consolidation period, followed by sustained synaptic plasticity via modified post-synaptic receptor expression and dendritic outgrowth. Further investigation is required to determine if VNS is a good candidate for ameliorating cognitive impairment. No DoD endorsement implied.

Disclosures: S. Jung: None. **L. Olsen:** None. **R. Moore:** None. **S. Harshman:** None. **C. Hatcher-Solis:** None.

Poster

157. Molecular Mechanisms of Memory

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 157.20

Topic: H.08. Learning and Memory

Title: Macroh2a1.1-parp1 interactions are relevant in memory formation

Authors: *T. A. B. MCLEAN[1], S. D. CREIGHTON[2], G. STEFANELLI[2], M. A. BRIMBLE[4], A. M. LEONETTI[1], A. M. DAVIDOFF[5], B. J. WALTERS[3], I. B. ZOVKIC[2];
[1]Cell & Systems Biol., Univ. of Toronto, Toronto, ON, Canada; [2]Psychology, [3]Biol., Univ. of Toronto Mississauga, Mississauga, ON, Canada; [4]Immunol., [5]Surgery, St Jude Children's Res. Hosp., Memphis, TN

Abstract: The formation of long-lasting memories requires learning-induced changes in gene expression. Basal levels of inducible genes are tightly regulated by epigenetic factors, including histone variant deposition, that modulate DNA accessibility and transcription factor binding. Although a role for post-translational modification of canonical histones in memory is well-established, histone variants were only recently identified as epigenetic regulators of memory, with functional roles described for the variants H2A.Z and H3.3. Our lab recently characterized macroH2A1 (mH2A1), a structurally unique H2A variant bearing a large non-histone macrodomain, as another novel regulator of memory. Hippocampal depletion of mH2A1 induces widespread de-repression of hippocampal transcription and impairs hippocampal-dependent memory in mice. Here, we investigate the molecular and mechanistic basis of these mH2A1 phenotypes by assessing the function of the mH2A1 splice isoforms mH2A1.1 and mH2A1.2, which bear structurally distinct macrodomains. Only the macrodomain of mH2A1.1 binds poly(ADP)-ribose (PAR) and inhibits activity of poly(ADP-ribose)polymerase 1 (PARP-1), a nuclear protein which positively regulates memory formation and activity-dependent neuronal transcription. Selective knockdown of mH2A1.1 upregulated *PARP1* expression and increased baseline expression of several memory-relevant immediate early genes (IEGs) in cultured neurons. Moreover, mH2A1.1 knockdown blocked activity induction of IEG expression in vitro and impaired long-term contextual fear memory consolidation in mice. Co-depletion of *PARP1* reduced basal expression of a subset of mH2A1.1-regulated IEGs and rescued impaired fear memory in mH2A1.1 knockdown mice. These studies are the first to investigate splice isoform-specific effects of mH2A1 on hippocampal-dependent memory and transcription, and characterize the functional relevance of PARP1-macrodomain interactions in these processes. We propose that regulation of *PARP1* expression and PARP-1 activity is a major mechanism by which mH2A1 regulates neuronal transcription and memory consolidation.

Disclosures: T.A.B. McLean: None. **S.D. Creighton:** None. **G. Stefanelli:** None. **M.A. Brimble:** None. **A.M. Leonetti:** None. **A.M. Davidoff:** None. **B.J. Walters:** None. **I.B. Zovkic:** None.

Poster

157. Molecular Mechanisms of Memory

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 157.21

Title: WITHDRAWN

Poster

157. Molecular Mechanisms of Memory

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 157.22

Topic: H.08. Learning and Memory

Title: Effects of Chronic L-α-glycerylphosphorylcholine (α-GPC) Ingestion on Spatial Memory and the hippocampal formation in Adult Male Rats

Authors: *A. ISHII[1], T. HATAKEYAMA[2,3], S. MORIYA[4], M. KAWAGUCHI[1,2], T. OHKUBO[5];
[1]Grad. Sch. of Agriculture, Meiji Univ., [2]Sch. of Agriculture, Meiji Univ., Lab. of Animal Behavior and Envrn. Sci., Kawasaki, Japan; [3]Meiji Universuty, Organization for the Strategic Coordination of Res. and Intellectual Property, Kawasaki, Japan; [4]Chiba Univ., Grad. Sch. of Med., Chiba, Japan; [5]Sendai Shirayuri Women's Col., Sendai, Japan

Abstract: It can be possible for choline to enhance memory of animals in juvenile and elder. However, little is known about adult. We human beings eat eggs and fishes, including water-soluble choline, or α-GPC, but few studies assess the effect of α-GPC intake on memory ability. Furthermore, it is still unknown whether the length of period in α-GPC intake can affect memory-related behavior. In addition, the molecular mechanisms of memory enhancement are still unclear. Thus, the purpose of this study is to determine whether chronic feeding of α-GPC in the diet of healthy adult rats can improve their spatial memory, and to support to identify the molecular mechanism underlying any α-GPC-induced memory improvement. Additionally, by comparing between 5-week and 10-week feeding periods, we investigated behavioral changes caused by feeding duration of α-GPC. 10-week-old male Wistar-Imamichi rats were divided into two equal-sized groups. One group (SUP) received a special diet containing 1.5 % α-GPC of total diet weight, while the other group (STA) was fed a standard diet. Water and food were available ad libitum throughout the experiment. At 15 and 20 weeks of age, all rats underwent a spontaneous place recognition (SPR) test. Each rat was exposed to two identical objects, and then after a retention interval of 24 hours, they were tested with one of the objects moved to a novel location. The SPR test utilizes the tendency of rats to explore novelty, so if the rats remember the original object location, they tend to explore the novel object location in the test. After the SPR test at 20 weeks, microarray analysis was conducted with the hippocampal formation taken from the rats. In the SPR test at 15 and 20 weeks of age, the SUP group significantly showed a preference for the novel object location compared with the STA group. At 20 weeks of age, the difference between the STA group and the SUP group was more clearly

than that of 15 weeks. From this point of view, the effect of α-GPC could depend on the span of feeding. Furthermore, memory-related genes were isolated by microarray analysis in the hippocampal formation of the SUP group. In conclusion, we found that chronic α-GPC ingestion improved the spatial memory of rats, and could change a molecular mechanism underlying spatial memory depending on the hippocampus.

Disclosures: A. Ishii: None. **T. Hatakeyama:** None. **S. Moriya:** None. **M. Kawaguchi:** None. **T. Ohkubo:** None.

Poster

157. Molecular Mechanisms of Memory

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 157.23

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

Support: Fondation Pour l'Audition FPA RD-2019-13
Retina France Association and Foundation
Intramural Research Program of the National Institute on Drug Abuse/NIH
Italian Association for Cancer Research (AIRC: IG-23670)
Associazione Ricerca Oncologica Sperimentale Estense (A-ROSE)
Progetti di Rilevante Interesse Nazionale (PRIN2017E5L5P3)
Association syndrome de Wolfram

Title: Activation of the sigma-1 receptor chaperone alleviates symptoms of Wolfram syndrome in preclinical models.

Authors: *B. DELPRAT[1], L. CROUZIER[3], A. DANESE[4], Y. YASUI[5], E. RICHARD[2], J.-C. LIEVENS[2], S. PATERGNANI[6], S. COULY[5], C. DIEZ[2], M. DENUS[2], N. CUBEDO[2], M. ROSSEL[2], M. THIRY[7], T.-P. SU[8], P. PINTON[9], T. MAURICE[10];
[1]Inserm U1198, Inserm U1198, Montpellier cedex 5, France; [2]Inserm U1198, Montpellier, France; [3]INSERM UMR-S1198, INSERM UMR-S1198, Montpellier, France; [4]Uniserity of Ferrara, Ferrara, Italy; [5]NIDA, Baltimore, MD; [6]Univ. of Ferrara, Ferrara, Italy; [7]GIGA, Liege, Belgium; [8]NIDA-IRP, NIH, NIDA-IRP, NIH, Cockeysville, MD; [9]Unisersity of Ferrara, Ferrara, Italy; [10]Univ. Montpellier, EPHE, INSERM, MMDN, Univ. Montpellier, EPHE, INSERM, Montpellier Cedex 5, France

Abstract: The Wolfram syndrome is a rare autosomal recessive disease affecting many organs with life-threatening consequences and currently no treatment is available. Therefore, the aim of this study was to identify and propose a novel relevant therapy. The pathology is related to the deficient activity of wolframin, an endoplasmic reticulum (ER) transmembrane protein involved in contacts between ER and mitochondria termed mitochondria associated-ER membranes (MAMs). Inherited mutations usually reduce the protein's stability, altering its homeostasis and ultimately reducing ER to mitochondria Ca^{2+} transfer resulting in mitochondrial dysfunction and

cell death. We here demonstrate that activation of the sigma-1 receptor (S1R), an endoplasmic reticulum resident protein involved in Ca^{2+} transfer, could counteract the functional alterations of MAMs due to wolframin deficiency. The S1R agonist PRE-084 restored Ca^{2+} transfer and mitochondrial respiration *in vitro*, corrected the associated increased autophagy and mitophagy, and was able to alleviate the behavioral symptoms observed in the genetic animal models of the disease, *i.e.* hyperlocomotion in *wfs1ab*^{KO} zebrafish and memory deficits and anxiety in *Wfs1*$^{\Delta Exon8}$ mice. Our findings provide a new therapeutic strategy for Wolfram syndrome patients, by efficiently boosting MAM function using the ligand operated S1R chaperone. Moreover, such strategy could be expanded to other degenerative and mitochondrial diseases involving MAMs dysfunction.

Disclosures: B. Delprat: None. **L. Crouzier:** None. **A. Danese:** None. **Y. Yasui:** None. **E. Richard:** None. **J. Lievens:** None. **S. Patergnani:** None. **S. Couly:** None. **C. Diez:** None. **M. Denus:** None. **N. Cubedo:** None. **M. Rossel:** None. **M. Thiry:** None. **T. Su:** None. **P. Pinton:** None. **T. Maurice:** None.

Poster

157. Molecular Mechanisms of Memory

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 157.24

Topic: G.05. Mood Disorders

Title: Binding and Signal Profiling of Full and Partial M4 Agonists

Authors: S. S. PIN[1], A. QUINN[2], D. L. SMITH[3], L. TE[1], M. TOH[5], H. NGUYEN[1], P. A. IREDALE[4];
[2]In Vitro Pharmacol., [3]Neurosci., [1]Cerevel Therapeut., Cambridge, MA; [4]Cerevel Therapeut., East Greenwich, RI; [5]Cerevel, Cambridge, MA

Abstract: The M4 muscarinic acetylcholine receptor (mAchR) is one of 5 mAchR subtypes (M1-M5) in the G-protein coupled receptor (GPCR) superfamily. It is a 7-transmembrane Gαi-coupled receptor that is expressed in neurons both pre- and post-synaptically, in brain regions associated with psychotic and cognitive functions, including the striatum, the cortex, and the hippocampus. The aim of this study was to understand the agonism and the binding profile of M4 ligands with different degrees of intrinsic activities, by using multiple probes, evaluating different signaling events/pathways, and by performing experiments at steady state as well as at multiple time points. By combining classical radioligand binding and modern receptor pharmacology, we analyzed known M4 selective molecules in-depth at both the binding and functional levels to determine their preferences for allosteric vs. orthosteric binding sites, as well as their preferred signaling pathways. In general, M4 activators have a broad range of binding affinities, kinetics profiles, and functional potencies that can be mediated through multiple binding sites. Thus, functional profiling was done at the G-protein, and at the second messenger cAMP level, as well as at the at β-arrestin recruitment pathway. Measurements of direct G-

protein activation were done using the GTPγS assay, as well as using the Bioluminescence Resonance Energy Transfer (BRET) assay to evaluate individual G-proteins including Gαi1, Gαi2, Gαi3, GαoA, GαoB, and GαZ. Compounds that appeared to have the same profile from a single assay sometimes exhibited distinct signaling signature profiles when all functional data were examined together. Thus, due to the overlapping properties of these molecules, it was necessary to assess the muscarinic activation beyond an individual assay to fully distinguish their overall profiles.

Disclosures: **S.S. Pin:** A. Employment/Salary (full or part-time):; Cerevel Therapeutics. **A. Quinn:** A. Employment/Salary (full or part-time):; Cerevel Therapeutics. **D.L. Smith:** A. Employment/Salary (full or part-time):; Cerevel Therapeutics. **L. Te:** A. Employment/Salary (full or part-time):; Cerevel Therapeutics. **M. Toh:** A. Employment/Salary (full or part-time):; Cerevel Therapeutics. **H. Nguyen:** A. Employment/Salary (full or part-time):; Cerevel Therapeutics. **P.A. Iredale:** A. Employment/Salary (full or part-time):; Cerevel Therapeutics.

Poster

157. Molecular Mechanisms of Memory

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 157.25

Topic: C.01. Brain Wellness and Aging

Support: NIH R01 GM121457

Title: Imaging age-associated disruption of excitatory/inhibitory balance in the C. elegans nervous system

Authors: G. S. WIRAK[1], C. CONNOR[2], ***C. V. GABEL**[3];
[1]Boston Univ. Sch. of Med., Boston Univ. Sch. of Med., Boston, MA; [2]Brigham and Women's Hopsital, Boston, MA; [3]Boston Univ. Sch. of Med., Sch. of Med., Boston, MA

Abstract: In the aging brain, many of the alterations underlying cognitive and behavioral decline remain opaque. Specifically, how normal aging and neurodegenerative states change neuronal connectivity and circuit function on the cellular level remains largely unknown. The nematode worm *C. elegans* is a powerful model for aging research, and with its simple, completely characterized nervous system, presents a unique opportunity to understand the system-wide functional alterations in neuronal senescence. Employing fluorescence microscopy, we have performed functional imaging across the aged *C. elegans* nervous system with single cell resolution. We measure a progressive age-associated breakdown in system-wide organization and temporal continuity that begins in mid-adulthood. Interestingly, we also measure a progressive increase in bouts of global neuronal quiescence with age that are similar to sleep states observed previously in *C. elegans*. At single-cell resolution, aging results in a shift in neuronal activity toward higher frequency dynamics and a specific loss of anti-correlated activity (*i.e.* inhibitory signaling) between neuron pairs. Importantly, the degree of positively correlated

activity (*i.e.* excitatory signaling) remains unchanged resulting in an overall disruption of the systems excitatory/inhibitory balance with age. These effects are recapitulated by mechanisms known to alter GABAergic signaling. During development, calcium channel subunit UNC-2/CaV2 activity triggers the removal of inhibitory GABAergic synapses in motor neurons through a CED-4 dependent pathway. We find that young adult animals with a gain of function *unc-2* mutation exhibit neuronal dynamics and behavior similar to that of aged animals, while *ced-4* loss-of-function mutation limits neuronal decline with age. Likewise, we find that increases/decreases in inhibitory GABA signaling also partially ameliorate/accelerate effects of aging. Our findings are consistent with those in mammals, suggesting a conserved shift in the balance of excitatory/inhibitory signaling with age that leads to breakdown in global neuronal dynamics. Our results here suggest that it is specifically a loss of inhibitory signaling that drives the disruption in excitatory/inhibitory balance with age.

Disclosures: **G.S. Wirak:** None. **C. Connor:** None. **C.V. Gabel:** None.

Poster

157. Molecular Mechanisms of Memory

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 157.26

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

Support: Ministry of Health & Welfare (HU22C0150)
Ministry of Science & ICT (NRF-2022R1A2C3009749)
Ministry of Science & ICT (NRF-2017R1A5A1014708)
2022 Joint Research Project of Institutes of Science and Technology
GIST Research Institute (GRI) IIBR grant funded by the GIST in 2022

Title: 40 hz acoustic stimulation improves sleep-wake control and reactive astrocytosis in an animal model of alzheimer`s disease

Authors: *M. PARK, V. J. DREW, J. JUNG, T. KIM;
Biomed. Sci. and Engin., Gwangju Inst. of Sci. and Technol., Gwangju, Korea, Republic of

Abstract: Alzheimer's disease (AD) is majority cause of dementia patients and amyloid beta (Aβ) accumulation have been implicated as major biomarkers and pathology of AD. Recently, it has been known that gamma entrainment reduced Aβ in the brain, and a growing body of evidence supports the relationship between sleep and dementia. In addition, GABA+ reactive astrocytes were found near Aβ plaques and inhibit neuron activities. However, investigation and information of sleep-wake behavior in the animal model of AD is lacking. Furthermore, it is not clear whether GABA+ reactive astrocytes were decreased with the reduction of Aβ. Therefore, we would examine the sleep-wake control in an AD model and their changes caused by acoustic stimulation at 40 Hz. We used 6 month old 5xFAD. AD treated group got two-hour daily acoustic stimulation of click sound at 40 Hz for 14 days. We performed the 24-hour

electroencephalogram (EEG) recordings for the sleep-wake analyses at baseline day and 13 and analyzed using Sirenia Sleep software. The brain sections were rinsed three times with 1% PBST and blocked in 3% normal donkey serum. Using the free-floating method, we stained the tissue to target GFAP and GABA. Image acquired with a confocal microscope and was analyzed by the ImageJ program. We found that the number of Aβ decreased in the brain after 2 weeks acoustic stimulation. Also, we found AD mice slept less and shorter sleep than WT in the baseline day. At day 13, AD treated group showed the similar NREM sleep amount and length to WT group. We confirmed astrocytes near Aβ plaques release the GABA. After two weeks of acoustic stimulation at 40 Hz, the percentage of GABA+ reactive astrocytes was reduced. Repeated acoustic stimulation resulted in decrease levels of amyloid beta and more consolidated sleep and wake stages. These changes may reflect improved amyloid pathology could also ameliorate the continuity of wakefulness in AD mice. Additionally, acoustic stimulation at 40 Hz can reduce GABA+ reactive astrocytes in the cortex. Consequently, we suggest that non-invasive acoustic stimulations at 40 Hz might have therapeutic effect on mouse model of Alzheimer's disease.

Disclosures: **M. Park:** None. **V.J. Drew:** None. **J. Jung:** None. **T. Kim:** None.

Poster

157. Molecular Mechanisms of Memory

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 157.27

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

Support: KHIDI grant HI18C1801

Title: Trametinib rescues neurodegeneration by enhancing TFEB-dependent autophagic lysosomal function in Alzheimer’s Disease model mice

Authors: ***Y. CHUN**[1], M.-Y. KIM[1], S.-Y. LEE[1], M. KIM[1], H. KIM[1], T.-I. KAM[2,3], S. HAN[1]; [1]Genuv Inc., Seoul, Korea, Republic of; [2]Neuroregeneration and Stem Cell Programs, Inst. for Cell Engineering, Johns Hopkins Univ. Sch. of Med., Baltimore, MD; [3]Dept. of Neurology, Johns Hopkins Univ. Sch. of Med., Baltimore, MD

Abstract: Alzheimer’s Disease (AD) is a progressive neurodegenerative disorder, characterized by cognitive deficit due to synaptic loss and neuronal death. Extracellular amyloid β plaques and intracellular tau tangles are pathological hallmarks of AD, and their enhanced clearance by exploiting cellular intrinsic homeostatic systems has been an attractive therapeutic approach for this devastating disease. We observed that a MEK1/2 inhibitor, trametinib (GSK1120212, SNR1611), reduced Aβ deposition in the 5XFAD mice (2.5 month-oral administration to 5-month-old) and thus protected against Aβ-mediated apoptotic neuronal death. In addition, trametinib also showed an effect on the recovery of impaired neuronal structures and cognitive deficits in 5XFAD mice. To elucidate the underlying mechanisms of these results, we performed RNAseq from the whole brain of wild-type C57BL/6 mice and found that trametinib induces the

expression of genes regulating the autophagic-lysosomal pathway, which is essential for maintaining cellular homeostasis by driving clearance of aberrant protein aggregates and is known to be dysfunctional in AD. In addition, lysosomal inhibitors prevented the protective effect of trametinib on Aβ42-induced-dendritic spine loss in primary hippocampal neurons. We further demonstrated that trametinib inhibited the phosphorylation of transcription factor EB (TFEB) at Ser142 by ERK, promoting its nuclear translocation, which in turn induced the expression of autophagic lysosomal-related genes. Knockdown of TFEB eliminated the effect of trametinib on the increase of mature cathepsin B, degradation of p62, and prevention of apoptosis in primary cortical neurons treated with Aβ42 oligomers. Finally, we showed that the level of pTFEB is higher in AD patient brains than in age-matched normal brains, indicating the relevance of our studies in human disease. Altogether, we have demonstrated that MEK inhibition by trametinib provides neuronal protection from Aβ burden through increased autophagic lysosomal activity and present it as a potential therapeutic strategy for AD.

Disclosures: **Y. Chun:** None. **M. Kim:** None. **S. Lee:** None. **M. Kim:** None. **H. Kim:** None. **T. Kam:** None. **S. Han:** None.

Poster

157. Molecular Mechanisms of Memory

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 157.28

Topic: I.06. Computation, Modeling, and Simulation

Support: National Science Foundation [DGE-1845298 (V.P.A)]
Department of Veterans Affairs [I01-BX003748 (D.K.C.)]

Title: Hippocampal Cellular Aggregates Display Emergent In Vivo-like Structural and Functional Properties

Authors: *V. ACERO[1], O. RIVELLINI[1], S. DAS[1], D. O. ADEWOLE[1], D. CULLEN[2]; [1]Univ. of Pennsylvania, Philadelphia, PA; [2]Neurosurg., Univ. of Pennsylvania, Media, PA

Abstract: Hippocampal neural networks are distinctly capable of integrating multi-modal sensory inputs to drive memory formation. Neuroscientific investigations using simplified *in vitro* models have greatly relied on planar (2D) neuronal cultures made from dissociated neural tissue. While these models have served as useful, simple, cost-effective, and high-throughput tools for examining various morphological and electrophysiological characteristics of hippocampal networks, 2D cultures fail to reconstitute critical elements of the brain microenvironment that may be requisite for the emergence of sophisticated integrative properties of neural networks. To address this, we utilized a previously reported *forced aggregation* technique to generate high-density (~100,000 cells/mm^3) multi-cellular three-dimensional (3D) aggregates using E18 rodent hippocampal tissue. We contrasted the emergent structural and functional properties of aggregate and 2D cultures over 28 days *in vitro* (DIV). Hippocampal

aggregates displayed robust axonal fasciculation across large distances and significant neuronal polarization, i.e. spatial segregation of dendrites and axons, at earlier time points compared to 2D counterparts. Moreover, we found that astrocytes in aggregate cultures self-organized into non-overlapping quasi-domains and developed highly stellate morphologies resembling astrocyte structures *in vivo*. In addition astrocytes in aggregate cultures, relative to 2D cultures, had significantly longer and greater number of main branches, junctions, and process length. We also demonstrated that a dual-aggregate culture developed synchronous bursting activity by 14 DIV with repeating motifs, along with increases in theta and ripple band power. Taken together, our findings demonstrate that the high-density, multi-cellular, 3D microenvironment of hippocampal aggregates supports the recapitulation of emergent *in vivo*-like morphological and functional properties. Currently, we are employing advanced micro-imaging techniques to further contrast neuronal-astrocytic structural interactions as well as further characterizing neurophysiological properties across these culture systems. This study is the first step towards utilizing neural aggregates as segregated, modular building blocks for the development of complex, multi-nodal neural network topologies, towards the goal of mimicking the tri-synaptic pathway in the hippocampus critical for modeling the mechanisms underlying learning and memory formation.

Disclosures: V. Acero: None. **O. Rivellini:** None. **S. Das:** None. **D.O. Adewole:** None. **D. Cullen:** None.

Poster

158. Spatial Navigation: Interactions With Other Cognitive Systems and Abstract Navigation

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 158.01

Topic: H.10. Human Learning and Cognition

Support: NSERC #2020-05169
NSERC #2018-05661

Title: Impulsivity is Associated with Decreased Landmark Use within a Spatial Navigation Task

Authors: *R. DAGENAIS[1], K. CLOUTIER-GUIMOND[1], V. D. BOHBOT[2], G. L. WEST[1]; [1]Univ. de Montréal, Montréal, QC, Canada; [2]Dept. of Psychiatry, McGill Univ., Douglas Mental Hlth. Univ. Inst., Verdun, QC, Canada, QC, Canada

Abstract: Impulsivity is a multidimensional concept usually associated with externalizing behavior. As measured by the Barratt Impulsiveness Scale (BIS-11), it consists of a lack of planning and a tendency to act spontaneously without forethought. Studies have shown that the structure of psychiatric disorders has in common one general psychopathology factor, the p Factor, which includes a measure of impulsivity as a contributor to most psychopathologies. Impulsivity correlates with more activity and gray matter in the caudate nucleus, while showing opposite relationships with the hippocampus. These two structures are involved in navigation.

The hippocampus is used for the “spatial strategy”, which involves building relationships between landmarks to form a cognitive map. The caudate nucleus is used for the “response strategy”, which requires learning a sequence of stimulus-response associations where a landmark can act as a stimulus without much consideration for the relationships between landmarks. Navigational strategies are interesting to better understand the implication of the caudate nucleus, which is a part of the reward system, and the associations between the response strategy and other variables related to impulsivity (substance use, risk-taking, ADHD). We investigated if the use of distinct navigational strategies would be associated with different levels of impulsivity. Fifty participants (33 women, 27 men) were tested on the 4/8VM. The 4/8VM is a navigation task that can be solved by using a hippocampus or caudate nucleus dependant strategy. It includes multiple trials where the participant must learn the position of objects situated in an 8-arm radial-maze surrounded by landmarks which are removed upon reaching a performance criterion. Participants using a spatial strategy do more error when landmarks are absent because their spatial strategy relies on them. Participants were also tested on the BIS-11. Our hypothesis was that response learners would score higher than spatial learners on the BIS-11. Results show that people who did not use landmarks on the 4/8VM, as measured by the lack of an increase in errors when landmarks were removed, presented a significantly higher score on the BIS-11 than those who did rely on landmarks, evidenced by an increase in errors when landmarks were removed (t = 3,009; $p < .005$). This study show an association, for the first time, between caudate nucleus dependent navigation strategies and impulsivity. Considering that impulsivity is an important characteristic of the p Factor which is common to most psychiatric illnesses, this study provides an avenue for investigating a common neurobiological underlying process.

Disclosures: R. Dagenais: None. **K. Cloutier-Guimond:** None. **V.D. Bohbot:** None. **G.L. West:** None.

Poster

158. Spatial Navigation: Interactions With Other Cognitive Systems and Abstract Navigation

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 158.02

Topic: H.10. Human Learning and Cognition

Title: Hippocampal-dependent navigation strategies are associated with increased vicarious trial-and-error in human virtual navigation

Authors: *N. SCHMITZER-TORBERT[1], G. WEST[2], V. D. BOHBOT[3];
[1]Wabash Col., Crawfordsville, IN; [2]Psychology, Univ. of Montreal, Montréal, QC, Canada; [3]Douglas Mental Hlth. Univ. Institute, Dept. of Psychiatry, McGill Univ., Verdun, QC, Canada

Abstract: Vicarious trial-and-error (VTE) in rodents occurs during deliberation between potential options and is associated with hippocampal activity. VTE is also associated with the

use of spatial (e.g. allocentric, flexible) navigation strategies in rodents, and VTE-like behavioral measures have been observed in humans using allocentric strategies in virtual navigation tasks. To determine if VTE is related to the use of hippocampal-dependent strategies in humans, we examined performance in two radial maze tasks (the 4 on 8 Virtual Maze, 4/8 VM, and the Concurrent Spatial Discrimination Learning Task, CSDLT) developed by our lab to assess the use of hippocampal-dependent memory in healthy adults. Both the 4/8 VM and CSDLT begin with a dual-solution phase, where either spatial (e.g. "choose the path next to the mountain") or nonspatial (e.g. "choose the left path") strategies can be used to find objects hidden in the radial maze paths. After reaching criterion performance, probe trials (removing the extramaze cues in the 4/8 VM, shifting the arms presented in the CSDLT) are administered to assess the use of hippocampal-dependent spatial strategies, and the 4/8 VM also includes a strategy assessment based on the participant's self-report. In a sample of undergraduates and Amazon Mechanical Turk workers tested on the 4/8VM (n = 521, 258 females), and the CSDLT (n = 140, 69 females), measures of VTE were associated with the use of hippocampal-dependent strategies in both tasks on probe trials, and with self-reported use of spatial strategies on the 4/8 VM. VTE was attenuated, but remained elevated, when distal cues were removed during the 4/8 VM probe trial, indicating that VTE was not simply related to scanning the environment for landmarks. Under dual-solution conditions, VTE in participants using spatial strategies was elevated in the first trial of the CSDLT, and throughout the 4/8VM. These behavioral patterns parallel imaging studies, indicating that elevated VTE is observed in spatial learners in each task when hippocampal activity is elevated, suggesting that episodes of VTE may serve as a behavioral index of hippocampal activation as spatial navigation strategies are employed.

Disclosures: **N. Schmitzer-Torbert:** None. **G. West:** None. **V.D. Bohbot:** None.

Poster

158. Spatial Navigation: Interactions With Other Cognitive Systems and Abstract Navigation

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 158.03

Topic: H.10. Human Learning and Cognition

Support: NSERC #2020-05169
NSERC #2018-05661

Title: Lower Hippocampus-Dependent Spatial Memory Performance Is Associated With Risk-Taking Behavior

Authors: *L. TRUDEL[1], G. L. WEST[2], V. D. BOHBOT[3];
[1]Fac. of Med., [2]Dept. of Psychology, Univ. of Montreal, Montréal, QC, Canada; [3]Dept. of Psychiatry, McGill Univ., Douglas Mental Hlth. Univ. Inst., Verdun, QC, Canada, QC, Canada

Abstract: Aim: When navigating in a novel environment, people use strategies dependent on one of two memory systems. They can either recruit their hippocampus to learn the relationship between landmarks (i.e., spatial strategy) or their caudate nucleus to use a rigid stimulus-response pattern (i.e., response strategy). Interestingly, response learners display more gray matter and activity in the caudate nucleus, but also less gray matter and activity in the hippocampus. In parallel, studies have shown that the caudate nucleus is also involved in decision-making, by either increasing or decreasing attention toward rewards depending on the incentive. Thus, blunted activations of the hippocampus may play an important role in risk-taking behavior. The present study examined the relationship between spatial memory during navigation and risk-taking behavior. More precisely, we hypothesized that there would be an association between lower hippocampus-dependent spatial memory performance and more risk-taking behavior. Methods: 23 participants underwent the Wayfinding task and the Iowa Gambling Task (IGT). The Wayfinding task was used to assess the hippocampus-dependent spatial memory performance. In this task, participants are required to navigate between specific landmarks in a previously encountered computer-generated virtual town. The IGT was used to evaluate the participant's risk-taking behavior. In this task, four decks of cards are presented to the participant. In terms of gains and losses, two of the decks are advantageous, while the last two are disadvantageous. The raw score represents the amount of money left to the participant at the end of the task. Results: More risk-taking and lower monetary gain as assessed by the IGT was associated with fewer targets found on the Wayfinding task, which is an indicator of poor hippocampus-dependent performance ($r = 0.43$, $p = 0.04$). Conclusion: These results suggest that spatial navigational performance, reflecting the integrity of the hippocampus memory system, might have a predictive value in terms of risk-taking behavior in decision-making.

Disclosures: L. Trudel: None. **G.L. West:** None. **V.D. Bohbot:** None.

Poster

158. Spatial Navigation: Interactions With Other Cognitive Systems and Abstract Navigation

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 158.04

Topic: H.10. Human Learning and Cognition

Support: NSERC #2020-05169
NSERC #2018-05661

Title: Navigational strategies and differential time perception

Authors: *C. SOCCIO[1], S. SHELDON[2], V. D. BOHBOT[3], G. WEST[4];
[1]Psychology, Univ. de Montréal, Montreal, QC, Canada; [2]Psychology, McGill Univ., Montreal, QC, Canada; [3]Dept. of Psychiatry, McGill Univ., Douglas Mental Hlth. Univ. Inst., Verdun, QC, Canada; [4]Psychology, Univ. of Montreal, Montréal, QC, Canada

Abstract: Aim: Spatial and response navigational strategies are dependent on two different memory systems in the brain. The spatial strategy is dependent on the hippocampus, and it involves learning the relationships between environmental landmarks, which allows the formation of a cognitive map. The response strategy is mediated by the caudate nucleus and involves implicit and inflexible behavioral responses (e.g. turn right) to stimuli in the environment (e.g. at the church) that act as triggers. The caudate nucleus is also activated during prospective time tasks related to prospective memory and plays the role of a pacemaker (Grondin, 2010). During prospective time tasks, participants perform time-flow procedure tasks which means that they are asked to focus on time. It has been shown that the pacemaker will be modulated by the level of arousal and the level of attention. The purpose of this study is to investigate the relationship between time estimation and navigation strategy. We hypothesized that response learners would be more accurate at time estimation and that spatial learners will experience more arousal when viewing scenes that are dynamic and visually stimulating, resulting in an underestimation of time. In contrast, we predicted that response learners would be more accurate at elapsed time estimation. Methods: The sample included 49 participants (21 spatial learners and 28 response learners). The 4-on-8 virtual-maze was used to assess navigation strategies used by participants. At some point in this task, all landmarks are removed, in order to assess the participant's reliance on landmarks (e.g. spatial strategy). Participants who did not use landmarks during the acquisition (e.g. response strategy). of the task do not show an increase in errors when landmarks are removed. In addition, participants were presented a series of video sequences of different lengths to assess their estimation of time. There were two conditions in this task, either dynamic or static videos which is a shot without any camera movement. Results: The results showed that participants who did not rely on landmarks during navigation, as evidenced by the lack in probe trial errors, were significantly more accurate at the estimation of time flow in the dynamic condition ($p < 0.05$), than those who relied on landmarks. Moreover, we found that participants who relied on landmarks significantly underestimated time flow in the dynamic condition. There were no significant differences in the static condition. Conclusion: Our results demonstrate that participant's spontaneous use of a given memory system when they are navigating in space has an impact on the perception of time.

Disclosures: **C. Soccio:** None. **S. Sheldon:** None. **V.D. Bohbot:** None. **G. West:** None.

Poster

158. Spatial Navigation: Interactions With Other Cognitive Systems and Abstract Navigation

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 158.05

Topic: H.10. Human Learning and Cognition

Support: NSERC #2020-05169
NSERC #2018-05661

Title: The interaction between hippocampus-dependent spatial memory and the val158met polymorphism of the COMT gene (rs4680) in healthy older adults

Authors: *M. IDRISS[1], V. D. BOHBOT[1], G. WEST[2];
[1]Dept. of Psychiatry, McGill Univ., Douglas Mental Hlth. Univ. Inst., Verdun, QC, Canada;
[2]Psychology, Univ. of Montreal, Montréal, QC, Canada

Abstract: Aim: There are different ways to navigate oneself within an environment. First, we have a spatial strategy supported by the hippocampus, which includes building relationships between specific landmarks to form a cognitive map (Dahmani & Bohbot, 2015; Tolman, 1948). We then have a response strategy which is supported by the caudate nucleus; this in turn involves learning a sequence of motor responses that become automatic and unconscious (Dahmani & Bohbot, 2015). Genetic variations can, in part, explain differences in the use of memory systems. A genetic polymorphism (val/met) affects the Catechol-O-Methyltransferase (COMT) enzyme, which degrades dopamine in the prefrontal cortex and plays a role in memory (de Frias et al., 2004). Val carriers code for the enzyme with more activity, therefore, have lower levels of dopamine in their prefrontal cortex in comparison to met carriers (de Frias et al., 2004). Past studies have shown that met carriers perform better on hippocampus dependent tasks such as episodic memory in comparison to val carriers (de Frias et al., 2004). In the present study, we have investigated the difference between met/val carriers on virtual navigation tasks dependent on the hippocampus. More specifically, our hypothesis was that val carriers would have poorer performance on hippocampus dependent memory tasks.Methods: A total of 139 healthy older adults participated (80 women and 59 men ; mean age 65.8 ; mean education of 16.2 years) and were selected through a phone screening questionnaire. The participants were tested on a virtual navigation tasks, in which they could either spontaneously adopt a hippocampus-dependent spatial strategy or a caudate nucleus-dependent response strategy. To eliminate any bias, this study was a double-blind design which means neither the participants nor experimenters were aware of the genotype of any of the participants during all the stages of data analysis. For both independent variables (COMT gene combinations) a separate ANCOVA was conducted with each dependent variable using age and education as covariates.Results and conclusion: Our results show that val carriers use landmarks to a significantly lesser extent than met carriers ($p<.05$). In addition, val carriers showed a significant higher number of trials to reach criterion ($p<.05$). These results highlight the role of certain genes, like the COMT gene, on physiological processes such as dopamine breakdown, which then impacts cognition.

Disclosures: M. Idriss: None. **V.D. Bohbot:** None. **G. West:** None.

Poster

158. Spatial Navigation: Interactions With Other Cognitive Systems and Abstract Navigation

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 158.06

Topic: H.10. Human Learning and Cognition

Support: NIH RO1MH123713

Title: Neural representations of context-dependent cognitive maps

Authors: *S. C. SWEIGART[1,2], S. A. PARK[2], N. A. NGUYEN[2], C. RANGANATH[1,3], E. D. BOORMAN[1,2];
[1]Psychology, [2]Ctr. for Mind and Brain, [3]Ctr. for Neurosci., UC Davis, Davis, CA

Abstract: Cognitive maps are representations that encode spatial or non-spatial relationships between entities. Although computationally demanding to construct and maintain, map-like structures support inferencing, generalization, and extrapolation beyond what simpler models can provide. Previous work has illustrated the role of regions such as the hippocampus (HPC), entorhinal cortex (ERC), and medial prefrontal cortex (mPFC) in cognitive map maintenance. While cognitive maps theoretically support flexibility and generalizability in their structure, we aim to examine if cognitive map representations reflect these abilities neurally. We designed a novel fMRI task where participants (n =21) leveraged a previously learned wine-attribute space to a novel task that benefited from cognitive map flexibility. We observed strong effects of context-dependent information in the HPC, ERC, and mPFC highlighting their role in cognitive map maintenance. Further, the orbitofrontal cortex (OFC), posterior cingulate cortex (PCC), temporoparietal junction (TPJ), and dorsolateral prefrontal cortex (dlPFC) show evidence of context-dependent distance coding. This work suggests representations and cognitive map information are more flexible and distributed than previously thought, involving complex mechanisms that recruit multiple regions to track, maintain different task features and dynamically utilize relevant information to solve novel task problems.

Disclosures: S.C. Sweigart: None. **S.A. Park:** None. **N.A. Nguyen:** None. **C. Ranganath:** None. **E.D. Boorman:** None.

Poster

158. Spatial Navigation: Interactions With Other Cognitive Systems and Abstract Navigation

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 158.07

Topic: H.10. Human Learning and Cognition

Support: 10102018.012

Title: Exploration-exploitation tradeoff during navigation of abstract task space

Authors: *T. HOUSER[1], D. ZEITHAMOVA[2];
[1]Univ. of Oregon, [2]Psychology, Univ. of Oregon, Eugene, OR

Abstract: Learning the abstract structure of a task space has been shown to facilitate statistical learning and abstract memory. Here, we asked how the processes of both exploitation and

exploration contribute to learning of the task space. We designed a novel behavioral paradigm, where people navigate a task space of 24 stimuli. The goal was to find reward associated with a subset of stimuli by transitioning between stimuli. Unbeknownst to participants, the options for transitioning between stimuli adhere to an underlying graph structure. We evaluated people's ability to learn the graph by measuring navigation efficiency through task space. The reward assignment to stimuli followed a "rule-plus-exception" structure to test whether participants would generalize from rule-following stimuli to the exception. Finally, we tested people's memory for stimulus values, which allowed us to assess another form of generalization, temporal credit assignment. Decisions during navigation were captured well by a traditional reinforcement learning model (Q-learning), suggesting that decisions were guided primarily by exploitation of remembered reward locations (PseudoR^2=73%, $p < .001$). This was further confirmed by accurate reward memory. Next, we added an *exploration bonus* to the model, which significantly enhanced its predictive accuracy (PseudoR^2=81%, $p < .001$). Intuitively, by splitting navigation trials into halves, we found that the exploration bonus was only utilized in early trials, whereas exploitation was dominant in later trials. Finally, we found that predictive accuracy reached its highest levels when the model also incorporated a measure of generalization (a graph Laplacian-based covariance function; PseudoR^2=88%, $p < .001$). Intriguingly, reward memory showed no signs that participants learned the underlying graph structure but rather seemed to memorize individual reward stimuli. Overall, we found evidence for the use of multiple decision-making heuristics during navigation, which became more and more exploitative over time. The data therefore suggest that exploration is more influential in novel environments while exploitation is almost solely relied upon in familiar environments. Lastly, our data hint at a potentially intriguing dissociation between navigation and memory.

Disclosures: T. Houser: None. **D. Zeithamova:** None.

Poster

158. Spatial Navigation: Interactions With Other Cognitive Systems and Abstract Navigation

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 158.08

Topic: H.10. Human Learning and Cognition

Support: Tate and Lyle

Title: Hippocampal-dependent spatial reconstruction task performance is not affected by test-retest conditions

Authors: *C. N. CANNAVALE, T. A. HOLTHAUS, S. MARTELL, R. SARMA, D. ALVARADO, T. MEHTA, H. D. HOLSCHER, N. A. KHAN;
Univ. of Illinois at Urbana-Champaign, Urbana, IL

Abstract: Accurate understanding of practice characteristics and performance stability is essential to maximize signal detection in clinical trials which aim to enhance cognition via dietary interventions. Thus, this study aimed to understand whether performance on a hippocampal-dependent spatial reconstruction task is impacted by repeat testing in adults. Further, we aimed to understand whether demographic characteristics of age, sex, and BMI are related to changes in performance over 2 sessions. We hypothesized that there will be no effect of repeat testing on performance and that demographics will not be associated with observed changes in performance.Data were analyzed for 23 adults (45-75 y, 18 females) at two baseline testing visits prior to enrollment in a randomized-controlled trial. A spatial reconstruction task where participants studied and reconstructed a randomized array of 6 ambiguous stimuli was completed at both visits. Randomized, counterbalanced assessments were utilized; therefore, no participant completed the same test trials at their second visit. Performance was scored on two metrics, misplacement (i.e., pixel-distance stimulus is placed from studied location) and object-location binding (OLB; i.e., number of stimuli placed within a radius surrounding its studied location). Differences in performance from visit 1 to 2 were assessed using a paired-samples t-test and reliability was measured via Cronbach's Alpha. Pearson's correlations were used to measure relationships between age, sex BMI, and change in performance from session 1 to 2. There was no significant change observed for misplacement ($t=-0.48$, $p=0.64$) or OLB ($t=0.28$, $p=0.78$) between the 2 test visits. OLB measurements were reliable ($\alpha=0.83$) across time points; however, misplacement displayed lower reliability ($\alpha=0.68$) from visit 1 to 2. Age, but not sex ($\rho=-0.03$, $p=0.89$) and BMI ($\rho=-0.04$, $p=0.77$), was significantly related to change in misplacement ($\rho=0.42$, $p=0.04$). OLB change was not correlated with age ($\rho=0.24$, $p=0.28$), sex ($\rho=0.13$, $p=0.54$), and BMI ($\rho=0.11$, $p=0.62$).These results indicate that there is no significant effect of repeated testing on performance for this spatial reconstruction task, however, misplacement scores may be less reliable after multiple assessments compared to OLB. Further, change in misplacement, but not OLB was associated with age of the sample. Thus, OLB may be less susceptible to practice effects, regardless of age.

Disclosures: C.N. Cannavale: None. **T.A. Holthaus:** None. **S. Martell:** None. **R. Sarma:** None. **D. Alvarado:** None. **T. Mehta:** None. **H.D. Holscher:** None. **N.A. Khan:** None.

Poster

158. Spatial Navigation: Interactions With Other Cognitive Systems and Abstract Navigation

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 158.09

Topic: H.10. Human Learning and Cognition

Support: Work supported by the FAU Foundation (Eminent Scholar in Science).

Title: The emergence of infant agency as a phase transition in sensorimotor coordination

Authors: *A. T. SLOAN, J. A. S. KELSO;
Ctr. for Complex Systems & Brain Sci., Florida Atlantic Univ., Boca Raton, FL

Abstract: It has been proposed that conscious agency, action towards an end, emerges in infancy as a phase transition in a (nonlinearly) coupled dynamical system (Kelso, *TiCS*., 2016; Kelso & Fuchs, *Biol. Cybern.*, 2016). The mobile conjugate reinforcement (MCR) paradigm, traditionally used to study infant learning, provides a window into the discovery of self as agent. When the infant's foot is tethered to a mobile, at some critical level of coordination infants suddenly realize they are causing mobile motion. The present MCR study tracked foot and mobile activity at 100 Hz through 3D motion capture in eight infants (*M*=105.38, *SD* = 118.56 days old). Cumulative displacement of the foot was computed for each infant during tethering and differentiated twice using 1-min. wide moving windows, shifted in 10ms increments, to calculate changes in movement rate (acceleration, m/min^2). Linear regression was applied to cumulative displacement during the minute preceding and following each infant's peak acceleration rate. Slopes changed significantly (p <.001) for all infants. Results for one infant are presented in Fig. 1a. The sudden burst in infant activity (i.e., slope increase at 90s) reflects a realization of agency and resembles a (nonequilibrium) phase transition (Fig. 1a). (For comparison, see the laser example, Fig. 1b). Importantly, the burst occurs after a change in coordination within the baby~mobile system. After 60s of tethering, the tethered foot~mobile relationship remains tight, whereas the unconnected foot couplings progressively weaken. All in all, our results suggest that conscious agency emerges as a perceived functional relation between brain, body, and environment. Further tests of the theory and identification of underlying processes are underway.

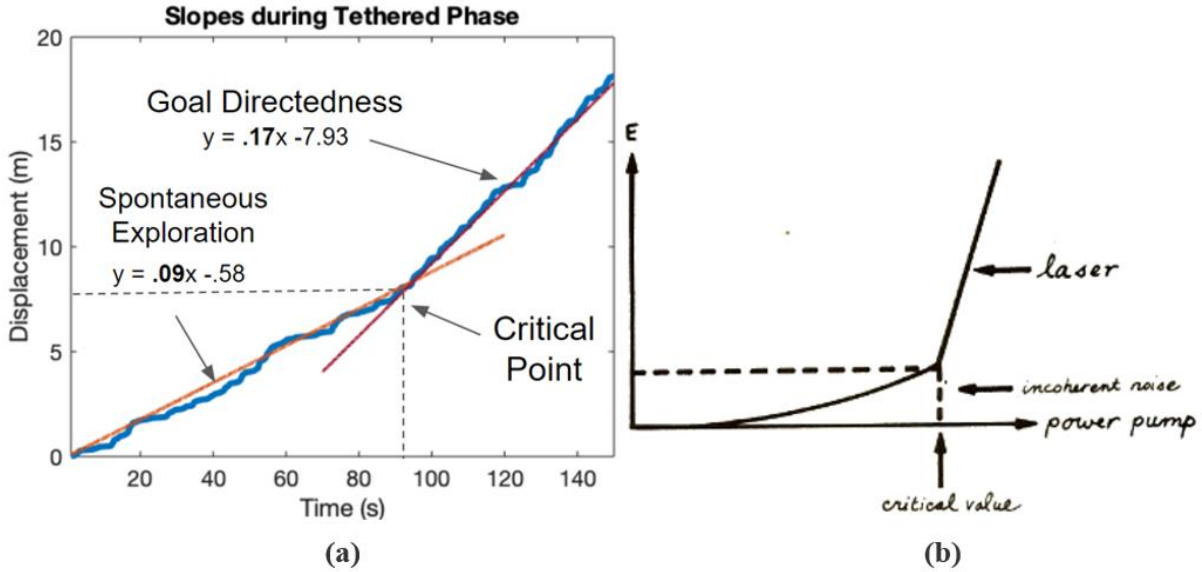


Fig.1 (a) Cumulative displacement (m) of tethered foot. After ~90s of tethering, infant foot movement rate suddenly increases, reflecting a transition from spontaneous to intentional action. (**b) Lasing dynamics.** Above critical pumping power, photons suddenly lock in phase, forming a coherent beam of light, a laser (Careri,1985).

Disclosures: A.T. Sloan: None. **J.A.S. Kelso:** None.

Poster

158. Spatial Navigation: Interactions With Other Cognitive Systems and Abstract Navigation

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 158.10

Topic: H.10. Human Learning and Cognition

Title: Neural signatures of certainty during continual learning

Authors: Q. WANG, P. BANSIYA, N. RABII, *S. NELLI;
Occidental Col., Los Angeles, CA

Abstract: Humans are able to rapidly assemble previously learned knowledge with minimal exposure to new information, while standard neural networks cannot (Nelli et al., 2022). One solution to this problem posits that certainty about relations between items is encoded during initial learning in a way that enables future knowledge restructuring, allowing neural network models to propagate new updates in a way that preserves these relations (Nelli et al., 2022). Interestingly, this certainty code could lead to the “horseshoe” shaped geometry akin apparent in previous fMRI signals (Nelli et al., 2022; Okazawa et al., 2021) as well as EEG (Luyckx et al., 2019). However, it remains unclear whether there is an analogous neural process for maintaining relevant relations while rendering irrelevant ones plastic. Additionally, it is unknown whether the temporal evolution of this signal is related to previous work focused on certainty during decision making (Kiani et al., 2014; Kiani & Shadlen, 2009).
Here, we designed an experiment in which human participants undergoing electroencephalography learned an arbitrary ordering among novel objects to a predetermined threshold (≥90%). Initially, these objects were split into two contexts, and participants were randomly assigned to one of three training curricula designed to manipulate contextual certainty via varying the degree of temporal autocorrelation between the two contexts. Specifically, curricula ranged from (i) “blocked”, in which participants were trained exclusively on how to order items from within one context before moving onto the second (ii) “alternating”, in which participants switched between blocks of trials comprised of items from each context, and finally (iii) “interleaved”, in which trials were randomly sampled within blocks, meaning participants effectively learned the two contexts simultaneously. We report the impact of initial training on participants' ability to assemble the two contexts, and then quantify the neural geometries supporting this behavioral ability using representational similarity analysis.

Disclosures: Q. Wang: None. **P. Bansiya:** None. **N. Rabii:** None. **S. Nelli:** None.

Poster

158. Spatial Navigation: Interactions With Other Cognitive Systems and Abstract Navigation

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 158.11

Topic: H.10. Human Learning and Cognition

Support: ONR MURI N00014-16-1-2832
ONR DURIP N00014-17-1- 2304

Title: Measuring human abstract reasoning with the Abstraction and Reasoning Corpus (ARC)

Authors: *C. AHN[1], Q. DO[1], J. GUO[2], M. E. HASSELMO[2], C. E. STERN[2];
[1]Grad. Program for Neurosci., [2]Psychological & Brain Sci., Boston Univ., Boston, MA

Abstract: Abstract reasoning is a core component of human general intelligence and key to our capacities for flexible problem-solving and decision-making. Despite recent technological advancements, this kind of fluid and flexible intelligence is still lacking in AI. The Abstraction and Reasoning Corpus (ARC) dataset is a set of complex visual reasoning tasks that was first introduced by Francois Chollet in 2019 as a way to measure fluid intelligence in AI programs. We adapted the ARC dataset for use in human subjects in order to better understand how people infer abstract rules and generate novel solutions from limited examples, and accomplish this across a wide variety of tasks. We report preliminary results from a behavioral study testing ARC in healthy young adults. A subset of 75 problems from the ARC set, selected to test a range of reasoning complexity across different conceptual categories, were presented to a group of Boston-area undergraduate and graduate students (n=41, 10 male). The computer-based task was administered online. For each problem, subjects viewed a set of 2-5 example input-output pairs, and were instructed to manually generate their own output solution from a test input by drawing on the task interface with their cursor. Subjects were generally skilled at the task, with mean accuracy of 89.53% (SD=10.24) and error rate of 33.33% (SD=16.19). There was considerable variability between subjects. Reaction time (the time between task load and first action taken) was negatively correlated with problem accuracy, suggesting that an element of intuitive reasoning is involved in solving the task. We manually grouped problems into four main conceptual categories (Object, Geometry, Numbers, Goal-Directedness). Overall, participants were most successful in solving “Object” problems. State space analysis mapping and comparing participants' action sequences per problem revealed a propensity towards object identification and manipulation as the preferred approach to abstract problem-solving. The findings from this study support the validity and usefulness of ARC as a measure of human abstract reasoning that can provide insight into the human-machine gap in fluid intelligence.

Disclosures: C. Ahn: None. **Q. Do:** None. **J. Guo:** None. **M.E. Hasselmo:** None. **C.E. Stern:** None.

Poster

158. Spatial Navigation: Interactions With Other Cognitive Systems and Abstract Navigation

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 158.12

Title: WITHDRAWN

Poster

158. Spatial Navigation: Interactions With Other Cognitive Systems and Abstract Navigation

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 158.13

Topic: H.10. Human Learning and Cognition

Support: NIH K08 NS105929
NIH R01 NS088748
NIH R21 NS122011
CURE Epilepsy
Woodruff Foundation

Title: Modern immersive virtual reality paradigm to investigate feelings of familiarity and déjà vu

Authors: *N. OKADA[1], K. MCNEELY-WHITE[3], T. MCMAHAN[4], T. PARSONS[5], J. NEISSER[6], D. DRANE[1], N. P. PEDERSEN[2], A. M. CLEARY[3];
[2]Neurol., [1]Emory Univ., Atlanta, GA; [3]Colorado State Univ., Fort Collins, CO; [4]Univ. of North Texas, Denton, TX; [5]Arizona State Univ., Phoenix, AZ; [6]Grinnell Col., Grinnell, IA

Abstract: The déjà vu phenomenon - a striking sense of familiarity with a situation while simultaneously feeling a sense of novelty - offers a unique means by which to study human memory. This includes both basic memory process, such as the mechanisms underpinning familiarity, and in clinical populations, particularly in medial temporal lobe epilepsy patients. Prior research has shown that déjà vu can be elicited when the spatial configuration of elements within an environment maps onto previously seen but unrecalled environments. Recent advancements in modern immersive virtual reality (VR) have enabled the development of experiments to fully immerse individuals in spatially distinct scenes. Using immersive VR, we examined how configurational similarity across VR scenes impacts feelings of familiarity and déjà vu. Across three experiments, each with varying levels of immersion (Experiment 1: $N = 56$ remote desktop-based, non-immersive VR; Experiment 2: $N = 62$ in-person laboratory desktop-based, non-immersive VR; Experiment 3: $N = 20$ in-person laboratory, immersive head-mounted displayed-based), participants were presented with test lists consisting of novel visual scenes that potentially shared spatial layouts with previously studied scenes. When participants failed to recall the spatially similar studied scene, they were more likely to find the test scene familiar, either through familiarity ratings (Experiment 1: $p = .002$; Experiment 2: $p < .001$) or through yes-no familiarity judgements (Experiment 3: $p = .002$) if it configurationally overlapped with a

studied scene than if it did not. Furthermore, participants were significantly more likely to indicate a sense of déjà vu for test scenes that spatially corresponded to previously studied scenes (Experiment 1: $p = .01$; Experiment 2: $p < .001$; Experiment 3: $p = .02$). These findings collectively indicate that the virtual environment stimuli developed for this project can be used to study déjà vu experiences, as demonstrated by the increased probability of experiencing déjà vu during retrieval failure. This validated VR paradigm will enable the development of highly controlled ecologically valid experiments to further explore the neural mechanisms underlying familiarity and déjà vu.

Disclosures: **N. Okada:** None. **K. McNeely-White:** None. **T. McMahan:** None. **T. Parsons:** None. **J. Neisser:** None. **D. Drane:** None. **N.P. Pedersen:** F. Consulting Fees (e.g., advisory boards); DIXI Medical USA. **A.M. Cleary:** None.

Poster

158. Spatial Navigation: Interactions With Other Cognitive Systems and Abstract Navigation

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 158.14

Topic: H.10. Human Learning and Cognition

Title: Influence of experience, sex, and sexual orientation on spatial abilities in young adults

Authors: *S. S. ALVAREZ-MERINO[1], N. ANGULO-RUÍZ[2], A. REYES-AGUILAR[1]; [1]Neurocognición Social, Univ. Nacional Autónoma de México, UNAM, MEXICO CITY, Mexico; [2]Univ. Autónoma de Nayarit, MEXICO CITY, Mexico

Abstract: Spatial ability includes representing, transforming, generating, and remembering symbolic information. It involves processes such as perception', mental rotation, and spatial visualization. It has been described that sex and sexual orientation generate differences in performance in spatial ability tasks. Otherwise, indirect training (daily experience) and specific training (specific tasks) improve spatial ability performance. However, the relationship between training, sex, and sexual orientation on spatial abilities is unknown. For this, the main objective was to compare the execution of spatial tasks according to sex, sexual orientation, and the degree of experience in spatial processing in young adults. Healthy volunteers participated (15 heterosexual women, 15 heterosexual men, 13 non-heterosexual women, 11 non-heterosexual men) between 18 and 30 years of age, right-handed, without dependence on any substance of abuse, and with high-level education. Spatial abilities were assessed using the Line Angle and Position-15 (JLAP-15) and Revised Purdue Spatial Visualization Test: Visualization of Rotations (PSVT:R). The spatial experience was recorded with a questionnaire about activities that involve spatial ability performed during the last four months and the hours spent on such activities per month. The preliminary results showed that men outperformed women in both tests: JLAP ($p < 0.01$) and PSVT ($p < 0.01$). No significant difference was detected between sexual orientation. Comparing groups by sex and sexual orientation, JLAP task showed significant differences

between heterosexual women and heterosexual men ($p < 0.05$), and PSVT task obtained significant results between heterosexual women and non-heterosexual men ($p < 0.05$). Finally, positive correlations were found between experience, i.e., number of activities and hours invested in each activity, and performance in both tasks: JLAP (number of activities, $r = 0.38$; hours invested, $r = 0.35$) and PSVT (number of activities, $r = 0.28$; hours invested, $r = 0.26$). We conclude that sex and sexual orientation, as well as training in spatial ability activities, play an important role in the performance of spatial ability tasks, i.e., spatial skills are likely to improve with training.

Disclosures: S.S. Alvarez-merino: None. **N. Angulo-Ruíz:** None. **A. Reyes-Aguilar:** None.

Poster

158. Spatial Navigation: Interactions With Other Cognitive Systems and Abstract Navigation

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 158.15

Topic: H.10. Human Learning and Cognition

Support: NIH R01 NS048281
NSF OIA-1632891

Title: Examining the relationship between visual memory network activation, verbal learning, and memory performance

Authors: *B. S. MITCHELL[1], R. NENERT[2], J. P. SZAFLARSKI[2], S. NAIR[1], J. B. ALLENDORFER[2];
[1]Psychology, [2]Neurol., Univ. of Alabama, Birmingham, Birmingham, AL

Abstract: Memory facilitates engagement with the environment by retaining prior experiences for problem-solving in novel situations by integrating the senses and the context of an experience. A better understanding of memory processing and associated brain networks in healthy individuals allows for a greater understanding of how memory function is impaired in people with memory-related deficits. The current work examined the relationship between memory network activation on a visual scene encoding task during functional magnetic resonance imaging (fMRI) with verbal learning and memory performance. Twenty-four healthy adults completed a 3T MRI scan at the University of Alabama at Birmingham. An anatomical T1 scan and fMRI scans were collected. The fMRI task followed a jittered event-related task design comprised of discriminating between indoor/outdoor scenes (Scene condition) and same/different pixelated images (Match condition). Participants were told they would be tested for memory of scenes after the scan. SPM12 was used for fMRI data preprocessing and analyses. Single-subject general linear modeling was used to contrast fMRI task conditions. A group-level one-sample t-test identified brain regions involved in the visual encoding process while controlling for IQ. Multiple regressions were performed between fMRI task activation (i.e.

contrast of task conditions) with performance on the post-scan memory test and Hopkins Verbal Learning Test - Revised (Learning, Free Recall, and Recognition Discriminability (d') scores). Discrimination accuracy was 88% for Scene and 93% for Match conditions. Post-scan test accuracy was 88%. There was significantly greater activation for Match compared to Scene conditions in the Bilateral Calcarine Cortex and L. Lingual Gyrus [Family Wise Error-corrected (FWE-corr) $p < 0.05$]. Learning scores showed significant positive associations with the magnitude of fMRI activation differences between task conditions in the R. Pallidum, R. Postcentral Gyrus, L. Thalamus, and bilateral Posterior Cingulate Cortex, while d' scores showed significant positive associations with the magnitude of fMRI activation differences between task conditions in the L. Angular Gyrus and L. Cuneus [FWE-corr $p < 0.05$]. The observed pattern of fMRI task activation is consistent with visual network activation specified by a previous model of visual memory encoding (Nenert et al., 2014). Our results extend previous work by identifying activation differences in subcortical, posterior cingulate, visual and parietal regions that are associated with better verbal learning and recognition memory performance.

Disclosures: B.S. Mitchell: None. **R. Nenert:** None. **J.P. Szaflarski:** None. **S. Nair:** None. **J.B. Allendorfer:** None.

Poster

158. Spatial Navigation: Interactions With Other Cognitive Systems and Abstract Navigation

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 158.16

Topic: H.10. Human Learning and Cognition

Support: Postdoctoral Fellowship of Peking-Tsinghua Center for Life Sciences
National Natural Science Foundation of China Grants 31871101 and 32171095
Peking-Tsinghua Center for Life Sciences
National Science and Technology Innovation 2030 Major Program 2021ZD0204103
National Natural Science Foundation of China Grants 31930052

Title: Dynamic emergence of relational structure network in human brains: computational and neural evidence

Authors: *X. REN[1,2], H. ZHANG[1,2], H. LUO[1,2];
[1]Peking Univ., Beijing, China; [2]Sch. of Psychological and Cognitive Sci. and Beijing Key Lab. of Behavior and Mental Health, Peking Univ., Beijing, China

Abstract: Dynamic emergence of relational structure network in human brains: computational and neural evidence Xiangjuan Ren[1,2,3], Hang Zhang[1,2,3,4,5], Huan Luo[1,3,4]1. School of Psychological and Cognitive Sciences and Beijing Key Laboratory of Behavior and Mental Health, Peking University, Beijing, China 2. Peking-Tsinghua Center for Life Sciences,

Peking University, Beijing, China3. PKU-IDG/McGovern Institute for Brain Research, Peking University, Beijing, China 4. Key Laboratory of Machine Perception, Ministry of Education, Peking University, Beijing, China5. Chinese Institute for Brain Research, Beijing, China
Reasoning the hidden relational structure from sequences of events is crucial ability humans possess. Besides simple association-like relationships, humans also excel in learning complex relational networks. Meanwhile, less is known about how the relational network emerges from the human brain through trial-wise learning. Here in two studies, human subjects performed a probabilistic sequential prediction task on image sequences generated from a transitional graph-like network. We recorded their mouse trajectory (study 1) and electroencephalography (EEG) activities (study 2), to access the internal decision process and time-resolved neural mechanism, respectively. In study 1, we designed three independent experiments to examine the contributions of lower-order transition probability and higher-order community structure to the learning performance, which are found to be dissociable at different times within a trial. The learning process could be well captured by a computational model assuming dynamic competition between lower-order transition probability and higher-order community structure learning, with their respective weights updated through a gradient descent algorithm. Moreover, decreasing the autocorrelation of stimuli across trials breaks the equilibrium, leading to dominant reliance on lower-order transition probability. In study 2, EEG recordings reveal the emergence of the lower-order transition probability and higher-order community structure around 840 msec after image onset and well predict behavioral performance. Computational modeling further suggests that the formed higher-order community structure could be well characterized by a successor representation operation. Overall, human brains are constantly computing the temporal statistical relationship among discrete inputs, based on which new abstract knowledge could be inferred.

Disclosures: **X. Ren:** None. **H. Zhang:** None. **H. Luo:** None.

Poster

159. Human Cognition and Imaging: Learning Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 159.01

Topic: H.10. Human Learning and Cognition

Support: NSF Grant CCF183930
NSF GRFP 2139841

Title: A neural manifold learning framework for real-time fMRI neurofeedback

Authors: *E. L. BUSCH[1], J. HUANG[2], A. LETROU[1], G. WOLF[6,7], G. LAJOIE[6,7], S. KRISHNASWAMY[2,3,4,5], N. B. TURK-BROWNE[1,3];
[1]Dept. of Psychology, [2]Dept. of Computer Sci., [3]Wu Tsai Inst., [4]Program in Applied Mathematics, [5]Dept. of Genet., Yale Univ., New Haven, CT; [6]Mathematics and Statistics Dept., Univ. de Montréal, Montreal, QC, Canada; [7]Mila - Quebec AI Inst., Montreal, QC, Canada

Abstract: Why are some skills easier to learn than others? Learning a new behavior may be constrained by the geometry, or intrinsic manifold, of neural activity supporting that behavior. Through an invasive brain-computer interface (BCI), non-human primates can learn to operate a prosthetic device more efficiently when it is controlled by neural activity on versus off the intrinsic manifold of their motor cortex. We explore how this principle might explain human performance in BCI learning using noninvasive fMRI neurofeedback. Understanding how the intrinsic manifold constrains human learning could be used to optimize neurofeedback and accelerate training. In our framework, we introduce two main methodological advances integral to the use of intrinsic manifolds in fMRI neurofeedback. First, we designed a novel method, T-PHATE, that learns the intrinsic manifold of fMRI data in single subjects by accounting for the noise characteristics and spatiotemporal autocorrelation of BOLD activity. Compared with traditional linear dimensionality reduction methods like PCA, T-PHATE captures the dynamics of task-evoked brain activity in a small number of nonlinear dimensions, which can be mapped easily onto neurofeedback signals. However, nonlinear manifolds such as those learned with T-PHATE do not readily extend to out-of-sample data. This poses a challenge for use in real-time fMRI where models are trained incrementally on preceding data and tested online with new incoming data. Using a manifold representation of brain activity to inform the neurofeedback signal requires placing these new data on an existing manifold. Thus, we designed the manifold-regularized multidecoder autoencoder (MRMD-AE), a flexible solution that learns a common latent space across multiple subjects while respecting individual manifold geometry and allowing new datapoints to be embedded onto a pre-trained T-PHATE manifold. With MRMD-AE, we can pre-initialize models for online use as well as probe the similarity of BCI learning across subjects. Using T-PHATE and MRMD-AE together in a real-time fMRI neurofeedback experiment allows us to ask important questions about how humans learn to generate and regulate brain activity patterns via neurofeedback. This framework holds important applications for optimizing neurofeedback learning, informed by the intrinsic properties and plasticity of neural circuitry.

Disclosures: E.L. Busch: None. **J. Huang:** None. **A. Letrou:** None. **G. Wolf:** None. **G. Lajoie:** None. **S. Krishnaswamy:** None. **N.B. Turk-Browne:** None.

Poster

159. Human Cognition and Imaging: Learning Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 159.02

Topic: H.10. Human Learning and Cognition

Title: Neural mechanisms of Alpha and Delta (α-δ) quasi-stable oscillation's association during different phases of the Wisconsin Card Sorting Task

Authors: *E. RAJ[1,2], S. AGRAWAL[2], V. CHINNADURAI[2];
[1]Thapar Univ., Thapar Inst. Of Engin. And Technology, Patiala, New Delhi, India; [2]Cognitive Control and Machine Learning Ctr., Inst. of Nuclear Med. and Allied Sci., New Delhi, India

Abstract: The neural mechanisms of alpha-delta (α-δ) oscillation's interaction that explain local and global neural engagement during executive function are still poorly understood. Hence, the present study employs the EEG microstate analysis with Associative Rule Mining and Dynamical Functional Connectivity (DFC) measures to decipher neural mechanisms of α-δquasi-stable oscillation's association during various phases of the Wisconsin Card Sorting Task (WCST). Simultaneous EEG - fMRI data of 20 healthy volunteers(ages: 18 to 30) while performing WCST is acquired and preprocessed. The distinct quasi-stable microstates are estimated in α and δfrequencies and back-fitted at every individual data. The associative rule mining technique further estimated the mutual associations of back-fitted time-series α and δ frequencies. The significant quasi-stable α-δ associations are further subjected to fMRI GLM modelling as covariates to identify their neural correlates. Finally, the distant cortical interactions between the identified neural correlates of significant quasi-stable α-δ associations atdifferent phases of WCST are analysed using the dynamical functional connectivity approach. The quasi-stable α and δ oscillations were significantly associated with a min confidence level of 0.33, 0.28 and 0.31 during the correct, perseverative, and non-perseverative error phase. Further, neural correlates of these significant quasi-stable α-δ microstates and their mutual dynamical functional connectivity (Fig 1) revealed distinct cortical engagement in each WCST phase. Significant visual and motor engagements during perseverative error and robust global interactions of frontal, motor and parietal regions are observed during non-perseverative error phases. The correct task engagement revealed significant elicitation of temporal and limbic interactions. These distinct cortical sources of quasi-stable α-δ associationsconfirm the unique global and local engagement and distinct cognitive flexibility and executive functions of different phases of the WCST task.

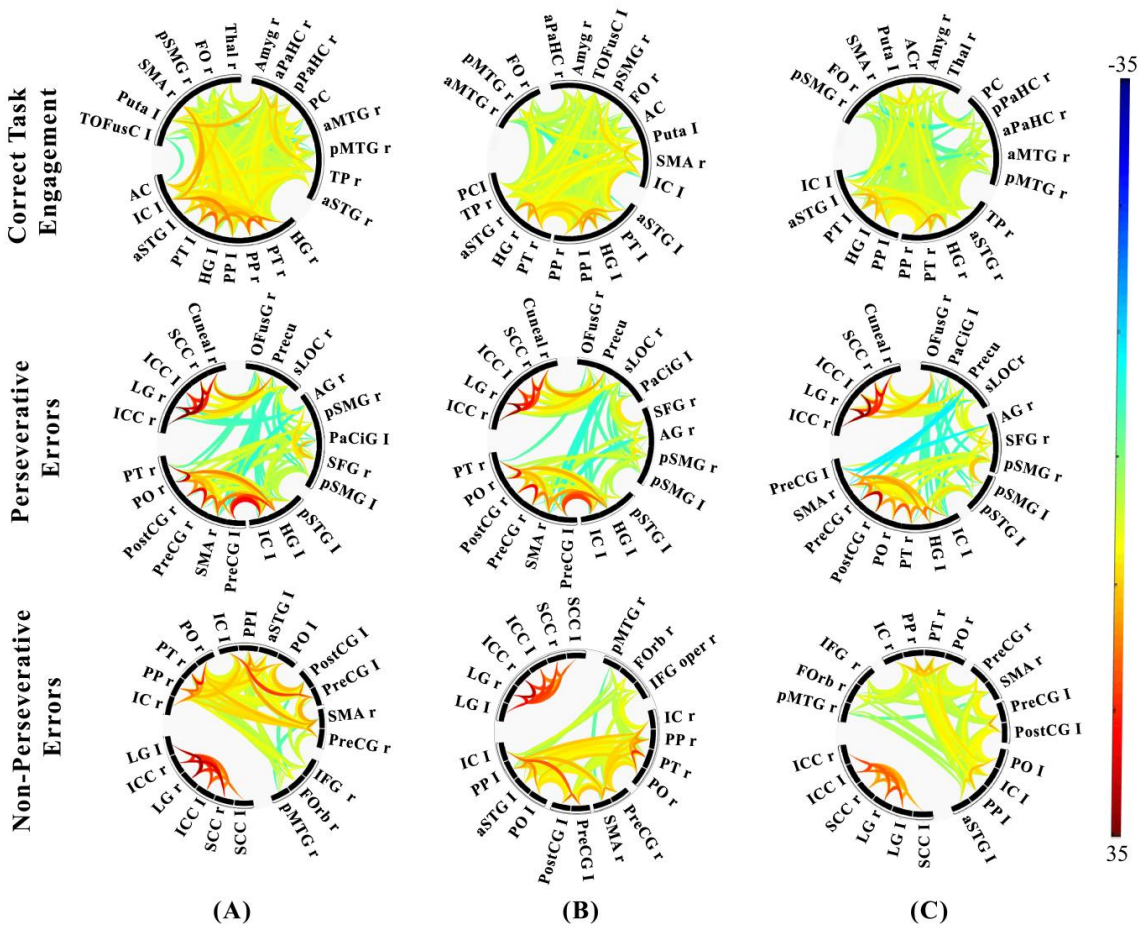


Fig 1: Spatial patterns of DFC matrices of distinct phases of WCST estimated over the time.A. Initial Stage, B. Intermediate Stage, C. Final Stage of WCST. Regions of connectivity matrices are selected from the significant neural sources of α and δ frequency-microstate associations.

Disclosures: **E. Raj:** None. **S. Agrawal:** None. **V. Chinnadurai:** None.

Poster

159. Human Cognition and Imaging: Learning Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 159.03

Topic: H.10. Human Learning and Cognition

Support: R01 DC015426-06
National Institute on Drug Abuse Intramural Research Program

Title: Orbitofrontal network-targeted TMS disrupts midbrain signaling of identity prediction errors

Authors: *Q. LIU, T. KAHNT;
Natl. Inst. on Drug Abuse Intramural Res. Program, Baltimore, MD

Abstract: Previous work in rodents and humans has shown that the orbitofrontal cortex (OFC) represents the identity of expected rewards. Single unit and functional magnetic resonance imaging (fMRI) activity in the dopaminergic midbrain responds to reward identity prediction errors, that is, value-matched mismatches between expected and received reward identity. We hypothesized that reward identity expectations in the OFC directly contribute to the computation of identity prediction errors in the midbrain. To test this, we used network-targeted transcranial magnetic stimulation (TMS) to modulate activity in the lateral OFC network bilaterally. Thirty-one healthy human subjects performed a trans-reinforcer reversal learning task inside an fMRI scanner in two separate sessions (order counter-balanced); once after sham stimulation and once after 40 seconds of continuous theta burst stimulation (cTBS) on each hemisphere. Stimulation coordinates in the left and right lateral prefrontal cortex (LPFC) were individually selected based on maximal resting-state fMRI connectivity with seed regions in the left and right lateral OFC, respectively. The trans-reinforcer reversal learning task required subjects to learn the associations between visual cues and equally-valued food odor rewards. Unpredictably for the subject, these associations were reversed multiple times throughout the task. Subjects responded faster on trials following a reversal compared to reversal trials ($p < 0.0012$). This effect was larger after cTBS relative to sham in the first block of the experiment ($p < 0.008$), suggesting that TMS affected behavioral adjustments after reversals. Consistent with previous findings, fMRI activity in the midbrain, OFC, LPFC, medial prefrontal cortex, posterior parietal cortex, and insula was significantly ($p < 0.001$) correlated with identity prediction errors, showing increased responses on reversal trials compared to the trial after the reversal. Importantly, these responses were significantly attenuated by cTBS relative to sham (midbrain: $p < 0.037$, OFC: $p < 0.028$, LPFC: $p < 0.001$, all FWE small-volume corrected), indicating that OFC network-targeted TMS disrupted the neural coding of identity prediction errors. These results suggest that representations of expected outcome identity in the OFC directly contribute to signaling of identity prediction errors in the midbrain, presumably by providing the predictions necessary for computing the error signal. Together, our findings support a model in which midbrain identity errors are generated by comparing incoming sensory information with outcome identity expectations represented in the OFC.

Disclosures: Q. Liu: None. **T. Kahnt:** None.

Poster

159. Human Cognition and Imaging: Learning Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 159.04

Topic: H.10. Human Learning and Cognition

Support: R01MH128187

Title: Neural encoding of risk and reward responses utilizing temporal difference learning parameters in the human brain

Authors: *R. COWAN[1], T. S. DAVIS[1], B. KUNDU[1], J. ROLSTON[2], E. H. SMITH[1]; [1]Dept. of Neurosurg., Univ. of Utah, Salt Lake City, UT; [2]Dept. of Neurosurg., Brigham & Women's Hosp., Boston, MA

Abstract: Optimal decision-making is modified and updated by previous experiences, uncertain environments, expectation, and prediction error (PE). For some individuals, decision-making is also modulated by maladaptive tendencies such as impulsive choice: a facet of impulsivity that leads to one opting for smaller, immediate rewards over larger, delayed rewards. To extend understanding of the neural basis of impulsive choice, we fit temporal difference (TD) learning models to behavior and broadband high frequency activity (70-150Hz) of 37 human neurosurgical patients performing the Balloon Analog Risk Task (BART). BART uses trials with increasing levels of pop risk relative to balloon color yellow, orange, and red, to assess impulsivity (measured as the Kullback-Leibler divergence (KLD)) between active and passive inflation time distributions. We categorized each subject as more impulsive (MI) or less impulsive (LI) using a gaussian mixture model on the log KLD values and estimated subject-specific optimal learning rates (α) for risk (cue-aligned responses to balloon appearance and color) and reward (outcome-aligned responses to points gained or balloon popped) TD learning models, using maximum likelihood estimation. Next, we verified whether α related to each subject's impulsivity score and depended on neural and behavioral risk and reward outcomes. Finally, we observed the gray matter brain regions preferentially encoded by risk value and PE and reward value and PE. We expected MI subjects to have greater task accuracy but reduced total points, therefore, we expected optimal α's for reward to differ between MI and LI subjects. As expected subjects were significantly less accurate for red balloons (65.5% ± 14.8) compared to orange (87.8% ± 8.1; $t(72) = -8.013$, $p < .001$) or yellow balloons (85.9% ± 8.9; $t(72) = -7.155$, $p < .001$). Linear regression revealed that increased impulsivity significantly predicted greater task accuracy ($R^2 = .223$, $F(2, 35) = 10.0$, $p = .0032$; $\beta = 7.86$) and a reduction in active trial points ($R^2 = .253$, $F(2, 35) = 11.8$, $p = .0015$; $\beta = 1820.6$). We found no differences in α's for risk and reward models based on KLD scores ($p > .05$).We report a higher percentage of significant electrode contacts for LI subjects compared to MI subjects for risk value (38.71%, 23.18%; $X^2(1) = 79.53$, $p < .01$) and for risk and reward value (15.51%, 10.82%; $X^2(1) = 13.57$, $p < .01$) preferentially encoded in the insula, middle temporal gyrus, and middle frontal gyrus regions (all other p's $> .05$). Impulsivity correlates to HFA encoding of risk and reward value providing insight to the neural underpinnings of impulsivity, addiction disorders, and decision-making.

Disclosures: R. Cowan: None. **T.S. Davis:** None. **B. Kundu:** None. **J. Rolston:** None. **E.H. Smith:** None.

Poster

159. Human Cognition and Imaging: Learning Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 159.05

Title: WITHDRAWN

Poster

159. Human Cognition and Imaging: Learning Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 159.06

Topic: H.10. Human Learning and Cognition

Support: NSF GRFP

Title: Reward prediction error modulates sustained attention

Authors: *J. E. TRACH[1], J. BURDE[1], M. T. DEBETTENCOURT[2], A. RADULESCU[3], S. D. MCDOUGLE[1];
[1]Yale Univ., Yale Univ., New Haven, CT; [2]Univ. of Chicago, Univ. of Chicago, Chicago, IL; [3]Ctr. for Computat. Psychiatry, Mount Sinai, New York, NY

Abstract: Attention and reinforcement learning (RL) are intertwined. While previous work has highlighted how selective attention shapes RL, the relationship between sustained attention, the ability to maintain a consistent attentional state over an extended temporal window, and RL has not been systematically explored. In addition, previous work primarily focuses on how attention might constrain RL, rather than asking if and how the dynamics of learning could influence attentional state. Here, we leverage reinforcement learning theory to investigate the moment-to-moment influence of rewards and reward prediction errors on sustained attention. Specifically, we integrate a continuous performance task with a probabilistic RL task in order to assess how trial-by-trial rewards and reward prediction errors (RPEs) might affect ongoing attentional vigilance. We tested two potential lawful relations between RPE and sustained attention. One possibility is that especially large unsigned RPEs boost attentional vigilance. In other words, surprise - unexpected rewards (positive RPEs) or unexpected omissions of rewards (negative RPEs) - could boost sustained attention. Alternatively, the magnitude and valence (positive or negative) of RPEs could jointly affect attentional vigilance. Some straightforward null hypotheses are that RPEs and sustained attention do not dynamically interact, or that RPEs act to distract subjects, perhaps leading to an inverted relationship between (signed or unsigned) RPEs and sustained attention. Here, we demonstrate that attentional vigilance is boosted by intermittent rewards. In addition, we find that the magnitude and valence (positive or negative) of recent reward prediction errors impacts sustained attention such that especially large, positive RPEs lead to higher attentional vigilance. This finding highlights the influence of RL computations on one's attentional state, and provides preliminary evidence for a potential role of the dopaminergic system in meditating the relationship between learning and attentional control.

Disclosures: J.E. Trach: None. **J. Burde:** None. **M.T. deBettencourt:** None. **A. Radulescu:** None. **S.D. McDougle:** None.

Poster

159. Human Cognition and Imaging: Learning Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 159.07

Topic: H.10. Human Learning and Cognition

Support: NSF Grant 1943767

Title: Contributions of attention to learning in high-dimensional reward environments

Authors: *M. C. WANG[1], A. SOLTANI[2];
[1]Psychological & Brain Sci., [2]Psychological and Brain Sci., Dartmouth Col., Hanover, NH

Abstract: In naturalistic environments, we face many decisions where a multitude of factors and their interactions could determine the reward outcome. The ability to identify and attend to signals that reliably predict reward allows animals to ignore task-irrelevant information, leading to more efficient learning and decision making. Most previous studies on reward learning have focused on environments where only one feature is predictive of reward. Therefore, it is unclear how humans learn and make decisions in environments where multiple features and/or conjunctions of features are informative and moreover, what the role of selective attention might be in these processes. To answer these questions, we examined human behavior (N=67) during a three-dimensional reward-learning task in which reward outcomes for different stimuli (each containing three visual features) could be predicted based on a combination of an informative feature and the conjunction of the other two features. Importantly, although multiple strategies could lead to good performance in this task, efficient and precise learning could be achieved by only keeping track of the values of the informative feature and informative conjunction of features. To understand learning and attentional processes, we fit participants' choice behavior using different reinforcement learning models that associate values with stimulus features, conjunctions of features, and/or each stimulus, and apply different types of value-based attention at the time of choice and/or learning. Using Bayesian Model Selection, we found that choice and estimation of reward probabilities were best described by a model that learned the values of features and conjunctions of features. We also found that attention was controlled by the difference in values and modulated learning and not choice behavior. Finally, instead of being driven by competition between the difference in feature or conjunction values, these two signals influenced attention in a cooperative manner such that attention to one feature was accompanied by attention to the conjunction of the other two features (protected exceedance probability=0.97). Together, our results suggest that when learning in high-dimensional environments, humans direct their attention not only to selectively process informative attributes, but also to find parsimonious representations of the reward environment to achieve more efficient learning.

Disclosures: M.C. Wang: None. **A. Soltani:** None.

Poster

159. Human Cognition and Imaging: Learning Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 159.08

Topic: H.10. Human Learning and Cognition

Support: DoD MURI W911NF2110328

Title: The role of latent learning in human hierarchical behavior

Authors: *C. GROSSMAN[1], J. P. O'DOHERTY[2];
[1]Caltech, Caltech, Pasadena, CA; [2]California Inst. Technol., Pasadena, CA

Abstract: In order to plan complex sequences of behavior to flexibly achieve its goals, the human brain uses an internal model of the relationships between states of the world and how its own actions affect those states. Research supports the idea that the brain uses this type of model of the world, demonstrating a role for prefrontal cortex in representing the model and computing value signals derived from it. But how the brain constructs and updates this model is still largely a mystery. In making efficient use of current information, part of this construction is driven by latent learning: incorporation of information about the structure of the environment that is not immediately reflected in behavior. The subsequent behavioral product of latent learning has been observed for decades but there is still no mechanistic explanation of the process. Understanding latent learning is complicated by the fact that it occurs in the absence of external rewards, necessitating an internal motivation. One possibility is that some latent learning is driven by latent, internal goals (i.e., states with internally-assigned value not currently being pursued). This possibility is inspired by studies of hierarchical behavior in which complex sequences of actions are reinforced at various levels of abstraction by nested subgoals with internal value. Separate lines of this research showed that humans use internal goals to guide hierarchical behavior and that prefrontal cortex is involved in processing the value of internal goals. In these cases, however, the internal goals were the current focus of behavior and were used immediately to learn the value of that behavior. Here, we designed a novel assay of sequential human decision making to elicit hierarchical, model-based behavior that relies on latent learning of environment structure that is driven by latent goals. 18 participants (9 female) completed 4,653 trials and demonstrated this type of behavior, evidenced by optimal choices that could only be made from knowledge of latent subgoals and the structure of the environment. We also designed a new theoretical framework to characterize the hidden variables and computations that the brain uses to produce this behavior. The model is adapted from a model-based version of the options reinforcement learning framework and its simulations accurately recapitulate human decisions. These results provide a novel quantitative framework for understanding hierarchical, model-based behavior. This framework will also be leveraged to test the hypothesis that separate regions of prefrontal cortex integrate internal goals into a model of the world and compute value signals derived from that model.

Disclosures: C. Grossman: None. **J.P. O'Doherty:** None.

Poster

159. Human Cognition and Imaging: Learning Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 159.09

Topic: H.10. Human Learning and Cognition

Title: Revealing neural signals encoding regret

Authors: *H. PARK, S. KIM, B. JEONG;
KAIST, Daejeon, Korea, Republic of

Abstract: Regret is a cognitive process when we make the wrong decision. Humans do better decisions by feeling regret after failure. Despite regret preventing doing the same failure, thus it is an innate cognitive process of humans, feeling too much regret sometimes prohibits optimal decision making. In some anxiety disorders, they panic because they regret too much for the past failure. We studied how regret occurs using behavioral modeling and electroencephalography. Forty participants performed reinforcement learning tasks in a stable and volatile environment. They were always given two choices, which are set red or blue, and they have the opportunity to earn 10 cents and lose 10 cents respectively. A total of 200 trials were performed, and the probability of a good outcome among two choices varied across time. Subjects were informed to maximize reward and minimize punishment, and the final score was given as actual compensation for motivation. They entered 방음실 and measured electroencephalography during the tasks. EEG was wet EEG and had 64 channels. On average, participants received 6742 won (~5 dollars). The average correct rate was 68% for a stable period, and 62% for a volatile period. Both were significantly different from the chance rate and the stable-period correct rate was higher than the volatile-period correct rate. Reward correct rate (blue choices) and punishment correct rate (red choices) were 65%, and 64%, and were not significantly different. Rescorla-Wagner model was utilized to model reinforcement behavior. Regret was higher when the prediction error was high and during the volatile period. They also had higher depression and anxiety scores, which were collected by self-reported questionnaire, when they feel more regret during a volatile period. This result implies that Individuals have lower depression and anxiety when they have the ability to separate irreducible error from individual failure. Individual prediction error and regret were correlated with feedback-related negativity which occurs at the frontal node on 300~400ms after the feedback. From this research, we claim that depression and anxiety differed with the ability to separate irreducible failure from individual failure, and prediction and regret were both represented in FRN.

Disclosures: **H. Park:** None. **S. Kim:** None. **B. Jeong:** None.

Poster

159. Human Cognition and Imaging: Learning Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 159.10

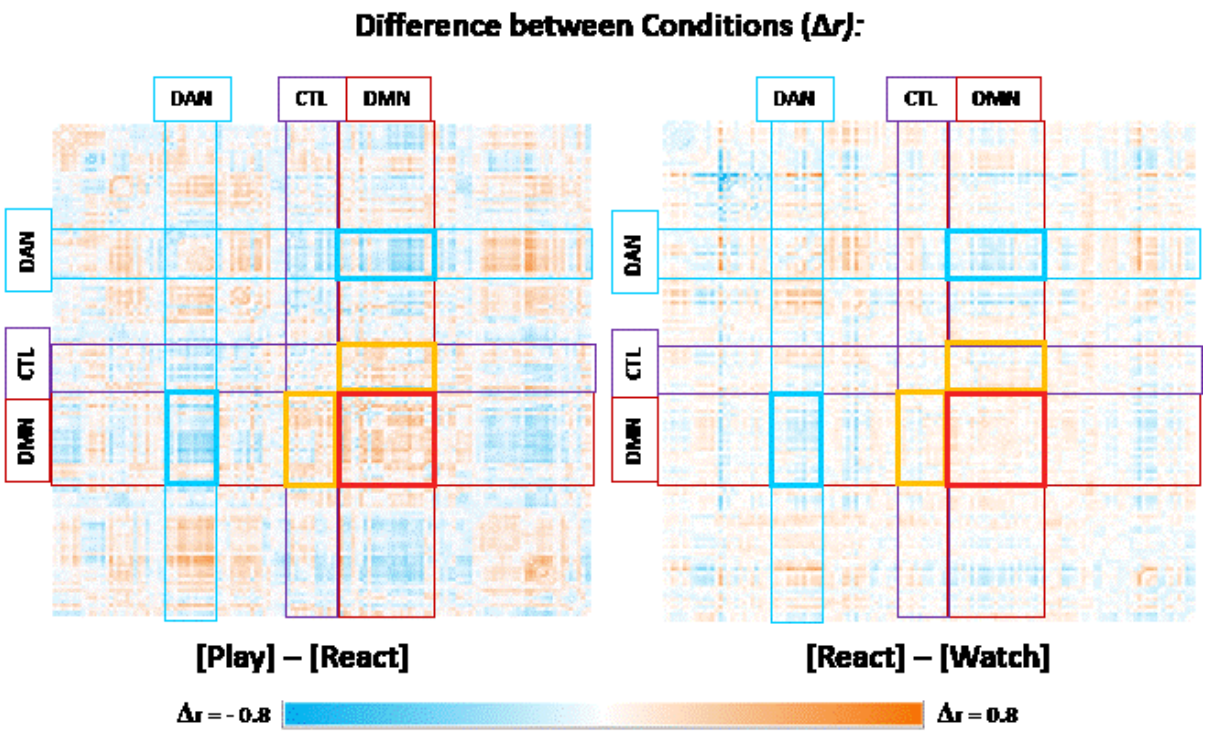
Topic: H.10. Human Learning and Cognition

Support: New Frontiers in Research Fund
Natural Sciences and Engineering Research Council of Canada
Canada First Research Excellence Fund BrainsCAN

Title: Human neuroimaging reveals that agency in a video game boosts functional connectivity within and between brain networks

Authors: *E. J. DAVIDSON[1], K. P. BABIN[1], C. EKSTRAND[4], M. L. ANDERSON[2], J. C. CULHAM[3];
[2]Dept. of Philosophy, [3]Dept. of Psychology, [1]Western Univ., London, ON, Canada; [4]Dept. of Neurosci., Univ. of Lethbridge, Lethbridge, AB, Canada

Abstract: Functional magnetic resonance imaging (fMRI) studies have begun to investigate more natural tasks like movie viewing, which have shown differences in functional connectivity when compared to resting state. We examined whether functional connectivity during a video game, Pac-man, would change with active control, rather than passive viewing, of game events. Right-handed participants (n=24, 14 F, ages 19-36) engaged in three conditions while undergoing 3-Tesla fMRI: Play (active Pac-man control with a game controller), React (reactively following Pac-man actions with a controller while watching the replay) and Watch (passively watching the replay). We computed the temporal correlation between 133 regions within brain networks (including 17 cortical/cerebellar networks) for each of the three conditions. We then compared the strength of intra- and inter-network correlations between conditions. Correlation matrices differed markedly between the Play condition and the React and Watch conditions, which did not significantly differ from one another (shown in figure below). Specifically, during Play, intra-network correlations were significantly stronger than during Play vs. the React and Watch conditions (e.g., areas in specific networks such as the Default Mode Network (DMN) were most strongly correlated with one another during Play). Inter-network correlations also showed large changes between Play vs. the React and Watch conditions, with some networks becoming more strongly positively correlated (e.g., DMN and Control Network, CTL) or more strongly anticorrelated (e.g., DMN and Dorsal Attention Network, DAN). Notably, Play differed considerably from React, even though both conditions were carefully matched for visual stimulation and motor output. This suggests that active control has a large impact on the way brain networks communicate with one another. As such, to fully understand brain function and connectivity in real-life situations, fMRI should investigate participants as agents rather than observers.



Disclosures: **E.J. Davidson:** None. **K.P. Babin:** None. **C. Ekstrand:** None. **M.L. Anderson:** None. **J.C. Culham:** None.

Poster

159. Human Cognition and Imaging: Learning Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 159.11

Topic: H.10. Human Learning and Cognition

Support: KIOM Grant KSN2021240
KIOM Grant KSN2211010

Title: A Neurofeedback Technique for Improving Working Memory Performance: Coupling with Volitional Attention on Breathing

Authors: *C. JUNG[1,2], J. KIM[1], S. EUN[3], K. PARK[2];
[1]Korea Inst. of Oriental Med., Daejeon, Korea, Republic of; [2]Kyunghee Univ., Yongin, Korea, Republic of; [3]Inst. for Basic Sci., Suwon, Korea, Republic of

Abstract: Various studies with neurofeedback have demonstrated that participants were able to regulate their own brain activity by repeated training. Since the training is based on unfamiliar neural activity, how to link a familiar and volitional control to the regulation of brain activity is a

crucial issue for neurofeedback performance. Here, we proposed a respiratory-mediated neurofeedback (RmNF) technique for improving working memory (WM) performance. A multivariate model was built to compute feedback scores of RmNF using our previous fMRI data for delayed-response WM tasks with or without attention on breathing (n = 51), which associated with brain regions for interoception of breathing (i.e., DMN) and working memory performance (R^2 = 0.30 for reaction time). Forty-one healthy participants underwent six fMRI scans for RmNF with the delayed-response WM tasks. The feedback scores were computed and displayed after each RmNF session, which led to find a self-control strategy of brain activity by volitionally adjusting patterns of breathing (i.e., breathing volume and rate). Additionally, baseline and transfer scans were performed before and after RmNF sessions to assess efficacy of the NF training. Our Results, twenty-eight participants (28 out of 41, 68 %) were able to increase feedback scores and their reaction time was improved following RmNF sessions (-85±210 ms, 3%; $p < 0.05$). Moreover, changes of feedback scores showed positive correlation with reduction of their reaction time ($r = 0.42$, $p < 0.01$). Then, reaction time weighted GLMs using concatenated BOLDs for six RmNF runs and baseline/transfer scans were performed to investigate underlying brain mechanisms of the RmNF effect on the reaction time. Whole brain group map demonstrated that right dlPFC, subcortical regions (bilateral thalamus and putamen), pons, and fastigii of cerebellum were associated with reaction time ($z > 3.29$, FWE at $p < 0.01$), as known to be involved in WM performance and respiratory/muscle control. Furthermore, we found interactive connectivity of DMN and fastigii ($p < 0.01$), pons ($p = 0.03$) for RmNF with ROI analysis for psychophysiological interactions. Our study suggested that RmNF may be a putative technique for neurofeedback. The authors declare no competing financial interests.

Disclosures: **C. Jung:** None. **J. Kim:** None. **S. Eun:** None. **K. Park:** None.

Poster

159. Human Cognition and Imaging: Learning Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 159.12

Topic: H.10. Human Learning and Cognition

Support: Social CDT Doctoral Funding

Title: Temporal Characterisation of the Neural Signatures of Appetitive versus Aversive Learning

Authors: *S. WESTWOOD[1], A. VINCIARELLI[2], M. G. PHILIASTIDES[3];
[1]Univ. of Glasgow, GLASGOW, United Kingdom; [2]Sch. of Computer Sci., [3]Sch. of Psychology and Neurosci., Univ. of Glasgow, Glasgow, United Kingdom

Abstract: We recently identified two separate but interacting neural systems associated with outcome valence during appetitive (reward) learning[1]. We showed a fast (Early) system initiates an automatic alertness response following negative outcomes, whereas a slower (Late) system is

consistent with value-updating after both negative and positive outcomes. Here we build on this work to investigate the extent to which these systems are involved in aversive (punishment) learning. We collected data from 33 participants using 64-channel EEG. Participants completed 6 blocks of a probabilistic reversal-learning task (3 appetitive, 3 aversive). These two contexts offered monetary win/no-win or loss/no-loss respectively, indicated with visual feedback. Using single-trial multivariate discriminant analysis, we identified temporal windows where the feedback-locked EEG signal was maximally different between 1) positive and negative outcomes separately for each context and 2) between appetitive and aversive blocks separately for positive and negative outcomes. We determined classification accuracy for each window with leave-one-out cross validation, which we compared to a bootstrapped significance threshold to obtain a temporal range of significant discrimination. Within this range, we identified subject-specific discrimination peaks, from which we extracted scalp topographies and trial-wise discriminant component amplitudes. In line with previous work, the weighted scalp topographies in the positive/negative discrimination formed distinct early and late components at ~240ms and ~400ms respectively. The spatial and temporal signatures were similar across the two conditions, as were behavioural measures such as accuracy and reaction time. However, we observed high classification accuracy in the appetitive/aversive discrimination when run independently for positive and negative outcomes, indicating that there exists a difference at the neural level. One possibility is increased arousal in aversive contexts, as suggested by greater post-feedback pupil dilation. We speculate that these differences could represent an increased vigilance response to facilitate threat avoidance, while at the same time further down-regulate the encoding of the subsequent value-updating in the late system.

References [1] Fouragnan, E., Retzler, C., Mullinger, K., & Philiastides, M. G. (2015). Two spatiotemporally distinct value systems shape reward-based learning in the human brain. *Nature communications*, *6*(1), 1-11.

Disclosures: S. Westwood: None. **A. Vinciarelli:** None. **M.G. Philiastides:** None.

Poster

159. Human Cognition and Imaging: Learning Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 159.13

Topic: H.10. Human Learning and Cognition

Support: 1RF1MH120830-01
R01 MH084840-08A1
T32MH115895

Title: Sleep's role in state-abstraction for sequential reinforcement learning

Authors: *A. JASKIR, M. J. FRANK;
Carney Inst. for Brain Sci., Brown Univ., Providence, RI

Abstract: When trained on specialized tasks, cutting-edge algorithms in deep reinforcement learning (i.e. learning through trial-and-error) can outperform human experts, but humans remain unsurpassed in quickly transferring learning between tasks with shared structure. Drawing upon recent work interfacing computer science and cognitive neuroscience (Lehnert et. al., 2020), we hypothesize humans may form “reward-predictive” state abstractions (RPAs) that support "deep transfer" between tasks. Furthermore, we propose that sleep plays a constructive role in these abstractions, akin to the Complementary Learning Systems framework. Rather than consolidating a specific memory, RPAs form a compressed state-space that allows an agent to exhibit "deep transfer," quickly reusing this compression even when goals and motor actions to achieve those goals change. For example, a musician trained on guitar can generalize a scale from one part of a fretboard to another and can apply this knowledge to speed learning to play a cello, despite differences in the desired song to play or the movements to achieve that song. RPAs comprise a compressed state space that preserves the ability to predict sequences of rewards, and are achieved by clustering states sharing analogous state-action-reward sequences (e.g., all fret positions on a guitar are reducible to twelve unique notes). While deep transfer can be demonstrated through simulations, it requires offline processing to form abstractions. We propose that replay mechanisms during sleep may facilitate their construction in biological agents. We developed a novel sequential decision-making task to test for deep transfer in human behavior and to investigate whether sleep plays a supportive role in this process. Specifically, participants in the Learning Block are asked to learn through trial-and-error which sequences of key presses lead to reward; the sequences share a hidden rule (uninstructed to participants) where pairs of keys can be arbitrarily exchanged in any sequence without affecting the resulting reward order and therefore are compressible. In the Generalization block, the sequence changes but the underlying hidden structure remains. Performance in the Generalization block would be enhanced if participants learn RPAs. Collecting participant data through the online platform Prolific, we demonstrate that human behavior reflects performance enhancements distinctive to RPAs; we further characterize the effects of sleep on this learning process. This work provides insight into the flexibility of human cognition and the underexplored role of sleep in reward learning for facilitating this flexibility.

Disclosures: **A. Jaskir:** None. **M.J. Frank:** None.

Poster

159. Human Cognition and Imaging: Learning Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 159.14

Topic: H.10. Human Learning and Cognition

Support: R21MH118409

Title: Resting state functional connectivity associated with habit and goal-directed learning in adolescent anorexia nervosa

Authors: *C. BROWN[1], A. BISCHOFF-GRETHE[2], C. WIERENGA[3];
[1]UC San Diego, San Diego, CA; [2]UCSD, La Jolla, CA; [3]Psychiatry, Univ. of California San Diego, San Diego, CA

Abstract: Aberrant decision-making is recognized as an important etiological feature of anorexia nervosa (AN). Theoretical models of decision-making outline the influence of two learning systems mediated by separate, yet overlapping, corticostriatal circuits: goal-directed learning reflects controlled actions based on anticipated outcomes, and habit learning reflects automatic and inflexible choices established by previously reinforced actions. Difficulty arbitrating between these systems, resulting in an over-reliance on one strategy over the other, may promote rigid or compulsive behavior in AN (e.g., dietary restriction). However, it is unclear which learning system is most implicated in AN, especially under conditions of loss. Given recent associations between atypical aversive learning and poorer outcomes in AN, this study examined whether 1) reliance on goal-directed or habit learning systems differed between adolescent girls with AN (n=42) and healthy controls (HC; n=24) during a two-step decision-making task involving monetary loss, and 2) whether group differences in resting-state functional connectivity (rsFC), using ventral striatum (VS) as a seed region, were associated with computationally generated decision-making parameters. We fit task data to a reinforcement learning model that incorporates a weighted combination of model-free (MF; i.e., habit) and model-based (MB; i.e., goal-directed) learning. Computational model parameters were estimated using a maximum likelihood procedure, generating a weighting factor (ω) that reflected the degree of MB (ω=1) versus MF (ω=0) behavior. The AN group (M=.35) did not significantly differ from the HC group (M=.40) on ω ($p>.05$), suggesting that both groups employed a similar ratio of MB to MF decision-making strategies during the task. For rsFC analyses, we conducted a group (AN vs HC) by interaction with rsFC of the VS as our dependent variable, controlling for mean-centered age and BMIz. Results suggested higher values are associated with greater rsFC of the VS to the left anterior cingulate, left anterior prefrontal cortex, right dorsolateral prefrontal cortex, right insula, and left postcentral gyrus ($ps_{corrected}$) in AN compared to HC. These findings indicate that, under conditions of punishment, greater rsFC of regions involved in cognitive control is associated with greater goal-directed learning strategies in AN. Despite no behavioral distinctions in decision-making strategies between groups, it is possible that stronger connectivity in these regions are needed to overcome habitual responding to punishment, highlighting important neural alterations in AN.

Disclosures: C. Brown: None. **A. Bischoff-Grethe:** None. **C. Wierenga:** None.

Poster

159. Human Cognition and Imaging: Learning Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 159.15

Topic: H.10. Human Learning and Cognition

Support: R01MH112746
R01MH112688
P50MH119569
Intelligence Community Postdoctoral Research Fellowship Program at Yale University, administered by ORISE through an interagency agreement between the U.S. Department of Energy and the ODNI

Title: Diversity in human use of prototype learning and discriminative attention during latent-state generalization

Authors: *W. PETTINE[1], J. D. MURRAY[2], A. D. REDISH[3], D. V. RAMAN[4];
[2]Dept. of Psychiatry, [1]Yale Univ., New Haven, CT; [3]Dept. Neurosci, Univ. of Minnesota, Minneapolis, MN; [4]Engin. Dept., Univ. of Cambridge, Cambridge, United Kingdom

Abstract: Latent causes that give rise to experience arise from a complex high-dimensional feature space. Current theories suggest that humans approximate this high-dimensional feature space with lower-dimensional internal state representations that generalize to novel examples or contexts. Categorization of latent states can align to two types of mechanisms, one based on discrimination boundaries between categories and the other based on generative prototypes and/or exemplars. To investigate how these two mechanisms interact, we developed theoretical models that form internal state representations through both discriminative and generative components and make decisions through instrumental reinforcement learning (RL). We then developed three new tasks to test the extent to which humans used discrimination boundaries, prototypes, and exemplars, and compared the model against these three human experiments.
In the model, internal state representations are either exemplars of past latent state encounters, or prototypes defined by the mean and covariance of an internal state's past examples. When faced with a decision, the model infers the context, then uses a discriminative component to allocate top-down attention according to which attributes maximally differ in that context. The model contains parameters that adjust the extent to which dimensions contribute to the discriminative boundaries and that allow dimensions to stretch, moving generative states together or apart.
Experiment 1 (online, mTurk, n=107) found that the majority of human subjects (99/107) generalized to novel latent state examples by using discriminative attention to maximally differentiate learned internal states, while a small subpopulation (8/107) failed to generalize over these discriminative boundaries. Experiments 2 (mTurk, n=53) and 3 (mTurk, n=49) identified three subpopulations distinguished by their generalization performance in novel contexts. One subpopulation (39/102) showed state-estimation errors characteristic of our prototype reinforcement learning algorithm. A second subpopulation (20/102) showed state-estimation errors characteristic of failing to develop distinct prototype or exemplar representations in each context. A third population (43/102) showed difficulty maintaining state information during generalization.
These novel tasks provide a comprehensive identification of the key processes that underlie latent state/category learning in humans. The model provides a framework for studying individual differences in these capacities.

Disclosures: W. Pettine: None. **J.D. Murray:** None. **A.D. Redish:** None. **D.V. Raman:** None.

Poster

159. Human Cognition and Imaging: Learning Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 159.16

Topic: H.10. Human Learning and Cognition

Support: NIH Grant R01-MH-112558
NIH Grant R01-MH-097320
ONR Grant N00014-18-1-2306

Title: Representing bad places: Representational similarity of aversively-associated and innocuous visual locations

Authors: *W. FRIEDL[1], A. KEIL[2];
[1]Univ. of Florida, Gainesville, FL; [2]Univ. Florida, Gainesville, FL

Abstract: Distinguishing between potentially threatening and benign objects is a key adaptive feature of the visual system, allowing sighted animals (including humans) to avoid foreseeable harm. Perceptual threat/no-threat decisions are usually assessed with overt behavioral responses that only indirectly reflect the underlying evaluation of sensory evidence. To directly investigate cortical changes associated with aversive associative learning, we applied representational similarity analysis (RSA) to EEG data recorded during a single classical conditioning session. High-density EEG was recorded while 51 healthy undergraduate students (mean age=19.49, 19 male) viewed individually presented, high-contrast Gabor patches appearing at one of five on-screen locations. One spatial location was made to predict an aversive outcome by pairing it with a 90 dB white noise auditory blast for the final 200 (out of 350 total) trials. The representational geometry of each stimulus was evaluated with RSA at each moment in time, separately for trial blocks with and without the aversive auditory unconditioned stimulus (US). RSA characterizes associations between presented stimuli in terms of correlation patterns, abstracting from the activity recorded at the electrodes. Representational distances between aversively-paired and unpaired stimuli were found to vary over time following conditioning. At short post-stimulus onset latencies Gabor patches adjacent to the conditioned location and the conditioned location were similar (i.e. separated by little distance in representational space) to each other and distinct from Gabor patches presented more distally. Later in trials, the adjacent and distal unconditioned spatial locations became more similar to each other and distinct from the conditioned location. Results suggest that associative learning via classical conditioning alters internal representations of the visual environment in a time-dependent manner, with different stimulus features (physical distance vs. US predictive value) driving similarity patterns at different latencies.

Disclosures: W. Friedl: None. **A. Keil:** None.

Poster

159. Human Cognition and Imaging: Learning Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 159.17

Topic: H.10. Human Learning and Cognition

Support: Taiwan Ministry Science and Technology Grant MOST 105-2410-H-002-055-MY3
Taiwan Ministry Science and Technology Grant MOST 107-2410-H-002-124-MY3
Taiwan Ministry Science and Technology Grant MOST 108-2321-B-006-022-MY2
Imaging Center for Integrated Body, Mind and Culture Research, National Taiwan University

Title: Dissociable progressive sequences of neural circuits engaged during active and passive abstract rule inferencing

Authors: *W.-R. LIN[1], Y.-S. SU[1,5], Y.-C. LIN[1], J. O. S. GOH[1,2,3,4];
[1]Grad. Inst. of Brain and Mind Sci., [2]Dept. of Psychology, [3]Neurobio. and Cognitive Sci. Ctr., [4]Ctr. of Artificial Intelligence and Advanced Robotics, Natl. Taiwan Univ., Taipei, Taiwan; [5]Taiwan Intl. Grad. Program in Interdisciplinary Neurosci., Natl. Taiwan Univ. and Academia Sinica, Taipei, Taiwan

Abstract: Inferencing is a key process in intelligent systems like the human brain for updating beliefs about environmental causes and future states. Inferencing can be an active process, in which hypothesis-driven actions manipulate contexts and link beliefs to environmental outcomes, or passive, in which prior beliefs and outcomes have no necessary causal links and posterior beliefs primarily stem from observations of associations. In this study, we evaluated how neural processing during posterior belief integration is distinguished between active and passive inferencing. Twenty human participants (mean age = 23.8, SD = 2.6, 9 females) underwent a visual rule-inference task (VRIT) functional magnetic resonance imaging (fMRI) experiment in which abstract rules mapped color configuration cues to target categories. In the Active condition, participants chose color cues to test their inferences about category rules. In the Passive condition, participants filled in predetermined color cues and also inferred the categories. Feedback was provided based on predetermined cue-category association rules. Behavioral performance times and tries-to-criterion were similar for both inference types, except choosing cues in the Active condition took longer. Critically, when observing cues, bilateral superior frontoparietal and middle frontal responses were higher for Active than Passive conditions. When choosing cues, occipital and fusiform responses were higher for Passive than Active conditions. When categorizing, temporal, anterior cingulate, insula, and putamen responses were higher for Active than Passive conditions. Feedback responses in caudate were higher for Active than Passive conditions. Finally, as rule certainty increased in later than earlier trials, right dorsolateral prefrontal increased more for Active than Passive conditions. These findings characterize progressive stages of neural processing that reflect hypothesis generation, implementation, and integration. Importantly, we identify distinct neural circuits involved in self-determined hypothesis-confirming actions compared to belief formation based on circumstantial information.

Disclosures: **W. Lin:** None. **Y. Su:** None. **Y. Lin:** None. **J.O.S. Goh:** None.

Poster

159. Human Cognition and Imaging: Learning Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 159.18

Topic: H.10. Human Learning and Cognition

Support: NIMH Grant MH116005

Title: Nucleus Reuniens: Modulating Negative Overgeneralization in Peripubertal Anxious Youth

Authors: *M. V. RIVERA NUNEZ[1], D. MCMAKIN[2], A. MATTFELD[1];
[1]Cognitive Neurosci., [2]Psychology, Florida Intl. Univ., Miami, FL

Abstract: Anxiety is a prevalent pediatric psychopathology affecting 4.4 million children in the United States. Its age of onset is between childhood and adolescence (i.e., peripuberty), a period marked by frontotemporal circuitry changes that can impact memory processes. Negative overgeneralization, or responding similarly to innocuous events that share features with past aversive experiences, is a recurrent anxiety-related memory deficit; yet, its neural underpinnings have focused on the role of the amygdala in the modulation of memory. Rodent work has demonstrated that the nucleus reuniens (RE) can exercise top-down control over fear memory by modulating medial prefrontal cortex (mPFC) afferents en route to the hippocampus (HPC). The current study investigated the activation and frontotemporal functional connectivity with the RE as neurobiological mechanisms of negative overgeneralization in anxious youth. We analyzed data from 34 children between 9-14 years of age with varying degrees of anxiety severity. To anatomically localize the RE, we combined probabilistic tractography with a k-means clustering approach based on ipsilateral connectivity to cortical and subcortical structures. During the Study session, participants rated images as negative, neutral, or positive. After 12-hours, participants performed a memory recognition test (Test Session) showing target, foil, and lure images. False alarming (FA) to negative relative to neutral lures was our operational definition of negative overgeneralization. Our results showed elevated RE activation (Study: $t(33) = 2.78$, $p = 0.01$; Test: $t(33) = 2.71$, $p = 0.01$) and functional connectivity with the HPC ($t(31) = 2.63$, $p = 0.01$) for negative compared to neutral images that were overgeneralized. Unlike FA negative images, neutral pictures exhibited decreased functional coupling between the RE and mPFC as anxiety severity increased ($z = -2.82$, $P < 0.01$, 95% CI [-0.04, -0.01]). Additional exploratory analyses revealed the contribution of the RE in the overgeneralization of positive stimuli ($Z = 154$, $p = 0.02$) and reductions in its functional connectivity with the mPFC for neutral relative to positive FA images as a function of anxiety severity ($z = 2.26$, $P = 0.02$, 95% CI [0.00, 0.04]). The present findings support the importance of the RE and its dynamic interaction with the HPC and mPFC as neurobiological mechanisms of negative overgeneralization in anxious youth.

Disclosures: **M.V. Rivera Nunez:** None. **D. McMakin:** None. **A. Mattfeld:** None.

Poster

159. Human Cognition and Imaging: Learning Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 159.19

Topic: H.10. Human Learning and Cognition

Support: 240-846401 NWA Startimpuls 2017
Crossover Program 17619 "INTENSE"
Agreement No. 945539, "Human Brain Project SGA3"

Title: Cells in the human medial temporal lobe are reactivated by pronouns that refer to concepts to which they are tuned

Authors: *D. DIJKSTERHUIS[1], M. SELF[1], J. POSSEL[1], J. PETERS[2], E. VAN STRAATEN[3], S. IDEMA[3], J. BAAYEN[3], S. VAN DER SALM[4], N. KLINK[4], P. VAN EIJSDEN[4], L. KOLIBIUS[5], S. HANSLMAYR[5], V. SAWLANI[6], D. ROLLINGS[6], F. ROUX[6], R. CHELVARAJAH[6], S. DEHAENE[7], P. ROELFSEMA[1,8,3,9];
[1]Netherlands Inst. for Neurosci., Amsterdam, Netherlands; [2]Maastricht Univ., Maastricht, Netherlands; [3]VU Univ. Med. Ctr., Amsterdam, Netherlands; [4]Univ. Med. Center, Utrecht, Utrecht, Netherlands; [5]Univ. of Glasgow, Glasgow, United Kingdom; [6]Queen Elizabeth Hosp., Birmingham, United Kingdom; [7]Univ. Paris Saclay, Paris, France; [8]Academic Med. Ctr., Amsterdam, Netherlands; [9]Sorbonne Univ., Paris, France

Abstract: Language comprehension accumulates over consecutive sentences. During discourse, ideas, actors and concepts that are introduced in one sentence often recur in later sentences. To avoid repetition and minimize utterance length, languages use short grammatical words such as pronouns, like the word "she", to refer to concepts that were introduced before. Language comprehension requires that pronouns activate the same neuronal representations as the concepts themselves. Here, we test this hypothesis on a single cell level by exploiting the ability to record from single neurons in the human medial temporal lobe, which respond selectively to certain people, animals or places. Some of these 'concept cells' respond to both pictures of individuals (e.g. an image of Jennifer Aniston) as well as textual information (e.g. the text 'Jennifer Aniston'). In this study, we recorded from concept cells during a reading task and examined whether pronouns reactivate representations of specific concepts indexed by an earlier noun. We first identified concept cells in the medial temporal lobe of 13 epileptic patients implanted with electrodes as part of their treatment. We then visually presented two sentences, word-by-word (0.5s per word) on a laptop screen. The first sentence contained two nouns and the second sentence contained one pronoun, referring to a previously presented noun (for example '*John* and *Marie* are watching the TV. *She* suddenly changed the channel.'). The subject had to indicate to whom the pronoun referred. Our results show that concept cells (n = 34) gave robust spiking responses to the nouns and they were reactivated by pronouns, but only if they refer to the cells'

preferred nouns ($p < 0.01$, paired t-test). A decoder analysis confirmed this result by showing that pronouns elicit the same neural activity pattern as the preferred noun of a cell, but only when they refer to it. These results imply that concept cells contribute to the rapid and dynamic construction of memory representations that emerge during language comprehension.

Disclosures: **D. Dijksterhuis:** None. **M. Self:** None. **J. Possel:** None. **J. Peters:** None. **E. Van Straaten:** None. **S. Idema:** None. **J. Baayen:** None. **S. van der Salm:** None. **N. Klink:** None. **P. van Eijsden:** None. **L. Kolibius:** None. **S. Hanslmayr:** None. **V. Sawlani:** None. **D. Rollings:** None. **F. Roux:** None. **R. Chelvarajah:** None. **S. Dehaene:** None. **P. Roelfsema:** None.

Poster

159. Human Cognition and Imaging: Learning Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 159.20

Topic: H.10. Human Learning and Cognition

Title: Listening to familiar music enhances visual item sequential learning performance: an fMRI and behavioral study

Authors: *Y. REN, T. BROWN;
Georgia Inst. of Technol., Atlanta, GA

Abstract: Music is a sequential arrangement of pitches and temporal intervals that has a statistical and predictable structure over time. Due to its ubiquitous role in daily life, studying how music interacts with other cognitive processes such as memory could help its utilization in both clinical and applied settings. Memory literature has shown that new information that is associated with a prior memory structure can be learned faster (Van Kesteren et al., 2012). Based on associated “schema theory”, our study used fMRI to investigate how listening to musical sequences with different levels of predictive properties influences parallel visual item sequence encoding.Forty participants learned 36 abstract visual shape sequences with different background music composed by our lab to be monotonic (control condition), syntactically less-regular, and syntactically regular (manipulating how predictive the statistical structure was). Participants learned half of the music stimuli in depth on the first day to manipulate memory of the specific compositions. The second day was composed of visual sequence encoding paired with music of these different features and a retrieval test. Behavioral results showed that participants learned visual sequences faster and better when learned with both less-regular and regular music in the background when compared to the monotonic control condition. Post-hoc comparisons indicated that listening to specifically familiar music (vs. novel) on day 2 facilitated parallel visual sequence encoding. fMRI data showed that during visual sequences encoding, learning sequences with this facilitative familiar music recruited the hippocampus and dorsal striatum more than unfamiliar music. Within familiar music, less-regular music activated ventral striatum more during visual sequence learning than regular music, consistent with a hypothesized role for

prediction errors in music's potential benefits. We also found suppressed activity in the top-down attention network (e.g., superior parietal cortex) for music conditions relative to control, which might suggest more efficient executive control and encoding processes during visual sequence encoding when music with an existing memory trace is played. Our results provide evidences that listening to music might help cross-modal visual sequential learning. Moreover, our data showed that music that was learned previously might show a stronger beneficial effect. Our brain data reveal differences across the medial temporal lobe, reward systems, and the top-down attention network that may underpin how listening to music can result in better learning performance for other elements of our lives.

Disclosures: Y. Ren: None. **T. Brown:** None.

Poster

159. Human Cognition and Imaging: Learning Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 159.21

Topic: H.10. Human Learning and Cognition

Title: Auditory stroop: Probing automatic associations of pitch representation and verbal labels in musicians with absolute pitch

Authors: *D. ROSENZWEIG[1], E. NING[2], O. RACCAH[1], D. POEPPEL[1], C. PELOFI[1]; [1]New York Univ., New York, NY; [2]Univ. of Illinois Chicago, Chicago, IL

Abstract: The automatic association of different stimuli representations constitutes a fundamental component of long-term learning processes. Although all trained musicians form associations between auditory tones and corresponding visual or verbal labels, the mechanisms by which these associations are formed vary across individual and style of musical training. Musicians with absolute pitch (AP) demonstrate an ability to automatically label tones without access to any external reference. AP is acquired in a critical learning period and linked with distinct and identifiable genetic markers. While most experiments studying priming effects for associative learning are tied to visual and language studies, we leverage AP to examine the automaticity of learned associations across auditory and visual modalities in trained musicians. This study uses a novel auditory Stroop paradigm to probe the timing and strength of interference in AP musicians when presented with matched or mismatched auditory tones and visual note labels. We synchronously presented tones and labels across three conditions. In matched trials, tones and labels were congruent (ie. 440 Hz piano note with correct visual label A). In mismatched trials, tones and labels were incongruent (ie. 440 Hz piano note with incorrect label C). In catch-trials, the visual label presented with a tone would not be a musical note (ie. 440 Hz piano note with H). We hypothesized that AP listeners would experience stronger interference for mismatch trials and that this would be reflected in increased differences in RT between mismatch and match trials. We measured AP as a continuous variable (using a pitch labeling test) and picked the 0.25 and 0.75 quantiles of AP ability as two levels to measure RT

differences. For high AP participants, the RT of mismatch trials was longer than that of match trials. For low AP participants, there was no significant difference in RT between match and mismatch trials. These findings indicate that high AP musicians may automatically activate internal representations of linguistic labels when processing auditory tones. This study presents an opportunity to examine how conflicting audiovisual information interferes with automatic associations of pitch categories and verbal labels in trained AP musicians. We now aim to implement the task in an MEG experiment to study neural implementation of how auditory and visual systems converge toward a shared representation of pitch label information.

Disclosures: **D. Rosenzweig:** None. **E. Ning:** None. **O. Raccah:** None. **D. Poeppel:** None. **C. Pelofi:** None.

Poster

159. Human Cognition and Imaging: Learning Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 159.22

Topic: H.12. Aging and Development

Support: Aalto Brain Centre
Academy of Finland
Arvo and Lea Ylppö Foundation
Finnish Cultural Foundation
Finska Läkaresällskapet
Foundation for Pediatric Research
Governmental Subsidy for Clinical Research

Title: Modulation of network functional connectivity between cognitive states is attenuated in school-aged children born extremely preterm

Authors: *M. TOKARIEV[1], V. VUONTELA[1], A. TOKARIEV[2], P. LÖNNBERG[3], A. LANO[3], S. ANDERSSON[3], H. MÄENPÄÄ[3], M. METSÄRANTA[3], S. CARLSON[1];
[1]Dept. of Neurosci. and Biomed. Engin., Aalto Univ., Espoo, Finland; [2]Children's Hospital, BABA Ctr., [3]Children's Hospital, Pediatric Res. Ctr., Helsinki Univ. Hosp. and Univ. of Helsinki, Helsinki, Finland

Abstract: Extreme premature birth (birth < 28th gestational week) may alter emerging neural networks during the early stages of brain development and affect future cognitive performance. Patterns of network functional connectivity (FC) are widely used to characterize the functional brain architecture and to identify connectivity-based features linked with impaired cognition. Moreover, changing cognitive demands result in redistribution of neural resources and flexible modulation of network FC to meet the challenges. This study investigated how extreme prematurity affects the modulation of network FC between resting-state and task performance and whether the differences in FC associate with cognitive performance. We used functional

magnetic resonance imaging (fMRI) during resting-state (Rest) and during the performance of visuospatial n-back tasks (Task), to investigate the reorganization of FC between the cognitive states in two groups of children. Subjects were 7.5-year-old extremely preterm-born children (N=13, 7 males) with normal global cognition and their age- and gender-matched term-born healthy controls (N=13, 6 males). Preprocessed fMRI data from Rest and Task states were used to construct two connectivity matrices (size 90 x 90) for each subject. All the matrices were pulled together and analyzed using the network-based statistics. We found significant between-group differences in network FC. The preterm-born group, compared with controls, demonstrated weaker FC changes between the cognitive states in two network components. The first component was characterized by FC among nodes of the fronto-parietal (FPN), default mode (DMN), visual (VN), and sensori-motor (SMN) networks ($p_{FWE} = 0.039$, Cohen's d = 0.73). The second component showed FC between nodes of the VN ($p_{FWE} = 0.049$, Cohen's d = 0.82). In the second component, the magnitude of the FC change between Rest and Task states correlated significantly with the performance of the n-back tasks: a larger change associated with fewer errors ($R = – 0.40$, $p_{FDR} = 0.045$). The results indicate that extremely preterm-born children fail to tune network resources according to changing cognitive demands and suggest that flexible modulation of network FC between cognitive states supports successful cognitive performance.

Disclosures: **M. Tokariev:** None. **V. Vuontela:** None. **A. Tokariev:** None. **P. Lönnberg:** None. **A. Lano:** None. **S. Andersson:** None. **H. Mäenpää:** None. **M. Metsäranta:** None. **S. Carlson:** None.

Poster

160. Human Memory Throughout Lifespan

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 160.01

Topic: H.07. Long-Term Memory

Support: JSPS KAKENHI Grant: JP20H05802
JSPS KAKENHI Grant: JP21K03128
The Kyoto University Foundation

Title: Dissociable neural mechanisms among subsystems in the default mode network underlying age-related differences in the survival effect on episodic memories

Authors: *Y. SHIOMI[1], R. IZUMIKA[1], M. CHO[1], R. NOUCHI[2], T. TSUKIURA[1]; [1]Cognitive and Behavioral Sci., Kyoto Univ., Kyoto, Japan; [2]Cognitive Hlth. Sci., IDAC, Tohoku Univ., Sendai, Japan

Abstract: The survival effect in memory is defined as the memory enhancement for items encoded in a survival-related context. This effect, which is consistently observed in young adults, is partly disturbed in older adults. Previous studies have demonstrated that the self-referential process and temporal distance from the present are important in imagining survival situations.

However, available evidence is scarce in how the neural mechanisms underlie these processes in the survival effect, and how the mechanisms are different between young and older adults. To tackle this issue, the present fMRI study investigated multivariate activity patterns (MVPA) and functional connectivity in the default mode network (DMN), when 36 healthy young and 36 healthy older adults encoded target pictures by imagining survival-related contexts, which were modulated by two factors of self-reference (Self, Other) and temporal distance from the present (Near, Far). After the encoding with fMRI scanning, outside fMRI, participants were presented with target and distracter pictures one by one, and were required to judge whether each picture was previously learned or not. In behavioral data, compared to the control condition related to the categorical judgment for pictures during encoding, young adults showed a significant survival effect in the retrieval of pictures encoded in survival-related contexts, whereas the survival effects were not significant in older adults. In fMRI data, MVPA for young adults demonstrated that the Self and Other conditions were significantly classified by multivariate activity patterns in the core system of DMN, and that the Near and Far conditions were significantly represented by activity patterns in both core and dmPFC systems of DMN. In MVPA for older adults, multivariate activity patterns in the core, dmPFC, and MTL systems of DMN significantly classified between Self and Other, and between Near and Far. In the functional connectivity analysis, in which the bilateral hippocampal VOIs reflecting the subsequently successful recollection were defined as seed regions, age-related decreases of functional connectivity with the DMN systems were significantly larger in contrasts of Other vs. Self and Far vs. Near than in contrasts of Self vs. Other and Near vs. Far. These findings suggest that roles of the DMN systems in the processing of self-reference and temporal distance from the present related to the survival effect are dissociable between young and older adults, and the dissociation patterns in MVPA and functional connectivity reflect the age-related dedifferentiation.

Disclosures: Y. Shiomi: None. **R. Izumika:** None. **M. Cho:** None. **R. Nouchi:** None. **T. Tsukiura:** None.

Poster

160. Human Memory Throughout Lifespan

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 160.02

Topic: H.07. Long-Term Memory

Title: Memory Consolidation with Orthogonal Gradients for avoiding Catastrophic Forgetting

Authors: *T. KANAGAMANI[1], R. KRISHNAMURTHY[1], S. V CHAKRAVARTHY[1], B. RAVINDRAN[2], R. N. MENON[3];
[1]Dept of Biotech., [2]Dept of Computer Sci., Indian Inst. of Technology, Madras, Chennai, India; [3]Dept of Neurol., Sree Chitra Tirunal Inst. of Med. Sci. & Technol., Trivandrum, India

Abstract: The human brain continuously acquires, processes, and transfers information from the world throughout its lifetime. In this lifelong learning scenario, the brain needs to retain the old information while adapting the new information. The behavior of forgetting old information while learning further information is called catastrophic forgetting/ interference. The human brain effectively avoids this catastrophic forgetting problem, but the models based on deep neural networks fail significantly in preventing this problem. In this way, we are still in an earlier stage of solving this problem of continual learning. Here we propose a regularization-based model to solve the problem of catastrophic forgetting. While training, the network allows the parameters to move orthogonally to the average of the gradients corresponding to the previously learned tasks at the neuronal level. The constraint used in the model follows the locality principle. The performance of the proposed model is evaluated on classification problems and autoencoders by comparing with the Elastic Weight Consolidation (EWC). Among the simple classification tasks (permuted MNIST and split MNIST), the proposed model shows up to 4.71% better average accuracy than EWC. With the core50 dataset (a complex dataset for continual learning), the proposed model shows better average accuracy, up to 6.14%, than EWC on various settings (new Instances and new Classes). In the autoencoder-based task, the proposed model demonstrates a better reconstruction among all the tasks than EWC. The proposed model gives a new view of plasticity at the neuronal level. In the proposed model, the parameter updating is controlled by the neuronal level plasticity rather than synapse level plasticity as in other standard models. The biological plausibility of the proposed model can be explained by relating the extra parameters to synaptic tagging, which represents the state of the synapse which controls the Long Term Potentiation (LTP). We hypothesize that astrocytes could be the key to this synaptic tagging process. The proposed model uses the copy of the average gradients from the previous tasks and the copy of the latest trained parameters, which can be considered tags for individual synapses.

Disclosures: T. Kanagamani: None. **R. Krishnamurthy:** None. **S. V Chakravarthy:** None. **B. Ravindran:** None. **R. N. Menon:** None.

Poster

160. Human Memory Throughout Lifespan

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 160.03

Topic: H.07. Long-Term Memory

Support: by ISF grant No. 1485/18 (SGD)
Bar Ilan University Gonda Multidisciplinary Brain Research Center student travel encouragement scholarship for international conferences (OK, SM)
Bar Ilan University Nassi Scholarship (SM)

Title: Images viewed for longer durations are better remembered during naturalistic encoding

Authors: *S. MASARWA[1], O. KREICHMAN[1], L. BROOK[1], S. GILAIE-DOTAN[1,2];
[1]Bar Ilan Univ., Ramat Gan, Israel; [2]UCL Inst. of Cognitive Neurosci., London, United Kingdom

Abstract: Everyday we encounter many visual scenes, and while freely viewing them only some are remembered. We have recently found that during naturalistic encoding image size influences image memory such that bigger images are better remembered. Here we hypothesized that presentation duration would also influence image memory during naturalistic encoding such that images presented for longer duration would be better remembered. After replicating the image-size-on-memory effect in an online experiment (n=69), we ran an additional online experiment with new naïve participants (n=90). The participants, who were not notified of any memory task that would follow, were asked to freely view the presented images. 160 8°x8° images of faces, people, indoors and outdoors were presented in 4 blocks, each block with specific presentation time (250, 500, 1000, or 2000 ms, ISI completed to 2500ms such that within-block image onsets were always 2500ms apart) and block order and image order within a block were random. They were then given a surprise old-new recognition test (320 8°x8° images, 500ms/image, 50% already seen). The results showed a main effect of presentation duration on memory ($p<0.0001$) with images presented for longer duration remembered better (250ms<500ms<1000ms, post-hoc p's<0.05). As in our previous study, we also found a main effect of visual category on memory with faces best remembered and outdoor scenes the least ($p<0.0001$). Two experimental versions (n1=45, n2=45, each participant participated in only one version) allowed us to also examine exposure duration effect on image memorability (images presented at 250ms in one version were presented at 2000ms in the other version and vice versa, and the same was done for 500ms and 1000ms presentations) and this was also found to be significant. These results further support our hypothesis that without top-down modulations, physical bottom-up image dimensions influence image memory.

Disclosures: S. Masarwa: None. **O. Kreichman:** None. **L. Brook:** None. **S. Gilaie-Dotan:** None.

Poster

160. Human Memory Throughout Lifespan

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 160.04

Topic: H.07. Long-Term Memory

Support: NSF 1651330
NIH R21 DA043568
NIH K01 MH111991

Title: The interaction between the spacing effect and encoding variability over multiple timescales

Authors: *E. T. COWAN[1], Y. ZHANG[2], B. M. ROTTMAN[2], V. P. MURTY[1];
[1]Temple Univ., Philadelphia, PA; [2]Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Our ability to recall long-term memories is critical for helping guide future behaviors. It's been shown that spacing or 'distributing' repeated learning sessions over time, compared to compressing learning into one session, leads to improved long-term memory. However, it remains debated why spacing confers such benefits. It's been hypothesized that with each exposure, the memory is encoded with slight differences, or greater 'encoding variability', resulting from factors like the slow drift in background context. On the other hand, spacing has also been hypothesized to provide an opportunity for consolidation, such that repeated exposure reactivates and further strengthens the stabilized memory trace. To adjudicate between these theories, we designed a large-scale study (N=157) involving a 24-day learning phase (1-4 sessions per day) and a test phase on day 25, which was completed entirely on participants' mobile phones. During the learning phase, participants were shown pairs consisting of one item with either four distinct scenes or one scene repeated four times. To modulate spacing, pairs are shown in a row in the same session, spread across the four sessions within the same day, or across sessions on four consecutive days. In addition to replicating the spacing effect ($p<0.001$), variability seems to benefit item memory over direct repetition, with greater memory for items paired with multiple scenes compared with items repeated with the same scene ($p<0.001$). However, a significant interaction between the spacing and variability conditions ($p=0.0004$) suggests encoding variability may have greater benefits for memory under massed learning conditions compared to longer spacing intervals between learning sessions.

Disclosures: E.T. Cowan: None. **Y. Zhang:** None. **B.M. Rottman:** None. **V.P. Murty:** None.

Poster

160. Human Memory Throughout Lifespan

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 160.05

Topic: H.07. Long-Term Memory

Title: Sleep and consolidation of false memory

Authors: *J. FRANCO[1], R. GREENSPAN[2], E. F. LOFTUS[3], K. M. FENN[1];
[1]Michigan State Univ., East Lansing, MI; [2]Univ. of Mississippi, Oxford, MS; [3]Univ. of California, Irvine, Irvine, CA

Abstract: Sleep is beneficial to the consolidation of veridical memory, but it is not clear if this benefit extends to false memory. In two experiments, we used the misinformation paradigm to investigate how sleep affects false memory. Participants completed three experimental phases - encoding, misinformation, and test. We manipulated the delay interval between encoding and test (Wake and Sleep) and the timing of misinformation. The Wake group completed encoding in the morning and test in the evening. The Sleep group completed encoding in the evening and test

the following morning, after a night of sleep. Half in each delay group received misinformation before the retention interval (shortly after encoding) and the other half received misinformation after the retention interval (shortly before the test). Both experiments followed the same general procedure except for one primary difference. In Experiment 1, participants were warned, prior to the test, that they had been exposed to misinformation but in Experiment 2, participants were not warned. In Experiment 1, the Sleep group performed better than Wake on correct items. For false recognition of suggested items, there was not a difference between Sleep and Wake, however, in the Sleep group, participants who were given misinformation prior to the retention interval showed higher false recognition than those who received misinformation after the interval. In Experiment 2, correct recognition was high for all groups. False recognition of suggested items was higher when misinformation was presented after the retention interval than prior to the retention interval, but false recognition in the Sleep group did not vary based on timing of misinformation, as it did in Experiment 1. Our results suggest that a warning prior to test may enable individuals to monitor their memory to avoid false memory, however, this benefit only emerges when conflicting information is encountered after a period of sleep. We speculate that sleep-dependent consolidation processes strengthen memory and protect it from distortion. In sum, we have provided new data showing that sleep can reduce false memory when conflicting information is encountered after a period of sleep, however, this outcome is contingent on awareness.

Disclosures: **J. Franco:** None. **R. Greenspan:** None. **E.F. Loftus:** None. **K.M. Fenn:** None.

Poster

160. Human Memory Throughout Lifespan

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 160.06

Topic: H.07. Long-Term Memory

Support: NIH R01 MH069456
Canadian Institute for Advanced Research
NIH K01 AA027832
NSF GRFP

Title: Acute stress modulates the use of hippocampal subsystems during learning

Authors: *B. E. SHERMAN[1], I. HUANG[2], E. G. WIJAYA[2], N. B. TURK-BROWNE[1,3], E. V. GOLDFARB[4,1,3];
[1]Psychology, [3]Wu Tsai Inst., [4]Psychiatry, [2]Yale Univ., New Haven, CT

Abstract: Stress is widely considered to negatively impact hippocampal function, thus impairing episodic memory. However, the hippocampus not only supports the distinct, separated representations underlying episodic memory. Rather, it also supports the overlapping, integrated representations underlying statistical learning — our ability to extract patterns across related

experiences. These two functions depend on different pathways in the hippocampal circuit, and rodent work suggests that stress may impair the pathway involved in episodic memory while sparing or enhancing the pathway involved in statistical learning. This leads to the novel hypothesis that stress will enhance statistical learning. Here we assessed how acute stress influences behavioral measures of both statistical learning and episodic encoding. Participants were randomly assigned to either a stress (socially evaluated cold pressor) or matched control condition. To elucidate differential effects of the temporally dynamic acute stress response, participants in the stress condition either had a short (0 minute) or long (10 minute) delay prior to the learning task. In the learning task, participants viewed a series of trial-unique scene images (allowing for episodic encoding of each image), in which certain scene categories reliably followed one another (allowing for statistical learning of associations between paired categories). Participants performed a cover task during learning, enabling measurement of statistical learning via performance benefits for statistically predictable items. Participants returned to the lab 24h later to undergo memory tests. Saliva samples were obtained throughout to measure alpha-amylase (a proxy for the fast-acting adrenergic stress response) and cortisol (a slower-acting stress response). Preliminary analyses indicate that acute stress can indeed enhance statistical learning: although all participants showed improved accuracy for statistically predictable items, only participants in the stress groups exhibited faster response times to predictable items. Notably, episodic memory differed between stress groups (relatively impaired memory in the short-delay group), suggesting that episodic encoding may be modulated by the timing of stress. Ongoing analyses will relate stress-induced alpha-amylase and cortisol responses to modulation of statistical learning and episodic encoding. Together, these data provide novel insight into how stress differentially modulates learning processes supported by the hippocampus, setting the stage for future investigations directly measuring acute stress effects on hippocampal circuitry.

Disclosures: B.E. Sherman: None. **I. Huang:** None. **E.G. Wijaya:** None. **N.B. Turk-Browne:** None. **E.V. Goldfarb:** None.

Poster

160. Human Memory Throughout Lifespan

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 160.07

Topic: H.07. Long-Term Memory

Support: NSF Grant DGE-1258923

Title: Prefrontal cortex-mediated inhibition supports face recognition

Authors: *H. FRITCH[1], B. JEYE[2], D. SPETS[3], R. SCALI[1], P. THAKRAL[1], S. SLOTNICK[1]; [1]Psychology and Neurosci., Boston Col., Chestnut Hill, MA; [2]Psychology, Worcester State Univ., Worcester, MA; [3]Dept. of Psychiatry, Massachusetts Gen. Hospital, Harvard Med. Sch., Boston, MA

Abstract: Inhibitory processes are thought to be important for memory function. A recent behavioral study that employed a face recognition paradigm reported that participants made fewer "old" responses to highly similar faces than less similar faces, providing evidence that memory for faces may rely on related-item inhibition. However, these results could also be explained by a non-inhibitory recall-to-reject process. The current study sought to use fMRI connectivity analysis to distinguish between these hypotheses. Although both hypotheses predict correct rejection of highly similar faces will produce activity in the prefrontal cortex, the inhibition hypothesis predicts negative connectivity between the prefrontal cortex and regions associated with memory retrieval and face processing, whereas the recall-to-reject hypothesis predicts positive connectivity between these regions. During the study phase, participants were presented with male and female faces. During the test phase, they viewed old faces, related face morphs (20-80% similar to old faces), and new faces, and made "old"-"new" judgements. Correct rejection of highly similar face morphs was associated with increased activity in the right lateral prefrontal cortex and negative connectivity between this region and regions associated with face processing and memory retrieval. These results indicate that prefrontal cortex-mediated memory inhibition supports face recognition.

Disclosures: H. Fritch: None. **B. Jeye:** None. **D. Spets:** None. **R. Scali:** None. **P. Thakral:** None. **S. Slotnick:** None.

Poster

160. Human Memory Throughout Lifespan

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 160.08

Topic: H.07. Long-Term Memory

Title: Rapid neocortical integration when encoding new information that relates to existing knowledge networks

Authors: *J. N. COUSINS[1], N. KOHN[1], M. JOOSTEN[2], R. SCARRATT[1], G. FERNANDEZ[1]; [1]Radboudumc, Nijmegen, Netherlands; [2]Radboud Univ., Nijmegen, Netherlands

Abstract: Prior knowledge benefits the long-term retention of new related information, but the extent to which this stems from enhanced encoding or subsequent "offline" consolidation remains unclear. This benefit of prior knowledge is proposed to reflect rapid integration of new information into existing neocortical networks (e.g., mental schemas), although the locus and time course of this integration has yet to be determined, particularly for semantic memories. To examine this, we developed a novel semantic learning task. Subjects (n=31) learned detailed information about 4 amphibians over one week (dense knowledge), while for another 4 amphibians they only learned a name and an image (sparse knowledge). During a subsequent laboratory session, participants knowledge of the dense amphibians was assessed with two-alternative choice questions (knowledge test) before they learned new facts about the same animals (dense and sparse) in the form of paired-associates. These new facts were learned while

undergoing functional Magnetic Resonance Imaging (fMRI) in two sessions (Day-1 and Day-8), each containing 4 blocks of repeated encoding and retrieval of 48 paired-associates without feedback. We found that the encoding of new paired-associates was significantly enhanced for the dense compared with the sparse condition on Day-1, with the effect being largest for the first block of encoding. Consistent with this, we found a positive correlation between the knowledge test and the size of the prior knowledge enhancement for new paired-associates in the first block (dense - sparse), suggesting that those subjects with denser prior knowledge gained a greater advantage during encoding. Retention of dense and sparse paired-associates did not differ across the one week retention interval, indicating no benefit of prior knowledge to consolidation. Retrieval of dense items showed a linear increase in anterior temporal lobe (ATL) activity across the first session, perhaps indicating integration of the new information with established networks of neocortical knowledge in this hub of semantic memory. Together, these findings support the notion that prior knowledge enhances the encoding of new information, and the integration of information into neocortical knowledge networks can occur rapidly across repetitions of encoding and retrieval.

Disclosures: J.N. Cousins: None. **N. Kohn:** None. **M. Joosten:** None. **R. Scarratt:** None. **G. Fernandez:** None.

Poster

160. Human Memory Throughout Lifespan

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 160.09

Topic: H.07. Long-Term Memory

Support: NSF CAREER Award BCS-1752921

Title: Predictive models can learn the spatial transformation of fMRI activity patterns from perception to memory retrieval

Authors: *Z. YE, B. A. KUHL;
Dept. of Psychology, Univ. of Oregon, Eugene, OR

Abstract: Remembering an event from the past involves the reinstatement of initial perceptual experiences. While reinstatement occurs in multiple brain regions-including visual and parietal cortex-and is associated with successful memory retrieval, common measures of reinstatement fundamentally rely on representations during retrieval being the same as those during perception. This reliance on a perception/retrieval match may be suboptimal given recent evidence that, whereas perceptual information is stronger than memory-based information in visual cortical areas, parietal cortex exhibits the opposite bias (Xiao et al., 2017; Favila et al., 2018;). This asymmetry raises the interesting possibility that transformations from visual cortex (perception) to parietal cortex (memory retrieval) are systematic and, therefore, can be predicted. Here, we used fMRI to record neural representations during separate perception and memory retrieval

tasks. Thirty human participants (21 females) first completed a perception fMRI session during which they viewed 80 video clips. Participants then learned associations between each video and a cue word. Finally, participants completed a memory retrieval fMRI session during which they recalled each video as vividly as possible when presented with each cue word. fMRI pattern similarity analyses confirmed an interaction wherein stimuli-specific representations were relatively stronger in visual cortex (lateral occipitotemporal cortex; LOTC) during perception and relatively stronger in parietal cortex (angular gyrus; AG) during memory retrieval. To test whether the memory-based representations in AG were a transformed version of perceptual representations in LOTC, we built a predictive model to map the LOTC activity patterns during perception to AG activity patterns during memory retrieval. Subject-specific models were trained and tested using a leave-one-video-out procedure thereby requiring that the models generalized to new stimuli. We found that activity patterns in AG during memory retrieval were reliably predicted from corresponding activity patterns in LOTC during perception, but, critically, the models were unsuccessful in the opposite direction (predicting LOTC patterns during retrieval from AG patterns during perception). Furthermore, cross-region prediction accuracy from LOTC (perception) to AG (retrieval) was significantly higher than within-region accuracy from AG to AG. Together, our findings provide novel evidence for systematic spatial transformations of neural representations, with perceptual information in visual regions predicting memory representations in parietal cortex.

Disclosures: Z. Ye: None. **B.A. Kuhl:** None.

Poster

160. Human Memory Throughout Lifespan

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 160.10

Topic: H.07. Long-Term Memory

Title: Mechanisms of Retrieval Practice

Authors: *A. T. CAWLEY-BENNETT[1], D. MINONDO[2], S. S. RIVERA[2], J. R. MANNS[3]; [1]Emory Univ., [2]Emory Univ., Atlanta, GA; [3]Emory Univ. Dept. of Psychology, Emory Univ. Neurosci. and Animal Behavior, Atlanta, GA

Abstract: We are better at remembering information that we test ourselves on compared to information we simply restudy. For example, cued recall (table - ????) of a studied word pair (table - window) leads to better subsequent memory for the target word (window) as compared to restudying the word pair. This benefit to memory is termed the retrieval practice effect, or testing effect. Theories regarding retrieval practice disagree as to whether mental effort, word associations, or recollection of the study episode best account for the effect. Theories regarding retrieval practice disagree as to whether mental effort, word associations, or recollection of the study episode best account for the effect. We sought to address this debate by examining how retrieval practice affected subsequent memory for both cue words and target words. The final test

consisted of a yes-no (old-new) recognition memory test in which each trial included a single cue word, target word, or new word. Participants were also asked to make confidence ratings for each yes-no judgment. Performance on the final recognition memory test in the retrieval practice condition was compared to performance in a restudy control condition. In a behavioral experiment that used a cued-recall retrieval practice intervention, final recognition memory performance was significantly better than the control condition for both target words and cue words, although the effect size was smaller for cue words. The benefit to cue words suggested that effortful memory search alone could not account for the retrieval practice effect. Ongoing work with fMRI as well as alternative interventions (e.g., associative recognition memory) in behavioral experiments aim to elucidate further the mechanisms supporting retrieval practice effects. The results of the studies have implications for basic memory research on the retrieval practice effect as well as classroom best practices.

Disclosures: A.T. Cawley-Bennett: None. **D. Minondo:** None. **S.S. Rivera:** None. **J.R. Manns:** None.

Poster

160. Human Memory Throughout Lifespan

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 160.11

Topic: H.07. Long-Term Memory

Support: Wellcome Trust Senior Investigator Award to K.N. (104571/Z/14/Z)
James S. McDonnell Foundation Understanding Human Cognition Collaborative Award (220020448)
Wellcome Centre for Integrative Neuroimaging is supported by core funding from the Wellcome Trust (203139/Z/16/Z)

Title: Comparing how contextual and probabilistic learning guide attentional orienting and subsequent recall.

Authors: *M. SEFRANEK[1], D. DRASCHKOW[1], M. KALLMAYER[2], N. ZOKAEI[1], K. NOBRE[1];
[1]Exptl. Psychology, Univ. of Oxford, Oxford, United Kingdom; [2]Goethe Univ. Frankfurt, Frankfurt, Germany

Abstract: During visual search, previous experience can efficiently focus our attention on an object's likely location, helping to shortcut clutter to find our target. Research has shown that this process is facilitated when learning of target locations is based on spatial contextual associations or probabilistic regularities. Here, we tested how these different types of learning aid the utilization of established memories to guide behaviour. In an online experiment, participants learned associations between targets and unique real-world scenes over two consecutive days. Depending on the scene category, the target consistently appeared at a specific

location (contextual association), within a hemifield (probabilistic association), or at an unpredictable location (random). Participants were faster and more accurate at identifying the target objects on the second day of learning in the contextual and probabilistic association conditions compared to random. On the third day, we evaluated how these different types of associations influence subsequent attentional orienting and memory recall. Participants first performed an attentional orienting task in which targets would appear briefly within a scene in locations abiding by the same rules as learned previously and were asked to identify the target identity. Both types of associations resulted in improved detection of targets that appeared briefly in scenes compared to targets for which there was no consistent association (random). This task was followed by a recall task in which participants had to identify the learned target's location. Both contextual and probabilistic learning led to adequate recall performance. Enhanced performance was most evident when the nature of learned associations aligned with subsequent behavioural tests: probabilistic learning resulted in accurate identification of the target's hemifield and contextual learning improved precise target localisation. Our findings demonstrate how different types of memory can be used to guide subsequent memory and attention. Further, our novel task design provides a promising avenue for studying the neurocognitive mechanism of memory-guided behaviour.

Disclosures: M. Sefranek: None. **D. Draschkow:** None. **M. Kallmayer:** None. **N. Zokaei:** None. **K. Nobre:** None.

Poster

160. Human Memory Throughout Lifespan

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 160.12

Topic: H.07. Long-Term Memory

Support: CX001375
AG066594

Title: Novel news event test is sensitive to mild cognitive impairment and heritable risk for dementia but it is not sensitive to genetic risk factors specific to Alzheimer's dementia

Authors: I. E. ASP[1], A. T. CAWLEY-BENNETT[3], J. C. FRASCINO[4], S. GOLSHAN[1,4], M. W. BONDI[4,2], ***C. N. SMITH**[1,4];
[1]Res. Service, [2]Psychology, Veterans Affairs San Diego Healthcare Syst., San Diego, CA; [3]Psychology, Emory Univ., Atlanta, GA; [4]Psychiatry, Univ. of California San Diego, San Diego, CA

Abstract: Amnestic mild cognitive impairment (MCI) is typically a cognitive risk factor for Alzheimer's dementia (AD), whereas non-amnestic MCI is typically risk factor for other types of dementias (e.g., vascular dementia or Lewy body dementia). Novel tests of semantic memory, such as retrograde memory for news events, are impaired in MCI and may provide a novel way

to assess cognitive risk for dementia. Genetic risk factors can also increase risk for AD and these include traditional measures of genetic risk for dementia (e.g., family history of dementia), as well as measures more specific to AD (e.g., APOE-4 allele and polygenic risk scores). To determine whether retrograde memory is similarly impaired in different subtypes of MCI, we examined memory for news events in older individuals with normal cognition (NC, N=34), amnestic MCI (N=27), and a small group with non-amnestic MCI (N=10) using the novel Retrograde Memory News Events Test (RM-NET). We also collected 3 measures of genetic risk for dementia with increasing specificity for AD to determine if increased genetic risk was related to performance on the RM-NET. The three measures of genetic risk were: family history of dementia, presence of APOE-4 allele, and polygenic risk for AD (Desikan et al., 2017). We asked if news event memory was sensitive to: 1) both amnestic and non-amnestic MCI, and 2) genetic risk for dementia. We found that the both the amnestic and non-amnestic MCI groups exhibited impaired RM-NET accuracy scores relative to the NC group. The effect size was larger in the amnestic group relative to the non-amnestic group. The temporal extent of retrograde amnesia was similar for the two MCI groups and both exhibited 45 years of impaired news event memory (relative to NCs), but spared memory for older news events. For the combined MCI groups (N=37), news event memory scores were lower in individuals with family history of dementia relative to those without such history. Scores were not sensitive to the more specific markers of AD genetic risk (APOE and polygenic risk). For individuals with normal cognition, news event memory was not related to any measures of genetic risk. In summary, MCI is a heterogeneous condition that can be caused by a number of factors that increase risk for dementia, one of which is the brain changes associated with AD. The RM-NET appears to reflect both cognitive risk for AD (and possibly other dementias) as well as heritable risk for dementia that is not specific to AD.

Disclosures: I.E. Asp: None. **A.T. Cawley-Bennett:** None. **J.C. Frascino:** None. **S. Golshan:** None. **M.W. Bondi:** None. **C.N. Smith:** None.

Poster

160. Human Memory Throughout Lifespan

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 160.13

Topic: H.07. Long-Term Memory

Support: NIH R01 MH069456 James S. McDonnell Foundation
https://doi.org/10.37717/2020-1208 NSF GRFP

Title: Subsequent memory in the hippocampus of human infants

Authors: *J. T. FEL[1], T. S. YATES[1], C. T. ELLIS[2], N. B. TURK-BROWNE[1,3];
[1]Dept. of Psychology, Yale Univ., New Haven, CT; [2]Haskins Labs., New Haven, CT; [3]Wu Tsai Inst., New Haven, CT

Abstract: The mature hippocampus supports episodic memory for individual experiences through two neurocomputational processes: pattern separation at encoding, which stores even similar memories distinctively, and pattern completion at retrieval, which reinstates full memories from partial cues. Little is known about the availability of these processes and the role of the hippocampus more generally in episodic memory during the first two years of human life. Results from toddlers indicate that the hippocampus may support retrieval from episodic memory during sleep. However, it remains unclear whether the role of the hippocampus in retrieval extends to infants, whether the infant hippocampus is involved in encoding, and whether this involvement entails pattern separation as in adults. To address these questions, we recorded fMRI activity from awake infants in a subsequent memory task adapted from adult research. Using an event-related design, infants were shown a series of single face, object, and scene images on a dynamic background used to keep attention between images. We assessed memory retrieval for each image by interspersing visual paired comparison test trials into the series. On each test trial, two images were presented on either side of fixation: an old item encoded at a lag of 30-90 s in the past (after intervening items) and a new item from the same category. Recognition memory was quantified as the proportion of looking time to the old item (familiarity preference). We have collected a partial sample of 10 infants aged 6-24 months to date. In a subsequent memory analysis predicting familiarity preference as a binary variable, hippocampal activation was greater during the encoding of images that were later recognized. In a continuous version of this analysis, hippocampal activation was positively related to familiarity preference as a proportion. Patterns of hippocampal activity at encoding were more dissimilar for images that produced a subsequent binary familiarity preference than for images that produced a novelty preference. We take this as evidence for pattern separation of subsequently remembered images. This effect was not observed in the broader medial temporal lobe or in an unrelated control region in early auditory cortex. We are investigating this relationship more continuously across items, hypothesizing that the degree of neural dissimilarity during the encoding of an item will predict the amount of subsequent looking to that item. This work provides an initial look into the computational role of the human infant hippocampus during episodic memory encoding and retrieval, with implications for why infants learn so much but remember so little.

Disclosures: **J.T. Fel:** None. **T.S. Yates:** None. **C.T. Ellis:** None. **N.B. Turk-Browne:** None.

Poster

160. Human Memory Throughout Lifespan

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 160.14

Topic: H.07. Long-Term Memory

Title: Predictive shifts in Object Representations with Statistical Learning

Authors: *D. SINGH, C. V. DONG, M. C. TANDOC, A. C. SCHAPIRO;
Dept. of Psychology, Univ. of Pennsylvania, Philadelphia, PA

Abstract: How do statistical relationships between objects in our environment shape their representations? We previously found that the hippocampus represents pairs of objects more similarly if they reliably co-occurred in a continuous sequence (Schapiro et. al., 2012, Curr. Biol.). But it is unclear whether and how these representational shifts manifest in behavior. Employing color memory as a continuous index of behavioral impact (Chanales et. al., 2021, Psychol. Sci.), we investigated how the strength and direction of co-occurrence statistics change object memory over the course of statistical learning. Participants viewed continuous sequences of colored shapes consisting of pairs, "AB", with asymmetric "A" to "B" transition probabilities. Objects from each AB pair were assigned colors nearby in a 2D slice of CIELAB colorspace. We found that memory for the A member of a pair was systematically distorted towards the color of the B shape over the course of learning, especially for pairs with high A to B transition probability. These findings indicate a warping of representations in the forward temporal direction, perhaps in service of prediction. A 3-layer fully-connected neural network model with an autoencoder architecture resembling the hippocampal monosynaptic pathway (Schapiro et. al., 2017, Philos. Trans. R. Soc. B: Biol. Sci.) was trained on an analogous task. Recapitulating our human behavioral results, we found that systematic shifts in hidden layer representations emerged over training: "A" representations were asymmetrically distorted toward "B", with the magnitude of the shift increasing monotonically with greater transition probability. These representational distortions positively correlated with the asymmetric predictive retrieval of B by the network when presented with A versus the retrieval of A when presented with B. These results indicate that the representational changes in the neural network model were associated with its predictive behavior. Together, our results provide insight into how our memory for an object is shaped by the statistical environment in which it has been experienced.

Disclosures: D. Singh: None. **C.V. Dong:** None. **M.C. Tandoc:** None. **A.C. Schapiro:** None.

Poster

160. Human Memory Throughout Lifespan

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 160.15

Topic: H.07. Long-Term Memory

Support: NIH-NINDS 1R01 NS107727
NIH-NINDS 2R01 NS089729

Title: Differentiation of Episodic Memories for Natural Scene Images Revealed by Natural Language Processing Methods

Authors: *A. BABU[1], B. A. KUHL[2];
[2]Univ. of Oregon, [1]Univ. of Oregon, Eugene, OR

Abstract: Human fMRI studies of episodic memory have found that when memories are highly similar, hippocampal representations are actively differentiated such that pattern overlap is

minimized (Chanales et al., 2017; Favila et al., 2016). Critically, this differentiation is thought to be an adaptive mechanism that reduces memory interference. However, an important open question is whether hippocampal differentiation is associated with changes in the actual qualities of the corresponding memories. Recent behavioral studies have provided some initial evidence that differentiation also occurs in behavioral expressions of memory when recalling highly similar object stimuli that differ along a single feature dimension (Chanales et al., 2021). However, the stimuli that have been used to measure hippocampal differentiation have generally been more complex images of naturalistic scenes that contain many features which could plausibly contribute to differentiation. Here, we used natural language processing methods to measure and quantify the contents of memories for highly similar, naturalistic scene images. In an initial behavioral study, N=187 participants learned arbitrary associations between visual textures (cues) and scene images (associates). Although each scene image was associated with a unique cue, some scenes were from a common category (e.g., pool, library, soccer stadium). Images drawn from the same category were intended to create interference. After extensive cue-associate training, participants were shown each cue and asked to verbally recall each scene. A separate group of participants generated verbal descriptions in a non-competitive baseline task where all images were drawn from distinct categories (i.e., no interference). Verbal descriptions from the competitive memory task and from the baseline task were then transformed into semantic vectors using MPNET, a natural language processing algorithm (Song et al., 2020). We then correlated semantic vectors from the competitive memory task with semantic vectors from the baseline task. We found that similarity (competition) between scene images induced significant ($p < 0.05$) and highly targeted representational changes: namely, semantic vectors in the competitive memory task 'moved away' from the baseline representations of highly similar scene images. These findings indicate that adaptive memory differentiation effects extend to—and can be measured using—verbal expressions of memory for complex naturalistic scenes. These findings also suggest a path forward for linking behavioral and hippocampal measures of memory differentiation—a topic we address with preliminary fMRI data.

Disclosures: **A. Babu:** None. **B.A. Kuhl:** None.

Poster

160. Human Memory Throughout Lifespan

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 160.16

Topic: H.07. Long-Term Memory

Support: EU-M-GATE 765549
European Union's Horizon 2020 Framework Programme for Research and Innovation under the Specific Grant Agreement No. 785907
Foundation Adelis

Title: Forgetting dynamics of items of different categories

Authors: *A. GEORGIOU, M. KATKOV, M. TSODYKS;
Weizmann Inst. of Sci., Rehovot, Israel

Abstract: The amount of forgetting that occurs when a list of items is required to be remembered, largely depends on the type of material being presented. It has been repeatedly shown for example, that images are remembered better than their labels. Nevertheless, the dynamic evolution of forgetting for different kinds of material has not been explored. It is unclear whether the rate of forgetting for items of different categories is the same, leading to retention curves that are scaled versions of each other. Alternatively, rates between categories could be distinctly different, but even then they might differ in a principled way. By using a common experimental paradigm of memory recognition with stimuli of different types (nouns, verbs, sketches and sentences) we were able to directly cross examine the differences in the dynamics of forgetting. Even though we designed the differences between sets to be minimal, such as nouns versus verbs or nouns versus sentences and sketches of the same conceptual items, the obtained curves appear to fall into a discrete non-overlapping spectrum. Furthermore, we have proposed a model of forgetting based on the notion of retrograde interference. Every item is encoded as a multidimensional vector, representing memory valences in different domains. Each newly acquired item is committed to memory and it erases all previously stored items who have dimension-wise smaller values across all dimensions. The model has only one integer parameter, namely the number of dimensions and can be solved analytically. It appears that all measured curves were described well by the model for different values of the parameter, hinting at a potential common underlying mechanism of forgetting.

Disclosures: **A. Georgiou:** None. **M. Katkov:** None. **M. Tsodyks:** None.

Poster

160. Human Memory Throughout Lifespan

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 160.17

Topic: H.07. Long-Term Memory

Support: NRF-2020M3E5D9079908
NRF-2019R1A2C2005213
Neurological Disorder Research Program (NRF-2020M3E5D9079913) of National Research Foundation of Korea
Creative-Pioneering Researchers Program through SNU

Title: Looking into the multi-memory retrieval process with human gaze patterns

Authors: *S. PAENG, H. F. KIM;
Sch. of Biol. Sci., Seoul Natl. Univ., Seoul, Korea, Republic of

Abstract: In real life, one item can be associated with multiple meanings, and people can select and utilize the appropriate one based on the context. This process requires selection from

multiple candidate memories. We sought to understand the cognitive process of how multiple memories are retrieved and selected, using the human gaze patterns guided by the memory of object-associated multiple locations. To do so, we conducted an experiment in which human participants (n=16) learned two locations of each of four objects in the object-location learning task, and tested their memory of object locations in the retrieval task. Both tasks required the participants to respond with a joystick while they were allowed to gaze freely. The gaze patterns were collected with IR-based eye tracker throughout the experiment. The learning task was designed so that the participants could learn all locations associated with the objects one at a time, and was conducted for 5 consecutive days.On each day before the learning task, the object-location retrieval task was conducted. In each trial, one object was shown for 500 ms and turned off. To investigate retrieval behavior through gaze patterns, a delay of 3000 ms followed. Then, a boundary box was shown to indicate which of the two associated locations should be responded by joystick manipulation. The participants successfully learned two associated locations of each object, with the error distance between the responded and correct location in the retrieval task plateauing from day 3 ($1.17 \pm 0.07°$ on the last retrieval day). Analysis of the gaze patterns during the delay period of the retrieval task shows that the participants looked at associated locations, although the screen provided no indication of them. Across all trials, people gazed at the two associated locations before boundary presentation and gazed at the target location after boundary presentation. The portion of the trials in which the participants looked at both associated locations was $45.89 \pm 5.62\%$ on the last day of retrieval. This gazing at learned two locations was retained ($47.07 \pm 5.15\%$) even 3 days after the last learning day, suggesting that memories of multiple locations associated with an object were stored and retrieved simultaneously or sequentially within a trial.Our results show the alternating gaze pattern between the two associated locations until the context is given. Overall, our data imply that the object-location memory retrieval process can be indicated by the gaze patterns of humans. Notably, the behavior of participants alternating their gaze between the two associated locations may provide a starting point in understanding the multi-memory retrieval process.

Disclosures: **S. Paeng:** None. **H.F. Kim:** None.

Poster

160. Human Memory Throughout Lifespan

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 160.18

Topic: H.07. Long-Term Memory

Support: NSERC RGPIN-2017-06753
OGS
Canada Foundation for Innovation and Ontario Research Fund (36601)
CIHR PJT-178337
Brain Canada Future Leaders in Canadian Brain Research Grant

Title: Representational differentiation in flexible category learning

Authors: *Y. XIE, M. L. MACK;
Psychology, Univ. of Toronto, Toronto, ON, Canada

Abstract: Categories in nature often contain exceptions that disobey the perceptual rules followed by most members. Human neuroimaging evidence suggests learning such exceptions relies on the modulation of object representations in the hippocampus, but the representational shifts that are key to learning remain poorly understood. We hypothesize that exception learning involves pattern differentiation—a hippocampal-based function that reduces representational overlap between experiences with shared features—to disentangle exceptions from rule-following items. We aim to elucidate the learning-induced representational shifts by leveraging a clustering model of hippocampal function and representation. Participants (n = 42) learned novel categories in which they encountered rule-followers and exceptions in succession. We fitted the model to participants' category learning performance and extracted participant-specific latent stimulus representations throughout learning. We found that exception learning led to a significant decrease in the representational similarity between rule-followers and exceptions, which indicates that pattern differentiation between these two types of stimuli occurs during the learning. With multidimensional scaling, we further showed that exceptions in each category formed a representational cluster away from the rule-followers and that the differentiated rule-follower and exception clusters constituted a hierarchically structured category representation. To understand the nature of stimulus representations in exception learning, we test how feature dissimilarities (i.e., dissimilarities between stimuli's features), prototype dissimilarities (i.e., dissimilarities to category prototypes), and concept similarities (i.e., dissimilarities between stimuli's category labels) predict the representational similarities of stimuli. We found that feature and prototype dissimilarities, but not concept dissimilarities, were predictive of the model-predicted representational similarities throughout exception learning. This result contrasts with participants' explicit similarity judgments, which were predicted by concept dissimilarities during learning. Altogether, our findings illuminate the latent representational dynamics underlying exception learning. We also provide a novel modeling approach for inferring the representational mechanisms of category learning. With this approach, we generate predictions for future neuroimaging studies on how the hippocampus supports rule-plus-exception category learning.

Disclosures: Y. Xie: None. **M.L. Mack:** None.

Poster

160. Human Memory Throughout Lifespan

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 160.19

Topic: H.07. Long-Term Memory

Support: NSF Grant IIS-1822683
NSF Grant IIS-1822929

Title: Time-dependent contributions of hippocampus and vmPFC to distributed learning

Authors: *F. ZOU[1], T. NASELARIS[2], K. N. KAY[3], B. A. KUHL[1], S. DUBROW[1], J. HUTCHINSON[1];
[1]Dept. of Psychology, Univ. of Oregon, Eugene, OR; [2]Neurosci., [3]Radiology, Univ. of Minnesota Twin Cities, Minneapolis, MN

Abstract: Neuroimaging studies of human memory have reported that when a stimulus is encountered multiple times, greater neural pattern similarity across encounters predicts better subsequent memory (Xue et al., 2010; Ward et al., 2013). However, these studies have not directly considered whether this relationship depends on the temporal spacing (i.e., lag) between encounters. Indeed, prior studies have focused only on short timescales, with repetitions occurring within a single experimental session (and day). In contrast, behavioral studies of memory have consistently shown that the temporal spacing up to years between stimulus repetitions is a powerful determinant of subsequent memory. This raises the important question of whether the relationship between neural pattern similarity and subsequent memory depends on the lag between stimulus repetitions. In particular, it is unknown whether this relationship holds or changes when stimulus repetitions occur across days, or longer. Here, we tested this question in a human fMRI study (Allen et al., 2022) using high spatial resolution (1.8-mm) and ultra-high field strength (7T). Human participants (n=8) performed a continuous recognition memory task across 30-40 fMRI sessions distributed over 8-10 months. Across these sessions, thousands of natural scene images were pseudo-randomly presented up to three times, with a repetition lag (i.e., the delay between the first two presentations) ranging from 4 seconds to 288 days. Consistent with prior behavioral evidence of spacing effects in learning, we found that longer lags between the first two presentations were associated with better subsequent recognition. Additionally, better subsequent recognition was predicted by greater fMRI pattern similarity across stimulus repetitions in parietal, parahippocampal and visual cortical areas and these relationships were robust and consistent across lags (from minutes to months). Strikingly, however, the hippocampus and vmPFC exhibited time-dependent relationships: greater pattern similarity in these regions only predicted better subsequent recognition when stimulus repetitions were separated by a day or more. Follow-up analyses confirmed that these relationships in hippocampus and vmPFC reflected item-specific representations and therefore were not likely to be explained by general learning mechanisms. Together, these findings reveal that the link between subsequent memory and neural pattern similarity depends on the timescales involved between study episodes and further suggest that multiple neural mechanisms might underlie distributed learning.

Disclosures: F. Zou: None. **T. Naselaris:** None. **K.N. Kay:** None. **B.A. Kuhl:** None. **S. DuBrow:** None. **J. Hutchinson:** None.

Poster

160. Human Memory Throughout Lifespan

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 160.20

Topic: H.07. Long-Term Memory

Support: NSF IIS-1822683
NSF IIS-1822929

Title: Non-monotonic coding of recognition memory signals in medial parietal cortex

Authors: *N. D. YOUNG[1], M. PRICE[1], E. J. ALLEN[2], Y. WU[3], T. NASELARIS[4], K. N. KAY[5], J. HUTCHINSON[1];
[1]Dept. of Psychology, Univ. of Oregon, Eugene, OR; [2]Psychology, Univ. of Minnesota, Minneapolis, MN; [3]Univ. of Minnesota, Saint Paul, MN; [4]Neurosci., Univ. of Minnesota Twin Cities Campus: Univ. of Minnesota Twin Cities, Minneapolis, MN; [5]Radiology, Univ. of Minnesota Twin Cities, Minneapolis, MN

Abstract: Whether we recognize something from the past strongly depends on how long it has been since we last encountered it. For over a century, the putative 'trace' of a memory has been argued to decrease in 'strength' or become less accessible gradually over time. In the brain, this is often operationalized as a continuous strength signal that decreases as recognition memory for a given item fades (e.g., as time between study and test increases). There remains substantial debate regarding where and how such a signal might be coded. On the one hand, activity in subregions of medial and lateral parietal cortex has been found to display a log-linear relationship with both subjective estimates of memory strength (e.g., recognition confidence) as well as the duration of time elapsed between a study and test episode (lag). On the other hand, in other studies, activity in parietal cortex has been found to display a discontinuous or non-monotonic relationship with these same variables. Here, we seek to address this apparent ambiguity in the nature of parietal contributions to recognition memory and the often confounded variable of the passage of time. Specifically, we conducted 7T fMRI during a continuous recognition memory task involving a wide range of timescales spanning seconds to months (Allen et al., 2022). Eight participants viewed up to 10,000 unique images repeated up to 3 times each across 30 to 40 scanning sessions distributed over approximately 9 months. This approach allowed us to explore parietal involvement during recognition memory across a wide range of delays as well as investigate how factors that promote recognition memory (e.g., repetition) interact with the passage of time. Consistent with prior literature, we identified multiple regions in parietal cortex whose activity increased or decreased linearly as a function of the logarithm of the lag between study and test episodes. In medial parietal cortex, however, we also found a significant proportion of voxels that expressed a non-monotonic relationship with lag. Distinct sets of voxels showed preferential activation for lags that were between relatively short and relatively long distances of time. Notably, such responses were found despite the nature of the task, which did not explicitly probe judgements of time. Preliminary evidence further suggests that such voxels were arranged in a topographic fashion, wherein voxels sensitive to longer lags were found more anterior and inferior relative to voxels sensitive to intermediate and shorter lags. Taken together, these results suggest that medial parietal cortex supports the encoding of time-dependent recognition using a set of multi-scale basis functions.

Disclosures: N.D. Young: None. **M. Price:** None. **E.J. Allen:** None. **Y. Wu:** None. **T. Naselaris:** None. **K.N. Kay:** None. **J. Hutchinson:** None.

Poster

160. Human Memory Throughout Lifespan

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 160.21

Topic: H.07. Long-Term Memory

Support: NRF of Korea Grant 2020R1A2C2007770
NRF of Korea Grant 2020R1A4A1018714
NRF of Korea Grant 2020M3E5D9079913

Title: Maintenance of goal-dependent contents in the dorsolateral prefrontal and visual cortex during selective long-term memory retrieval

Authors: *J. PARK[1,2], J. KANG[1,2], S.-H. LEE[1,2];
[1]Dept. of Bio and Brain Engin., [2]Program of Brain and Cognitive Engin., Korea Advanced Inst. of Sci. and Technol., Daejeon, Korea, Republic of

Abstract: The relationship between working memory and long-term memory has long been a question of interest in memory research. One major view is that activated features from long-term memory are temporarily retained as working memory depending on the focus of attention. However, neural bases for this conception of working memory as temporary activations of representations remain still elusive. To address this, we performed here an event-related human functional magnetic imaging (fMRI) experiment based on a selective retrieval task comprising separate learning and retrieval sessions. During the learning session, participants memorized scenes in which multiple objects are naturally placed. On the following day, the participants were asked to retrieve a specific cued object from the scenes they had learned as vividly as possible inside the scanner, which was followed by the independent object perception scans. Based on representational similarity analysis (RSA), we found individual cued object-specific response patterns in the visual regions and the dorsolateral prefrontal cortex (dlPFC), which is known to play a crucial role in working memory processes. This indicates the maintenance of cued object information in the dlPFC and visual regions during selective retrieval from long-term memory. Moreover, we also directly compared the response patterns during selective retrieval with the response patterns evoked by object perception and found retention of the cued object but not the non-cued objects in high-level visual regions, including posterior fusiform sulcus (pFs) and lateral occipital cortex (LO). These results demonstrate that goal-dependent selective content retrieved from long-term memory was specifically maintained in the prefrontal and visual cortical areas, which are typically involved in maintaining representations in working memory.

Disclosures: **J. Park:** None. **J. Kang:** None. **S. Lee:** None.

Poster

160. Human Memory Throughout Lifespan

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 160.22

Topic: H.07. Long-Term Memory

Support: R01MH116914
F32MH130027

Title: Dissociation of posterior cingulate contributions to episodic memory

Authors: *S. R. KOSLOV[1], J. W. KABLE[2], B. L. FOSTER[1];
[1]Neurosurg., [2]Psychology, Univ. of Pennsylvania, Philadelphia, PA

Abstract: During episodic memory retrieval human neuroimaging studies routinely observe the engagement of specific cortical regions beyond the medial temporal lobe. Of these regions, posterior cingulate cortex (PCC) is of particular interest given its distinct functional characteristics during different types of retrieval tasks. For example, tasks requiring item-recognition consistently engage dorsal PCC (dPCC), while autobiographical retrieval tasks are associated with ventral PCC (vPCC) activity. Such findings promote a putative dissociation of memory related processes across PCC subregions. Whereby, convergent data suggests that dPCC may support fine-grained memory-based decisions while vPCC supports coarser semantic representation of memory content. To test this dissociation, we took advantage of the recently released Natural Scenes Dataset (Allen et al., 2022), which contains high resolution 7T fMRI data from eight participants as they performed a large number of recognition decisions on a semantically rich database of visual images. Specifically, we hypothesized that activity in dPCC would be associated with memory decisions, but not with semantic representations, while the opposite pattern would be true for vPCC responses. To delineate regions responsive to memory decisions, we compared activity during hits versus correct rejections. Whereas semantic representation regions were identified as those where activity patterns during successful recognition were correlated to a semantic model applied to each image (Google USE_v5). Across individuals, these analyses isolated two distinct regions within PCC, a dPCC localized memory-decision region, and a vPCC localized semantic representation region. Similar to this dissociation, item-representation specificity is hypothesized to shift within the hippocampus from fine to coarse-grained along its posterior to anterior axis, respectively. We found that activity during recognition decisions and rest within dPCC was strongly correlated with the posterior hippocampus, while vPCC activity was more correlated with the anterior hippocampus. While the occurrence of these functional dissociations within PCC were consistently observed, each individual displayed a unique spatial configuration. These findings support growing evidence for an important functional dissociation within PCC during episodic memory decisions, along its dorsal-ventral axis. Furthermore, precision imaging suggests this dissociation displays complex, though predictable, organization across individuals, promoting further use of such methods to better understand PCC functional neuroanatomy.

Disclosures: S.R. Koslov: None. **J.W. Kable:** None. **B.L. Foster:** None.

Poster

161. Spatial Transcriptomics Profiling

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 161.01

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: NIH Grant U01MH10913301
NIH Grant RF01MH117070-01
NIH Grant R21HG009750
Autism Science Foundation

Title: Inducible Calling Cards: a mouse reagent for temporally controlled recording of neural activity and activity-dependent gene expression

Authors: *S. SARAFINOVSKA, A. YEN, K. MCCULLOUGH, A. VENKATESAN, R. MITRA, J. DOUGHERTY;
Washington Univ. Sch. of Med., Saint Louis, MO

Abstract: Genetically identical rodents often display dichotomous behavioral responses, e.g., "susceptible" vs. "resilient", to the same environmental manipulation. In models of addiction and other psychiatric disorders, identifying the molecular landscapes and neural circuits that mediate resilience may lead to new treatments. Resilience implies that a pre-existing factor protects against disease/behavior, so these factors must be recorded or preserved before phenotypic read-out *in the same animal*. Current techniques for molecular read-out require prematurely sacrificing the animal, while phenotypic read-out destroys the molecular state from before the manipulation. Hence, we introduce mJun-iCC, which can nondestructively record molecular states for later read-out.

mJun-iCC introduces temporal control to Calling Cards, a recently published method to record transcription factor-DNA interactions nondestructively in the live mouse brain. With mJun-iCC, we can 1) fluorescently tag transiently active neurons and 2) record their activity-dependent gene expression for post-mortem read-out. To enable temporal control, mJun-iCC contains a tamoxifen-inducible domain, which allows specification of time windows for fluorescent tagging and recording.

Here, we demonstrate proof-of-principle in the mouse CNS that mJun-iCC only records under control of tamoxifen and requires induction by neural activity. We establish this using both fluorescent reporters and next-generation sequencing. Next, to validate the broad applicability of mJun-iCC, we show that mJun-iCC records activity-dependent gene expression in relevant brain regions. Finally, we benchmark the mJun-iCC transgenic reagents and characterize efficacy, general health, and behavior of these animals.

Our results indicate mJun-iCC may uniquely allow retroactive, temporally controlled analysis of molecular landscapes and neural activity *in vivo* prior to environmental manipulation. We anticipate mJun-iCC will have broad applications with epigenetic and circuit mapping and enable significant advancements for neuroscience research in fields including but not limited to addiction resilience, early-life adversity, and social development.

Disclosures: S. Sarafinovska: None. **A. Yen:** None. **K. McCullough:** None. **A. Venkatesan:** None. **R. Mitra:** None. **J. Dougherty:** None.

Poster

161. Spatial Transcriptomics Profiling

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 161.02

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: 1-DP2-ES027992
U01MH117072

Title: Effective preservation of biomolecules in frozen human brain tissues for 3D spatial multi-omic analysis

Authors: *S. CHOI[1], M. E. KIM[1], Y. TIAN[1], L. KAMENTSKY[1], N. B. EVANS[1], J. PARK[1], C. D. KEENE[2], K. CHUNG[1];
[1]MIT, Cambridge, MA; [2]Pathology, Univ. of Washington, Seattle, WA

Abstract: Effective preservation of biomolecules in frozen human brain tissues for 3D spatial multi-omic analysis
Seo Woo Choi, Minyoung E. Kim, Yuxuan Tian, Lee Kamentsky, Nicholas B. Evans, Juhyuk Park, C. Dirk Keene, Kwanghun Chung
Profiling spatial landscape of molecules at cellular resolution can accelerate our understanding of the brain function and dysfunction. While several spatial transcriptomics and tissue processing technologies demonstrated their ability to map mRNAs and proteins in mammalian brain tissues, their application to human brain has been limited due to the challenges in preserving the endogenous molecules, particularly in thick samples. Here, we introduce hSHIELD (human tissue SHIELD: stabilization under harsh conditions via intramolecular epoxide linkages to prevent degradation) that enables maximal preservation of both mRNAs and proteins in thick human brain tissues by modulating the rate of chemical reactions during tissue preservation. hSHIELD allows rapid anchoring of biomolecules during the tissue thawing process to minimize structural damage and the loss of the key biomolecules. Using hSHIELD, we demonstrated uniform preservation of mRNAs and proteins in 4mm-thick cleared human brain slabs and rapid 3D mapping of the molecules at single cell resolution. We anticipate that hSHIELD can provide a simple yet effective method to preserve biological information in human brain tissues which can facilitate the study of human brains at their healthy and diseased states.

Disclosures: S. Choi: None. **M.E. Kim:** None. **Y. Tian:** None. **L. Kamentsky:** None. **N.B. Evans:** None. **J. Park:** None. **C.D. Keene:** None. **K. Chung:** None.

Poster

161. Spatial Transcriptomics Profiling

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 161.03

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Title: Powerful spatial tool reveals neuronal microenvironment changes during neurodegeneration

Authors: B. WANG, R. CHEN, T. WIGGIN, N. FERNANDEZ, Y. SUN, Y. CAI, Y. SUN, *G. EMANUEL, J. HE;
Vizgen, Cambridge, MA

Abstract: Neurodegenerative diseases (NDDs), such as Alzheimer's disease (AD) and Parkinson's disease (PD), have long been recognized among the most debilitating human diseases. Physiological changes during aging accompanied by pathological changes lead to the alteration of the neuronal microenvironment in the brain, which plays a key role in disease progression. However, the underline mechanism of which specific cell types and how they contribute to the cognitive, sensory, and motor declines remains unclear. A powerful spatial tool, such as the MERSCOPE^{TM} Platform, can facilitate a more complete understanding of the microenvironment in NDDs at the cellular and subcellular level and most importantly, in a spatially resolved context. As a result, MERSCOPE^{TM} can help advance the basic research, as well as the discovery and screening of potential drug targets. In this study, we used MERSCOPE^{TM} to perform multiplexed error-robust fluorescence *in situ* hybridization (MERFISH) with RNA-protein codetection on aged human AD and PD patient brains. We used a pre-designed neuro 500-gene panel, which includes various cell type genes, neuronal activity genes, and disease-related genes. Additionally, we included antibody staining targeting cell markers (NeuN, Iba-1, GFAP, MBP, CD31) and disease-driven proteins (Aβ, phosphorylated-tau, α-synuclein, TDP-43). The spatial transcriptomic profiling via MERFISH resulted in detecting 500-1000 transcripts per cell from 500-gene panel and showed high correlations ($r>0.8$) to bulk RNA-seq data. Protein staining identified several specific cell types and various post-translational modified proteins. In human AD and PD brains, we identified more than 30 neuronal activity-related genes significantly reduced, and simultaneously, over 25 disease-related genes increased in NeuN-positive cells. We also observed many immune response-related genes boosted in Iba-1-positive and GFAP-positive cells. Moreover, the spatial metric of genes provided additional comprehensive detail of how these genes and cells were distributed and organized in NDDs. Furthermore, the single-cell analysis identified over 20 clusters of cells which revealed the neuronal microenvironment in each cell cluster. The spatial organization and cell morphology obtained via MERFISH provided deeper insights into both AD and PD. With a powerful spatial tool such as MERSCOPE^{TM} that provides exceptional spatial resolution, throughput, multiplexing power and sensitivity, we can easily understand the genetic mechanisms underlying NDDs which will lead to the development of novel therapeutic interventions for these devastating diseases.

Disclosures: **B. Wang:** A. Employment/Salary (full or part-time):; Vizgen. **R. Chen:** A. Employment/Salary (full or part-time):; Vizgen. **T. Wiggin:** A. Employment/Salary (full or part-time):; Vizgen. **N. Fernandez:** A. Employment/Salary (full or part-time):; Vizgen. **Y. Sun:** A. Employment/Salary (full or part-time):; Vizgen. **Y. Cai:** A. Employment/Salary (full or part-

time):; Vizgen. **Y. Sun:** A. Employment/Salary (full or part-time):; Vizgen. **G. Emanuel:** A. Employment/Salary (full or part-time):; Vizgen. **J. He:** A. Employment/Salary (full or part-time):; Vizgen.

Poster

161. Spatial Transcriptomics Profiling

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 161.04

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Title: An automated variant scoring system to prioritize deleteriousvariant discovery to facilitate diagnosis and treatment of neuropsychiatric conditions

Authors: *A. BASKYS[1], J. G. STENZEL[2];
[1]Med. Ctr., Western Univ. of Hlth. Sci., Pomona, CA; [2]Med., Univ. of Arizona Col. of Med., Phoenix, AZ

Abstract: To facilitate application of next generation sequencing in the clinic, we developed a variant scoring algorithm and show its utility in a clinical example. Whole exome sequencing was performed by Tempus Laboratories(www.tempus.com, NovaSeq 6000). Sequencing data were annotated with SnpEff and SnpSift (Cingolani et al, 2012) and variants called with freebayes (Garrison et al, 2012). Pathogenicity values for each variant were calculated by giving 1 point for each of the following: MAF < 2%, MAF < 0.5%, GERP > 5.5, “High” impact, CADD >20, CADD > 30, CADD > 40, “deleterious” prediction by PROVEAN, SIFT or FATHMM, “deleterious” prediction by either Polyphen2 or MutationTaster. Additional points were given if a variant was deemed “Pathogenic” or “Likely Pathogenic” by ClinVar. These values were multiplied by a SNP weight based as described by OpenTargets Platform (doi.org/10.1093/nar/gkw1055) to obtain a pathogenicity score for each variant. Associated genes were linked to a gene-disease database generated by combining relational data from the highly curated sources DisGenet (Janet et al, 2017) and Human Phenotype Ontology (Sebastian et al, 2008). Using the UMLS Metathesaurus and its associated Semantic Network (Bodenreider, 2004), diseases were mapped to organ systems including nervous and mental disorders. We present a case of a 23 year old man with autism, depression, anxiety and seizures. Thirty three variants were identified automatically and reviewed manually using American College of Medical Genetics (ACMG) guidelines. Three variants were “likely benign”, 23 “uncertain significance,” 3 “likely pathogenic” and 4 “pathogenic.” Of the 7 variants labeled “likely pathogenic” or “pathogenic”, 2 had known gene-disease relationships. One of these 2 variants is located in the Na channel, voltage-gated, type II, alpha subunit (*SCN2A*) gene and the other in the Ca channel, voltage-dependent, P/Q type, alpha 1A subunit (*CACNA1A*) gene. The patient had a rare (GnomAD frequency < 0.00003) missense variant resulting in amino acid change (Arg1902Cys) in *SCN2A* predicted to be pathogenic by ACMG criteria using VarSome calculator (Kopanos et al, 2019). The rs1272886269 variant of the *CACNA1A* gene was found to be a rare (GnomAD frequency <0.000005) splice region variant (1082+1G>A) deemed

pathogenic by ACMG criteria. Both genes are associated with early infantile epileptic encephalopathy and episodic ataxia 2 with *SCN2A* having additional associations with intellectual delay and autism. This case illustrates application of a NGS data integration into a clinical decision-making process to facilitate diagnosis and treatment of neuropsychiatric conditions.

Disclosures: A. Baskys: None. **J.G. Stenzel:** None.

Poster

161. Spatial Transcriptomics Profiling

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 161.05

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Title: High plex in situ profiling of mouse brain sections on CosMx™ Spatial Molecular Imager

Authors: *A. HECK, L. WU, K. YOUNG, N. DUNAWAY, Z. REITZ, E. PIAZZA, M. WALTER, E. BROWN, R. KHAFIZOV, M. RHODES, J. BEECHEM;
NanoString Technologies, Inc., Seattle, WA

Abstract: Spatially resolved transcriptomics is greatly advantageous in the brain where spatial relationships largely define cellular function. Among emerging technologies, CosMx™ Spatial Molecular Imager (SMI) supports high plex detection of RNA with subcellular resolution and delivers highly quantitative results. Here, we demonstrate the capability of SMI to detect ~1000 genes focused on neuroscience. This high plex assay covers robust neural and glial cell typing, neurodegeneration, neurodevelopment, and key aspects of cell state and signaling, including numerous ligands and receptors involved in neuron-glia communication. Using the SMI platform, we collected spatially resolved single-cell data from two fresh frozen, serial whole coronal mouse brain sections from a young adult male mouse and identified 42 cell types. The distribution of these cell types and their marker genes is well aligned with previous reports, and their discrimination enables numerous possibilities for biological inquiry. For example, microglia, the innate immune cell of the brain, surveil and respond to signals from neighboring cells. SMI recapitulates the diverse range of microglial phenotypes, which are highly dependent on the activity of other cells within their local environment. Moreover, we highlight SMI's ability to discriminate among cell types and states involved in adult neurogenesis, a localized and dynamic process that is modulated by glia, as well as stress, disease, and other changes in physiological status. Due to the broad scope of the high plex mouse neuroscience panel and the spatial resolution offered by SMI, it is possible to create a spatial cell atlas of the brain and probe numerous pathways and cellular phenotypes including, but certainly not limited to, the examples provided.

Disclosures: **A. Heck:** None. **L. Wu:** None. **K. Young:** None. **N. Dunaway:** None. **Z. Reitz:** None. **E. Piazza:** None. **M. Walter:** None. **E. Brown:** None. **R. Khafizov:** None. **M. Rhodes:** None. **J. Beechem:** None.

Poster

161. Spatial Transcriptomics Profiling

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 161.06

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: NIDA U01DA043098
Office of Naval Research (ONR) 00014-19-1-2149
The Hope for Depression Research Foundation (HDRF)
The Pritzker Neuropsychiatric Research Consortium

Title: Spatial transcriptomics reveal basal differences in immediate early gene profiles associated with temperament: studies in a rat model of emotional reactivity

Authors: *M. WASELUS, E. HEBDA-BAUER, M. DAI, F. MENG, H. AKIL, S. J. WATSON, Jr.;
Univ. of Michigan, Ann Arbor, MI

Abstract: The selectively-bred lines of high- and low-responder rats (bHR and bLR, respectively) model two temperamental phenotypes representing both contrasting emotionality and reactivity to the environment. These include differences in exploratory locomotion, propensity to self-administer drugs of abuse, and anxiety-like behaviors. Using anatomical methods such as *in situ* hybridization, we have implicated several specific transcripts and brain regions in these behavioral differences. But these classical anatomical tools allow only a finite number of genes to be examined in any given brain structure or subject. Yet, expression profiling (e.g. RNAseq) reveals profound differences between the lines across a large number of transcripts. To better link gene expression regulation with neural circuitry and behavioral outcomes, we relied on an anatomically precise expression profiling approach to capture basal gene expression differences in a regionally defined manner. Spatial transcriptomics solutions such as Visium developed by 10X Genomics combine RNAseq with spatial registration to provide a global picture of RNA expression with anatomical specificity. As a proof of principle, we examined a set of immediate early genes to determine whether there are differences in basal expression between the bHR and bLR lines. Brains from the 68th generation of our selective breeding colony were used to examine bHR/bLR differences in gene expression in an upper quadrant of the adult rat brain which included the dorsal hippocampus. One section per "condition" (bred line x sex) was collected from a bHR and bLR family per slide, allowing each slide to function as its own independent study. Adjacent sections were collected on a second slide to serve as a technical replicate, and a second bHR and bLR family was included as a biological replicate. While extensive gene expression differences were noted between the lines,

our gene list focused on prototypical immediate early genes (IEGs; e.g., Arc, Fos, zif-268) as well as other genes known to show time-dependent responses to growth factor activation (Tullai, et al., 2007). While bHRs exhibited a higher basal expression of immediate early genes in the brain vs. bLR rats, fewer differences between lines were found at later timepoints. These findings are relevant to the bHR/bLR lines given well-established differences in response to psychostimulants such as cocaine, and the effects of psychostimulants on IEGs. Thus, the unbiased investigation of bHR/bLR brain differences using the Visium platform promises to be a valuable tool for elucidating differences in gene expression and enables more refined anatomical queries in the future.

Disclosures: M. Waselus: None. **E. Hebda-Bauer:** None. **M. Dai:** None. **F. Meng:** None. **H. Akil:** None. **S.J. Watson:** None.

Poster

161. Spatial Transcriptomics Profiling

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 161.07

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: 5R35GM138636-03
5R01AG068331-03

Title: Long-read RNASeq in human brains aligned to CHM13 complete human genome reveals new RNA transcripts and allows for accurate quantificationof multiplehighly expressed annotated isoforms inkey neurodegenerative disease genes such as APP, SNCA, and MAPT.

Authors: *B. AGUZZOLI HEBERLE[1], J. A. BRANDON[1], K. NATIONS[1], M. PAGE[1], M. E. WADSWORTH[1], D. W. DICKSON[2], P. T. NELSON[1], J. B. MILLER[1], J. D. FRYER[3], M. EBBERT[1];
[1]Univ. of Kentucky, Lexington, KY; [2]Pathology & Neurosci., Mayo Clin., Jacksonville, FL; [3]Neurosci., Mayo Clin., Scottsdale, AZ

Abstract: Background: RNASeq experiments have traditionally been done with short-read sequencing technologies that, by nature, collapse all RNA isoforms for a given gene into a single expression measurement—a major oversimplification of the underlying biology. Collapsing all RNA isoforms for a single gene severely limits our ability to characterize all RNA isoforms and determine their individual downstream functions. While computational approaches for assembling short reads into full transcripts exist, these methods are inherently structurally inaccurate. In contrast, long-read sequencing technologies can sequence entire RNA molecules, allowing researchers to accurately quantify expression for the complete set of RNA isoform species, including de novo RNA isoforms. Here we sequenced post-mortem human brain tissue with long-reads and aligned them to the recently released telomere-to-telomere completed human reference genome (CHM13) to explore new gene bodies and transcript isoforms.

Methods: We sequenced pre-frontal cortex tissue from five post-mortem human brain samples using Oxford Nanopore Technologies long-read sequencing (cDNA). Data were basecalled using Guppy, reads were aligned to CHM13 using minimap2, and transcripts were assembled and quantified using Bambu.
Results: We discovered 202 new, high-confidence gene bodies having five or more reads in at least three samples. We also found 622 high-confidence new RNA isoforms in known gene bodies, of which 66 are from medically relevant genes. One interesting example was a novel *MAOB* gene isoform containing a novel exon that accounted for 7.7% of all reads found for that gene. *MAOB* inhibitors are used in the treatment of Parkinson's disease and a SNP in *MAOB* has been associated with changes in response to L-dopa treatment. Lastly, we detected 585 medically relevant genes with 2+ isoforms having 100+ reads across all five samples, including four *APP* isoforms, four *SNCA* isoforms, and three *MAPT* isoforms.
Conclusions: Our results suggest long-reads combined with the completed CHM13 human reference genome has the potential to reveal exciting new biology relevant to human health and disease, including new gene bodies and RNA isoforms that are overlooked with standard approaches. These methods can provide a more complete picture of the transcriptomic landscape of the human brain, with potential for clinically-relevant discoveries. Another advantage long reads provide is that we can accurately quantify the RNA at the isoform level. This enables us to investigate the roles of the several highly expressed isoforms in key neurodegenerative disease genes such as *APP*, *SNCA*, and *MAPT*.

Disclosures: B. Aguzzoli Heberle: None. **J.A. Brandon:** None. **K. Nations:** None. **M. Page:** None. **M.E. Wadsworth:** None. **D.W. Dickson:** None. **P.T. Nelson:** None. **J.B. Miller:** None. **J.D. Fryer:** None. **M. Ebbert:** None.

Poster

161. Spatial Transcriptomics Profiling

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 161.08

Topic: I.01. Molecular, Biochemical, and Genetic Techniques
Knut and Alice Wallenberg Foundation

Title: The transcriptomic landscape across 202 micro-dissected regions of the adult human brain

Authors: *N. MITSIOS[1], W. ZHONG[2], S. BARDE[1], M. KARLSSON[2], P. OKSVOLD[2], L. FAGERBERG[2], C. ZHANG[2], T. ZHENG[1], E. HUSEN[1], E. GERRITS[1], K. VON FEILITZEN[2], C. LINDSKOG[3], E. SJOSTEDT[1], V. YANG SWARTZ[4], Y. LUO[5], E. RENNER[6], M. PALKOVITS[6], T. HOKFELT[1], M. UHLEN[2], J. MULDER[1];
[1]Karolinska Institutet, Solna, Sweden; [2]Sci. for Life Lab., Solna, Sweden; [3]Uppsala Univ., Uppsala, Sweden; [4]MGI-BGI, Shenzhen, China; [5]Aarhus Univ., Aarhus, Denmark; [6]Semmelweis Univ., Budapest, Hungary

Abstract: The Human Protein Atlas (HPA; www.proteinatlas.org) is a public online database that provides an integrated overview of protein expression and distribution in all major human tissue types, including brain. There, a comprehensive overview of gene and protein expression in the main anatomical structures of the mouse, pig and human brain is provided, by combining in-house generated and publicly available transcriptomic data. In the current version (HPA21.1), released in May 2022, we have added in-house generated RNA sequencing data for 967 samples from 202 microdissected regions and areas of the human brain (Human Brain Tissue Bank, Budapest). These include 10 samples from different basal ganglia, 16 thalamic and 9 hypothalamic nuclei, 9 samples from the hippocampal complex, 5 from the amygdala, over 70 from brainstem (midbrain, pons, medulla) and 5 cerebellar cortical and nuclear samples. In addition, from the cerebral cortex, more than 70 areas, gyri and subregions have also been analyzed. Altogether, the HPA brain section provides gene-centric pages that give an extensive and integrated overview on transcript expression across regions and subregions of the brain and allow comparison between species. Furthermore, we classify all protein coding genes based on regional distribution and co-expression, thus providing lists of genes associated to brain regions, cell types and functions. As an example, the piriform cortex appears to have a unique transcriptomic signature, quite different from the rest of the cerebral cortex while the claustrum, although it anatomically belongs to the cortical subplate, its transcriptional profile shares more common characteristics with the subregions of the cortical plate. In addition, based on these data, the basal ganglia are further divided into 3 subclusters, with notable differences in the gene expression patterns between the globus pallidus (internal and external) and the striatal parts. All data presented are freely accessible based on the FAIR Data Principles.

Disclosures: **N. Mitsios:** None. **W. Zhong:** None. **S. Barde:** None. **M. Karlsson:** None. **P. Oksvold:** None. **L. Fagerberg:** None. **C. Zhang:** None. **T. Zheng:** None. **E. Husen:** None. **E. Gerrits:** None. **K. Von Feilitzen:** None. **C. Lindskog:** None. **E. Sjostedt:** None. **V. Yang Swartz:** None. **Y. Luo:** None. **E. Renner:** None. **M. Palkovits:** None. **T. Hokfelt:** None. **M. Uhlen:** None. **J. Mulder:** None.

Poster

161. Spatial Transcriptomics Profiling

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 161.09

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Title: Spatial Transcriptomic Profiling of Brain FFPE Tissues Sectioned on Glass Histology Slides by Automated Transfer of Analytes

Authors: A. PATEL, A. SANITAGO, L. GUTGESELL, D. SUKOVICH, H. SINGH, H. KIM, N. MIKHAIEL, D. LI, *C. UYTINGCO, S. RUSSELL, A. TENTORI;
Biol., 10x Genomics, Pleasanton, CA

Abstract: Defining the spatial arrangement of cells in brain tissue and their gene expression provides comprehensive understanding of nervous system development and disease states. Visium spatial gene expression assays detect and map RNA expression within the native morphological context of a tissue section. The recently introduced Visium CytAssist is a compact instrument that facilitates automated transfer of transcriptomic analytes from H&E- or IF-stained FFPE sections on standard glass slides to spatially-barcoded gene expression slides. The CytAssist workflow supports tissues over a range of input RNA quality, as assessed by DV200 index, that fit in either 6.5x6.5 or 11x11 mm capture array formats, giving researchers the ability to gain deeper insights into the spatial gene expression patterns on archived sections. Here we demonstrate spatial transcriptome-scale profiling of gene expression in both human and mouse brain FFPE tissues, sectioned on regular histology glass slides and with varying RNA quality, size, and origin. Using the CytAssist workflow, we showcase the ability to spatially resolve individual gene markers associated with neural development and degeneration, map markers back to distinct morphological features within the tissue, and use differential gene expression data to identify distinct cell types throughout the tissues. For example, genes such as AQP4, SNAP25, and MOBP in human brain tissue processed with the CytAssist workflow can be used to localize and differentiate between astrocytes, neurons, and oligodendrocytes, respectively, in the cortical layer. These studies demonstrate that CytAssist enables greater insights into cell-type specific neurobiology while also expanding the spectrum of samples that can be analyzed, including archived and previously analyzed tissues.

Disclosures: **A. Patel:** A. Employment/Salary (full or part-time):; 10x Genomics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); 10x Genomics. **A. Sanitago:** A. Employment/Salary (full or part-time):; 10x Genomics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); 10x Genomics. **L. Gutgesell:** A. Employment/Salary (full or part-time):; 10x Genomics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); 10x Genomics. **D. Sukovich:** A. Employment/Salary (full or part-time):; 10x Genomics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); 10x Genomics. **H. Singh:** A. Employment/Salary (full or part-time):; 10x Genomics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); 10x Genomics. **H. Kim:** A. Employment/Salary (full or part-time):; 10x Genomics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); 10x Genomics. **N. Mikhaiel:** A. Employment/Salary (full or part-time):; 10x Genomics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); 10x Genomics. **D. Li:** A. Employment/Salary (full or part-time):; 10x Genomics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); 10x Genomics. **C. Uytingco:** A. Employment/Salary (full or part-time):; 10 Genomics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); 10x Genomics. **S. Russell:** A. Employment/Salary (full or part-time):; 10x Genomics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); 10x Genomics. **A. Tentori:** A. Employment/Salary

(full or part-time):; 10x Genomics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); 10x Genomics.

Poster

161. Spatial Transcriptomics Profiling

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 161.10

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Title: Geomxspatial proteogenomics reveals distinct spatially resolved glioblastoma multiforme and giant cell glioblastoma multiforme proteomic and transcriptomic signatures

Authors: S. A. BONNETT, G. ONG, A. ROSENBLOOM, M. CONNER, A. RININGER, D. NEWHOUSE, F. NEW, H. SATO, C. PHAN, S. ILCISIN, J. LYSSAND, *E. SCHNEIDER, G. GEISS, J. M. BEECHEM;
NanoString Technologies, Inc., Seattle, WA

Abstract: The GeoMx® Digital Spatial Profiler (DSP) enables high-plex, high-throughput spatial profiling and quantification from a single slide for protein or RNA. To understand the interplay between RNA and protein within tissue with spatial resolution, we developed a novel Spatial Proteogenomic assay workflow on the GeoMx DSP that allows for simultaneous profiling of both RNA and protein from a single tissue section. We describe the development and performance of the GeoMx Spatial Proteogenomics assay using a high plex stacked GeoMx NGS Protein Panel (147 plex) and the GeoMx Human Whole Transcriptome Atlas (WTA). We successfully detected RNA and protein simultaneously from spatially resolved cellular neighborhoods, with comparable sensitivity and specificity to single analyte conditions. Simultaneous transcriptomics and proteomics of key biological pathways enables deeper multi-analyte characterization of precious biological samples. Glioblastoma multiforme (GBM) is a highly aggressive, grade IV astrocytoma. High intra- and inter-tumor heterogeneity presents an obstacle to developing therapeutic treatments. Giant cell glioblastomas (gcGBM) are associated with complete resection and improved survival. A better understanding of tumor microenvironment and heterogeneity in these tumors is needed for the development of targeted therapies. Using Spatial Proteogenomics, we profiled a set of gcGBM and GBM samples with the GeoMx Human WTA and the 147-plex stacked GeoMx Human NGS Protein Panels. Between gcGBM and GBM, we observed differential expression of protein targets CD3 and CD8, which are associated with infiltrating total T and cytotoxic T lymphocytes, respectively. Both CD3 and CD8 proteins were expressed at least two-fold higher in gcGBM compared to GBM. Differential RNA expression of *CD3* and *CD8* between gcGBM and GBM was less notable**.** CD44 expression has been shown to be critical for GBM invasion and migration. In our dataset, we observe higher *CD44* gene expression in gcGBM compared to GBM and the opposite for protein where we observed a 2-fold decrease in CD44 expression levels. The conflicting trend between the two analyte types suggests additional regulation of this target. Phosphorylation of Ser9 leads to the inactivation of the GSK3β, and has been shown to result in the suppression

of β-catenin expression and subsequent proliferation. In our analysis, protein levels of phospho-GSK3B (Ser9) were 2-fold higher in gcGBM compared to GBM, whereas RNA levels remain similar. This study exemplifies the potential of Spatial Proteogenomics with GeoMx DSP in expanding our understanding of subsets of GBM molecular pathology.

Disclosures: **S.A. Bonnett:** None. **G. Ong:** None. **A. Rosenbloom:** None. **M. Conner:** None. **A. Rininger:** None. **D. Newhouse:** None. **F. New:** None. **H. Sato:** None. **C. Phan:** None. **S. Ilcisin:** None. **J. Lyssand:** None. **E. Schneider:** None. **G. Geiss:** None. **J.M. Beechem:** None.

Poster

161. Spatial Transcriptomics Profiling

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 161.11

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Title: A CRISPRi-based Approach to Dissecting Transcriptional Networks in the Mouse Cortex

Authors: *R. KIRK[1], R. XIAO[2], S. B. NELSON[3];
[1]Brandeis Univ., Cambridge, MA; [2]neuroscience, Brandeis Univ., waltham, MA; [3]Dept Biol MS#008, Brandeis Univ., Waltham, MA

Abstract: Healthy neuronal function and plasticity requires tight control over the relative abundance and distribution of ion channels and ionotropic receptors in the cell. Despite their established significance, little is known about the mechanisms that control the expression and abundance of mRNA encoding these critical proteins. Therefore, we sought to identify candidate transcriptional regulators of ion channel genes by leveraging bulk RNA-seq and ATAC-seq data collected in parallel from multiple neuronal cell types in the adult mouse brain. Motif enrichment analysis from our data implicated the Kruppel-like factor (KLF) and Regulatory Factor X (RFX) families of transcription factors as potential novel regulators of ion channel gene expression. To test our predictions, we developed an *in vivo* CRISPR-interference (CRISPRi)-based knockdown strategy to knock down members of either transcription factor family individually (RFX3 & KLF9) or in combination (RFX3/RFX7 & KLF9/KLF13). By injecting neonatal Emx1-Cre;LSL-dCas9-KRAB mice with AAV9 containing guide RNA's (gRNA) targeting our genes of interest, we are able to reliably knock down multiple genes by 90-95% using a single virus. By sequencing the RNA of infected cells, we identified the cell-autonomous effects of individual or combinatorial transcription factor knockdown(s) on the neuronal transcriptome. While ion channels were scarce among the genes affected by these knockdowns, differentially expressed genes *are* enriched for DNA motifs recognized by the transcription factor(s) targeted for knockdown. Furthermore, the effects of knocking down multiple members of either transcription factor family appear to be largely predictable from effects observed in the single-knockdown experiments. This suggests there is some biological logic to the observed effects and offers an opportunity to update our model to understand which genomic features are relevant for

predicting transcriptional output. Together, our results offer novel examples of redundancy and synergy in transcription factor function while demonstrating the utility of genetic perturbation experiments for constraining computational models of transcriptional regulation.

Disclosures: **R. Kirk:** None. **R. Xiao:** None. **S.B. Nelson:** None.

Poster

161. Spatial Transcriptomics Profiling

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 161.12

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: LIBD Internal Funding

Title: Single-molecule cartography of the human postnatal dentate gyrus throughout lifespan

Authors: ***A. D. RAMNAUTH**[1,4], S. C. PAGE[4], H. R. DIVECHA[4], M. TIPPANI[4], E. A. PATTIE[4], T. M. HYDE[4,2,3], K. MARTINOWICH[4,1,2];
[1]Neurosci., [2]Psychiatry and Behavioral Sci., [3]Neurol., Johns Hopkins Sch. of Med., Baltimore, MD; [4]Lieber Inst. for Brain Develop., Baltimore, MD

Abstract: The hippocampus (HPC) plays a well-established role in learning and memory across the lifespan, with developmental and plasticity-related gene expression changes observed from infancy through old age. Despite this, the postnatal development of the dentate gyrus (DG) throughout the human lifespan has yet to be fully characterized in the same molecular and spatial detail as other species. As an example, despite extensive characterization of the functional importance of postnatal neurogenesis in DG of rodents, indisputable evidence of adult neurogenesis in the human DG (hDG) remains elusive and its persistence throughout the lifespan remains controversial. Although there has been a recent increase in genome-wide and single-cell transcriptomic studies, the majority of research on human HPC has relied on antibody-based methods, including immunohistochemistry and western blotting, which are highly sensitive to variability in post-mortem tissue processing and are limited to a small number of markers. Another limitation of antecedent studies is the small age ranges of brain donors used. We hypothesize that the hDG has divergent postnatal transcriptomic architectural trajectories compared to other mammals. Thus, we generated spatially-resolved, transcriptome-wide gene expression profiles using the Visium Spatial Gene Expression platform, in fresh-frozen hDG from neurotypical donors ranging from infancy to 70+ years of age. Using BayesSpace, an R package for unsupervised spatial clustering, we compared gene enrichment across hDG subregions in an unbiased manner, and identified postnatal developmental markers including neurogenesis, plasticity, and apoptosis, among others. We then performed multiplexed single-molecule fluorescent *in situ* hybridization (smFISH) to define expression patterns of these gene combinations at cellular resolution. We annotated the entire granular cell layer (GCL) of the hDG, performed nuclear and transcript segmentation, and quantified the density of co-expressing

nuclei, as well as abundance of expression for commonly used neurogenesis markers, including doublecortin (*DCX*), neurogenin 2 (*NEUROG2*), sex determining region Y-box transcription factor 2 & 11 (*SOX2* & *SOX11*), neuronal differentiation 1 (*NEUROD1*), & Minichromosome Maintenance Complex Component 2 (*MCM2*), while excluding astrocytes via expression of Solute Carrier Family 1 Member 3 (*SLC1A3*). Preliminary Visium results indicate that many genes relating to neurogenesis are enriched in the GCL, while smFISH for common neurogenic markers reveals that co-expression drops dramatically after infancy.

Disclosures: A.D. Ramnauth: None. **S.C. Page:** None. **H.R. Divecha:** None. **M. Tippani:** None. **E.A. Pattie:** None. **T.M. Hyde:** None. **K. Martinowich:** None.

Poster

161. Spatial Transcriptomics Profiling

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 161.13

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Title: Isolation of neural cell subsets using a fast and gentle microfluidic cell sorter results in highly viable cells that can be used for downstream culture, imaging, and transcriptomics

Authors: *M. CIARLO[1], E. RODRIGUEZ-MESA[2], R. BARHOUMA[2], V. TRAN[3], A. GADKARI[3], J. MANSMUCKER[3];
[1]Miltenyi Biotec Inc., San Diego, CA; [2]Owl Biomed., Santa Barbara, CA; [3]Parse Biosci., Seattle, WA

Abstract: Recovering highly viable and pure populations of neural cell subtypes from brain tissue has been historically challenging. Neural cells often have complex morphologies that require careful dissociation and once dissociated they can be especially sensitive to the harsh conditions of traditional flow-based cell sorting technologies. The high pressure, long fluidics pathway, electrostatic charges, and long processing times of traditional jet-in-air/droplet-based sorters are often not well-tolerated by neural cells and can have significant negative effects on the cells' ability to perform well in downstream assays. We were able to overcome these challenges by using a proven, automatic dissociation technique that utilizes mild enzymatic and mechanical mechanisms to dissociate the tissue in combination with a gentle microfluidic cartridge and microchip-based sorting technology to isolate cell subtypes. Here we show fast, efficient, and high purity sorting of neurons, microglia, and astrocytes from dissociated adult mouse brain while still preserving the viability and functionality of the sorted cells. Sort purities were greater than 90% and viability was greater than 95% for all cell types. After sorting, we assessed the cells' functionality by culturing the sorted cells for 7 days under the optimal conditions for each cell type. In all cases, we saw attachment of the cells to the plates within 24 hours and significant growth over the next 7 days, demonstrating that the cells were highly functional after the dissociation and sorting procedure. After 7 days of culture, we used microscopy and immunocytochemistry techniques to confirm that the morphology and cell

surface/intracellular protein expression was consistent with the expected isolated cell type. Finally, single-cell RNA sequencing (scRNA-seq) of the sorted cells was performed using the Evercode whole transcriptome technology which revealed no significant difference in gene expression or clustering between the sorted and unsorted cells.This data demonstrates a complete workflow for gentle and efficient isolation of neural cell subtypes from whole brain tissue that preserves cell viability, functionality, and transcriptome.

Disclosures: **M. Ciarlo:** A. Employment/Salary (full or part-time):; Miltenyi Biotec Inc. **E. Rodriguez-Mesa:** A. Employment/Salary (full or part-time):; Owl Biomedical Inc. **R. Barhouma:** A. Employment/Salary (full or part-time):; Owl Biomedical Inc. **V. Tran:** A. Employment/Salary (full or part-time):; Parse Biosciences. **A. Gadkari:** A. Employment/Salary (full or part-time):; Parse Biosciences. **J. Mansmucker:** A. Employment/Salary (full or part-time):; Parse Biosciences.

Poster

161. Spatial Transcriptomics Profiling

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 161.14

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Title: Spatial Transcriptomic Characterization of Rhesus Macaque Brain

Authors: *S. DAN[1], J. OTTEN[3], T. KLENGEL[2];
[2]Harvard medical Sch., [1]McLean Hosp., Belmont, MA; [3]Dept. of Psychiatry, Univ. medical centre Gottingen, Gottingen, Germany

Abstract: Non-human primates are essential animal models for translational neuroscience due to their genetic, immunological, behavioral, and neuroendocrine similarities to human. Recent single cell transcriptomic and epigenomic studies provided a deep insight in the heterogeneity and functionality of the central nervous system, in both healthy and diseased. However, the spatial distribution of gene expression remains largely understudied, particularly in primates. Thus, we aimed to characterize the gene expression in-situ in the brain of rhesus macaque (*Macaca mulatta*) using spatial transcriptomics technologies.
A healthy male rhesus macaque brain was harvested at the age of 13 years (n = 1). Cortical and subcortical regions including the hippocampus, amygdala, caudate, putamen, superior temporal gyrus and cortex, posterior cingulate cortex, primary cortex, and globus pallidus were selected and placed on 10x Visium chips across 20 capture areas for spatial transcriptomics sequencing. Downstream data analysis was carried out in R (v 4.0.2) using custom scripts.
Spots with low quality as well as genes with low counts were filtered out. Data from all panels were combined, normalized, and clustered using unsupervised clustering algorithm. 12 broad regions and 25 sub clusters were identified matching known anatomical pattern. Differentially expressed (DE) and variable genes ($p_{fdr} < 0.05$) in each cluster resulted in a cluster-specific marker gene list that can be utilized as a reference in future research. DE genes in some clusters

also include known risk genes for various psychiatric disorders, indicating that there might be region specificity to these disorders that should be further explored. Additional analyses are ongoing to determine the gene networks across different brain regions.
Our findings present the first characterization of spatial pattern in both cortical and subcortical areas in the rhesus macaque brain. The results can be used as a reference dataset and serves as the foundation to future translational research in non-human primates.

Disclosures: **S. Dan:** None. **J. Otten:** None. **T. Klengel:** None.

Poster

161. Spatial Transcriptomics Profiling

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 161.15

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Title: Cell type identification in brain tissue using high throughput in situ gene expression profiling

Authors: R. SHELANSKY, X. QIAN, F. WAGNER, A. JANESICK, *K. MILLER, B. NGUYEN, F. MESCHI, K. BELHOCINE;
10x Genomics, Pleasenton, CA

Abstract: RNA expression profiles generated by single cell and spatial transcriptomic studies reveal the relationships between tissue morphology and the transcriptome. Here we investigated human and mouse brain tissue using the Xenium platform, a novel high throughput in situ technology. Xenium uses a microscopy based read-out and curated, pre-validated gene panels to identify spatial patterns of gene expression with subcellular resolution in either fresh frozen (FF) or formalin-fixed paraffin-embedded (FFPE) tissue sections. Xenium derived RNA expression data can be used to accurately cluster and identify cells within neural tissue.
To investigate transcript detection sensitivity, optical signatures were decoded to transcripts and assigned to cells based on nuclei morphology. We performed unsupervised clustering and used known markers to annotate cell types, allowing us to accurately identify expected brain cell types, thus validating our choice of genes for the brain panel. We then compared the number of transcripts observed per cell in the Xenium derived brain tissue data to the mean UMI from a publicly available Chromium Single Cell 3′ dataset and found that the Xenium sensitivity was on average higher.
To investigate transcript specificity, we observed that the spatial localization of excitatory cells in anatomical brain regions such as the layers of the cortex and the dentate gyrus matched closely with expected expression patterns. Counts from negative DNA probe controls and negative decoding controls were extremely small relative to the gene counts.
We further demonstrated that tissue sections used for Xenium targeted in situ analysis could subsequently be stained for H&E and processed using the Visium CytAssist workflow to obtain whole transcriptome information, thus revealing new gene targets for future custom gene panel

design.
The newly developed Xenium platform with high sensitivity and specificity accurately identified cell types in neural tissue and provided the detailed subcellular resolution needed for high plex classification of cellular spatial organization in brain tissue.

Disclosures: **R. Shelansky:** A. Employment/Salary (full or part-time):; full. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); stock. **X. Qian:** A. Employment/Salary (full or part-time):; full. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); stock, patent holder. **F. Wagner:** A. Employment/Salary (full or part-time):; full. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); stock. **A. Janesick:** A. Employment/Salary (full or part-time):; stock. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); stock. **K. Miller:** A. Employment/Salary (full or part-time):; full. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); stock. **B. Nguyen:** A. Employment/Salary (full or part-time):; stock. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); stock. **F. Meschi:** A. Employment/Salary (full or part-time):; full. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); stock, patent. **K. Belhocine:** A. Employment/Salary (full or part-time):; full. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); stock, patent.

Poster

162. Bioinformatics and Systems Biology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 162.01

Topic: I.02. Systems Biology and Bioinformatics

Support: P50DA037844

Title: Genetic analysis of multiple measures of locomotor activity in 4,233 outbred Heterogeneous Stock rats

Authors: *A. S. CHITRE[1], O. POLESSKAYA[4], J. GAO[2], A. P. HORVATH[5], A. HUGHSON[5], T. WANG[7], C. ST. PIERRE[3], H. BIMSCHLEGER[2], R. CHENG[2], K. HOLL[8], J. TRIPI[9], C. P. KING[10], J. RICHARDS[9], P. MEYER[11], L. C. SOLBERG WOODS[12], T. E. ROBINSON[13], S. B. FLAGEL[6], H. CHEN[14], A. A. PALMER[15];
[1]Univ. of California San Diego, La Jolla, CA; [2]Univ. of California San Diego, San Diego, CA; [3]Psychiatry, Univ. of California San Diego, La Jolla, CA; [4]Psychiatry, Univ. of California - San Diego, San Diego, CA; [6]Michigan Neurosci. Inst., [5]Univ. of Michigan, Ann Arbor, MI; [7]Dept. of

Pharmacol., Univ. of Tennessee Hlth. Sci. Ctr., Memphis, TN; [8]Med. Col. of Wisconsin, Madison, WI; [9]Univ. at Buffalo, Buffalo, NY; [10]Psychology, State Univ. of New York, Univ. at Buffalo, Buffalo, NY; [11]Psychology, Univ. At Buffalo, Buffalo, NY; [12]Wake Forest Baptist Med. Center,, Winston-Salem, NC; [13]Dept Psychol, Univ. of Michigan Dept. of Psychology, Ann Arbor, MI; [14]Dept Pharmacol, Univ. Tennessee Hlth. Sci. Ctr., Memphis, TN; [15]Psychiatry, UCSD, La Jolla, CA

Abstract: Locomotor activity has been equated with a constellation of related personality dimensions including extraversion, externalizing behaviors and sensation seeking. Locomotor behavior is also of significant biological interest because it is correlated with measures of anxiety, substance abuse and other behaviors, and because it can sometimes confound other more complicated behavioral measures. We performed a genome-wide association study (**GWAS**) of locomotor behavior in outbred rats and examined genetic correlations across several cohorts in which locomotor activity was measured. The cohorts differed in age, and procedural details like size of arena and test length. All subjects were N/NIH heterogeneous stock (**HS**) rats, which were derived from an intercross among 8 inbred strains and have been maintained as an outbred population for more than 80 generations. Locomotor traits were measured in three phenotyping centers: Center 1 (*N= 1,376, age= 77 days ± sd 5.45*), Center 2 (*N= 1,246, age= 32 days ± sd 2.57)* and Center 3 (*N= 1,611, age= 65 days ± sd 10.53*). We estimated the SNP heritability (h^2) using GCTA-GREML. We used the GCTA Bivariate GREML analysis to estimate the genetic correlation *(rg*). We performed GWAS using the linear mixed model approach using GCTA MLMA-LOCO. We identified a total of 6 independent Quantitative Trait Loci(QTLs) for the three locomotor traits. We also integrated eQTL data from five brain regions to help identify causal genes. SNP heritability estimates ranged from 0.25 to 0.37. The genetic correlation between centers 1 and 3 were high (0.69 ± se .09), the genetic correlation between centers 2 and 3 was moderate (0.43 ± se .10) and the genetic correlation between centers 1 and 2 was low (0.23 ± se .10). Center 2, which showed the lowest correlations, included younger animals, used a larger open field, and included a longer test than centers 1 and 3; these factors may account for the low correlations between center 2 and centers 1 and 3. Our results confirm the relatively high heritability of locomotor behavior and begin to identify the specific genetic loci that influence inter-individual variability in this fundamental behavioral measure
Supported by P50DA037844

Disclosures: A.S. Chitre: None. **O. Polesskaya:** None. **J. Gao:** None. **A.P. Horvath:** None. **A. Hughson:** None. **T. Wang:** None. **C. St. Pierre:** None. **H. Bimschleger:** None. **R. Cheng:** None. **K. Holl:** None. **J. Tripi:** None. **C.P. King:** None. **J. Richards:** None. **P. Meyer:** None. **L.C. Solberg Woods:** None. **T.E. Robinson:** None. **S.B. Flagel:** None. **H. Chen:** None. **A.A. Palmer:** None.

Poster

162. Bioinformatics and Systems Biology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 162.02

Topic: I.02. Systems Biology and Bioinformatics

Support: 7R01MH118239-03
1R01DA052453-01A1

Title: Expanding on the number and strength of gene expression imputation models for the subgenual anterior cingulate cortex

Authors: *J. DRAKE[1,2], Z. TAYLOR[1,2], A. DENHAM[1,2], N. GILLESPIE[3], J. SHIN[4], T. M. HYDE[4], S.-A. BACANU[3], V. I. VLADIMIROV[1,2,4];
[1]Texas A&M Univ., College Station, TX; [2]Univ. of Arizona, Phoenix, AZ; [3]Virginia Inst. for Psychiatric and Behavioral Genet., Richmond, VA; [4]Lieber Inst. For Brain Develop., Baltimore, MD

Abstract: Background: For psychiatric illnesses, where the disease organ is the brain, researchers are limited to post-mortem samples for studying gene expression (GE). Unfortunately, such samples have numerous issues like high costs, RNA degradation, and a general difficulty in acquiring sufficient samples to detect small effect sizes, which often characterize psychiatric ailments. To circumvent these issues, GE imputation algorithms like PrediXcan were developed and impute GE using genomic data in subjects unrelated to the training datasets. Here, we used the PrediXcan elastic-net methodology to build mRNA models in the subgenual anterior cingulate cortex and incorporated neuronal cell fractions to improve the accuracy of those models. **Methods:** Utilizing a large postmortem brain sample with 279 subjects, on whom we had both GE and GWAS data, we built elastic net models for 20,383 genes. To increased robustness and ensure models of adequate predictability were selected, we applied 10-fold cross-validation and retained models with an average coefficient of determination (R^2) ≥ 0.10 and a Z-score p-value < 0.05. To increase the accuracy of our models, we conducted a secondary analysis that included cell brain fractions, which were derived using single cell GE data in CIBERSORT. The retained models were compared against PrediXcan's GTEx v8 anterior cingulate cortex elastic net models. **Results:** In the analysis containing genomic and expression data only, 1,127 mRNA models were retained (average $R^2 = 0.25$). In comparison to the PrediXcan models of the same R^2 threshold, there was a comparable number of models of similar accuracy, i.e., 1,249 PrediXcan models with an average R^2 of 0.24. In total, 454 models were found in both our analysis and the PrediXcan models. In the secondary analysis, we found that the inclusion of cell fractions increased the overall accuracy of our models and resulted in more retained models (12,921 models with an average R^2 of 0.30). Additionally, we observed that the addition of cell fractions led to more models of higher accuracy being retained for highly expressed genes than lowly expressed genes. More specifically, genes in the top quantile of expression (TMM log2 mean expression of 6.62) compared to the bottom quantile (TMM log2 mean expression of -0.20) had respectively 4,385 and 1,551 models retained with an R^2 of 0.33 and 0.24 (Welch Two Sample t-test p-value on R^2 values = 2.2×10^{-16}). **Conclusion:** Here we've expanded on the number of mRNA models for the subgenual anterior cingulate cortex and highlighted how tissue heterogeneity and expression levels impact imputation accuracy.

Disclosures: J. Drake: None. **Z. Taylor:** None. **A. Denham:** None. **N. Gillespie:** None. **J. Shin:** None. **T.M. Hyde:** None. **S. Bacanu:** None. **V.I. Vladimirov:** None.

Poster

162. Bioinformatics and Systems Biology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 162.03

Topic: I.02. Systems Biology and Bioinformatics

Support: IBS-R001-D2

Title: Resolving clustering bias during animal behavior mapping and kinematic profiling

Authors: *J. KWON, S. KIM, J. JOO, S. KIM, C. J. LEE;
Ctr. for Cognition and Sociality, Inst. for Basic Sci., Daejeon, Korea, Republic of

Abstract: In behavior science, deep-learning-based pose estimation systems allow us to easily collect large-scale motion datasets from freely moving animals. For behavior mapping and kinematic profiling of animal movements, a common computational practice pipeline includes clustering and differential analysis. However, during this process, if the same dataset is used for both clustering and differential analysis, a clustering bias, so-called 'P-hacking', can emerge, leading to false discoveries. Here, we introduce an alternative clustering approach to resolve this bias while retaining the clustering performance. We hypothesized that extracting the independent features for clustering can prevent the cross-contamination of datasets, which is a primary cause of clustering bias. To test this hypothesis, we used spectrograms as extra features for clustering, as they confer time-frequency information and are expected to be independent of kinematic features. Using both simulated and experimental animal behavior data, we found that the alternative clustering approach based on spectrograms effectively remove the clustering bias, approaching near the P-values of the ground truth. Moreover, we found that the clustering bias can occur regardless of the statistical tests, clustering algorithms, or embedding methods. Our empirical results show that the scalar angle differences of clustering-hyperplane and ground-truth-hyperplane projecting to the feature axis are highly correlated with false discoveries, providing clues for the origin of the clustering bias. In summary, we propose the clustering approach based on spectrograms as a practical solution for the clustering bias problem, providing a foundation for the universally applicable guideline for animal behavior mapping and kinematic profiling with minimal false discoveries.

Disclosures: **J. Kwon:** None. **S. Kim:** None. **J. Joo:** None. **S. Kim:** None. **C.J. Lee:** None.

Poster

162. Bioinformatics and Systems Biology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 162.04

Topic: I.02. Systems Biology and Bioinformatics

Title: The cellxgene suite is an online analytical platform and the largest repository of standardized single-cell data.

Authors: *B. AEVERMANN, P. GARCIA-NIETO, S. CHAMBERS, H. THOMAS, B. RAYMOR, M. LOMBARDO, K. LIANG, M. CZERWINSKI, S. BADAJOZ, C. MEGILL, T. SMITH, M. DUNITZ, D. HEGEMAN, A. MANI, T. HUANG, K. KATSUYA, E. BEZZI, B. MARTIN, A. TOLOPKO, A. INFELD, M. URISKO, J. COOL, A. CARR;
Chan Zuckerberg Initiative, Redwood City, CA

Abstract: Cellxgene (cellxgene.cziscience.com) is a free-to-use online data portal hosting a growing corpus of more than 350 single-cell datasets with over 24 million unique cells from human and mouse. The portal hosts single-cell data from modalities that include gene expression, chromatin accessibility, DNA methylation, and spatial transcriptomics. All data are standardized to include raw and normalized counts, and annotated using an ontological shared vocabulary for cell and gene metadata.
Data are easily searchable and can be downloaded in multiple formats via web or by programmatic API calls. Additionally we deploy UI-based analytical tools for exploration of single datasets that do not require download. We will showcase the main tools hosted in the portal. First, the cellxgene explorer which displays an interactive 2-dimensional representation of cells in a dataset and allows users to color cells by gene activity or metadata (e.g. cell type, disease, technical features, etc.), subset and analyze subgroups of cells, perform differential gene expression and create scatter plots of gene expression. Second, scExpression which allows querying the expression of any gene across all human and mouse cell types available in the concatenated data from the portal.
Cellxgene is intended for community use and contributions. By supporting multiple modalities and data generated by labs around the world, the cellxgene suite of tools and data aims to maximize rapid use of data. To date, we support data from over dozens of labs and consortia such as the Tabula projects, LungMap, BICCN, Allen Institute for Brain Science, KPMP and the Human Cell Atlas. New contributions are welcome, the cellxgene team actively supports curation of data, and we work to ensure that self-curation is easy.
We are continuously improving the usability of cellxgene and adding new features tailored to the needs of cell and computational biologists. Groups interested in submitting their own data can contact the cellxgene team at cellxgene@chanzuckerberg.com to explore whether your data would be a good fit for the cellxgene resource.

Disclosures: B. Aevermann: None. **P. Garcia-Nieto:** None. **S. Chambers:** None. **H. Thomas:** None. **B. Raymor:** None. **M. Lombardo:** None. **K. Liang:** None. **M. Czerwinski:** None. **S. Badajoz:** None. **C. Megill:** None. **T. Smith:** None. **M. Dunitz:** None. **D. Hegeman:** None. **A. Mani:** None. **T. Huang:** None. **K. Katsuya:** None. **E. Bezzi:** None. **B. Martin:** None. **A. Tolopko:** None. **A. Infeld:** None. **M. Urisko:** None. **J. Cool:** None. **A. Carr:** None.

Poster

162. Bioinformatics and Systems Biology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 162.05

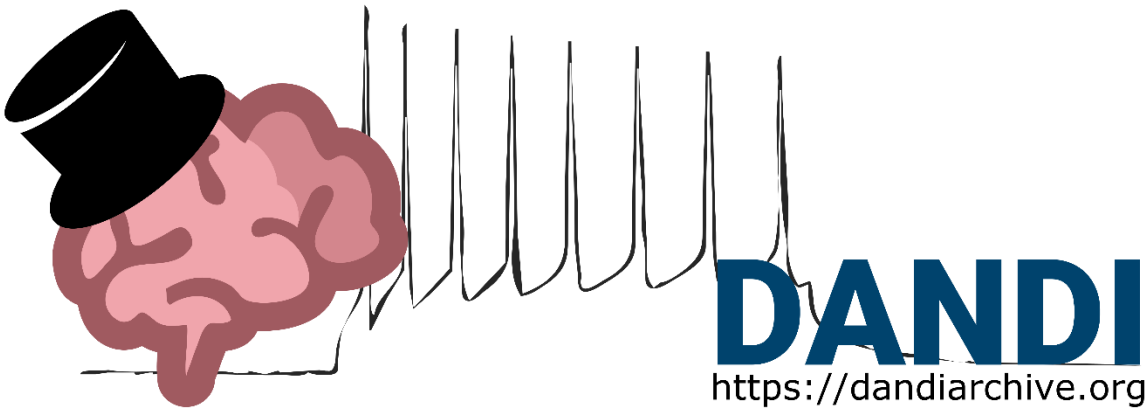
Topic: I.02. Systems Biology and Bioinformatics

Support: NIH 1R24MH117295-01A1
Amazon AWS Open Data hosting

Title: DANDI: An archive and collaboration space for cellular neurophysiology projects

Authors: *Y. O. HALCHENKO[1], S. S. GHOSH[2], B. DICHTER[3], R. CHOUDHURY[4], D. CHIQUITO[4], J. NESBITT[4], B. HELBA[4], M. VANDENBURGH[4], J. T. WODDER, II[1], H.-I. IOANAS[1], D. JARECKA[2];
[1]Dartmouth Col., Hanover, NH; [2]McGovern Inst. for Brain Res., MIT, Cambridge, MA; [3]CatalstyNeuro, Benicia, CA; [4]Kitware Inc., Clifton Park, NY

Abstract: DANDI is a cellular neurophysiology data archive and collaboration hub built to support multiscale, multispecies, and multimodal neuroscience research. The data and resources related to DANDI support theoretical neuroscience, drive biological applications, and help develop new analytic tools through standardized annotation and dissemination. The DANDI infrastructure is built on open-source technologies and in the cloud, to support dissemination, search, visualization, computation, collaboration, and coordination in neurophysiology research projects to promote FAIRness and efficiency. DANDI currently contains over 400TB of data from over 172 datasets, across 6 species, and multiple recording modalities including electrophysiology, optophysiology, optogenetic, and behavioral experiments, as well as multimodal MRI, OCT and immunostaining data from human ex vivo brain tissue samples. DANDI is a Web platform that provides data storage for the purposes of collaboration and dissemination of neurophysiology data with an option for embargoed/private access, easy to use tools for data submission and access, a Jupyter-based computation hub to introspect data in the archive, and integration with other archives and analytic platforms. DANDI is addressing challenges in standardization, data transfer, storage and access, and the culture of sharing through a community of practice. DANDI uses and participates in development of the BRAIN Initiative community data standards such as NWB and BIDS, and data formats such as Zarr and NGFF. DANDI provides an application programming interface server to attract software developers to interact with the archive programmatically and has also contributed to community efforts to provide efficient access to large data stored in the cloud. With DANDI, researchers can now validate, share, collaborate on, and publish citable datasets, and thereby increase rigor and reproducibility of cellular neurophysiology research. Work is ongoing to establish versatile search and further improve usability and efficiency of data deposition and access.



Disclosures: **Y.O. Halchenko:** None. **S.S. Ghosh:** None. **B. Dichter:** A. Employment/Salary (full or part-time):; CatalstyNeuro. **R. Choudhury:** A. Employment/Salary (full or part-time):; Kitware Inc. **D. Chiquito:** A. Employment/Salary (full or part-time):; Kitware Inc. **J. Nesbitt:** A. Employment/Salary (full or part-time):; Kitware Inc. **B. Helba:** A. Employment/Salary (full or part-time):; Kitware Inc. **M. VanDenburgh:** A. Employment/Salary (full or part-time):; Kitware Inc.. **J.T. Wodder:** None. **H. Ioanas:** None. **D. Jarecka:** None.

Poster

162. Bioinformatics and Systems Biology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 162.06

Topic: I.02. Systems Biology and Bioinformatics

Support: NIH T32 GM007752
NIH R56AG073965
NIH R01AG065541
NIH R01AG071465

Title: Long-read sequencing characterization of novel RNA isoforms in the human brain

Authors: *C. S. LIU[1,2], C. PALMER[1,2], J. CHUN[2];
[1]Univ. of California San Diego, La Jolla, CA; [2]Sanford Burnham Prebys Med. Discovery Inst., La Jolla, CA

Abstract: Advances in long-read sequencing technologies have made it possible to characterize the human transcriptome more fully. Long-read transcriptomic solutions, such as PacBio's Iso-Seq, can produce reads up to 10kb in length, resolving full-length RNA isoforms and allowing detailed characterization of splice sites and exon combinations. Previous studies have shown that the human brain expresses many isoforms that are not currently included in the reference transcriptome. These novel isoforms contain a variety of features that differentiate their structure

and sequence from those in the reference annotation. We modified a bioinformatics tool, SQANTI3, to identify these features and incorporate them as part of its annotation. We then analyzed Iso-Seq data from numerous human prefrontal cortex samples and identified novel isoform features such as intra-exonic junctions (IEJs), novel exons, and partial intronic retention. The prevalence of these novel isoforms and features highlights the potential for these diverse isoforms to contribute to various cellular functions in the human brain.

Disclosures: C.S. Liu: None. **C. Palmer:** None. **J. Chun:** None.

Poster

162. Bioinformatics and Systems Biology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 162.07

Topic: I.02. Systems Biology and Bioinformatics

Title: Choroid plexus and ambient RNA contamination

Authors: *K. TODD[1], K. OLNEY[1], P. PALLEGAR[1], T. JENSEN[3], J. D. FRYER[2]; [2]Neurosci., [1]Mayo Clin., Scottsdale, AZ; [3]Stanford Univ., Stanford, CA

Abstract: The choroid plexus is a highly vascular tissue found within the ventricles of the brain and is responsible for producing cerebrospinal fluid. This secretory tissue, composed of epithelial cells, connective tissue, and capillary networks, often proves difficult to avoid during brain tissue dissection. Transcriptomics and in situ hybridization studies have shown that the transthyretin (Ttr/TTR) gene is a marker of the choroid plexus in the central nervous system. We queried Gene Expression Omnibus using the Ttr/TTr gene and identified a level of likely choroid contamination in 586 human or mouse studies. Most studies we examined were categorized as “likely high contamination”, with tissues closer in physical proximity to the choroid plexus exhibiting greater contamination. This has the potential to confound downstream analyses. Furthermore, we analyzed the Allen Brain Atlas Aging, Dementia and TBI and the Genotype Tissue Expression (GTEx) bulk RNA-sequencing datasets and assessed differential expression between “likely high contamination” and “likely low contamination” groups. Results showed an enrichment of additional choroid markers, including FOLR1 and PRLR, and choroid gene ontology. We cannot guarantee that differentially expressed TTR is an artifact in all studies as some comparisons may be due to biology. We propose qPCR or western blot as a quick check before costly transcriptomic studies. Choroid contamination is not limited to bulk RNA-Seq and can confound single cell transcriptomics. Cell type specific markers expressed at low levels in other cell populations can be indicative of ambient RNAs, representing extracellular mRNAs in cell suspensions due to stressed cells, apoptotic cells, or released from intact cells during high pressure fluidics. Here, we test a less abrasive single cell platform and implement computational tools to reduce ambient RNAs.

Disclosures: **K. Todd:** None. **K. Olney:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Arizona State University. **P. Pallegar:** None. **T. Jensen:** None. **J.D. Fryer:** None.

Poster

162. Bioinformatics and Systems Biology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 162.08

Topic: I.02. Systems Biology and Bioinformatics

Support: NRF-2021R1A2C109399112

Title: Exploring exercise-induced myokines directly transmitted to the brain

Authors: *H. KIM[1,2], H.-W. RHEE[3], H. PARK[1,2];
[1]Korea Brain Res. Inst., Korea Brain Res. Inst. (KBRI), Daegu, Korea, Republic of; [2]Daegu Kyeongbuk Inst. of science & technology, Daegu, Korea, Republic of; [3]Seoul university, Seoul, Korea, Republic of

Abstract: Cognitive functions such as learning and memory is enhanced after physical exercise, and such cognitive enhancement is known to be regulated by exercise-induced peripheral organ-brain communication that is partly mediated by peripheral organ-originated hormonal proteins. Skeletal muscles are the endocrine organ secreting cytokines called as “myokine” during exercise. Among exercise-induced myokines, some of them may be directly transmitted to the brain and are involved in memory enhancements after exercise. However, due to the insufficient methods for detecting in vivo secretory proteins, molecular identities directly transmitted to the brain and mediating exercise-induced cognitive enhancements are not fully understood. To detect myokines released from skeletal muscle by exercise and transmitted to the brain over the blood brain barrier (BBB), we here adopted a proximity labeling tool by employing the promiscuous biotin ligase, TurboID. we directed TurboID expression in the endoplasmic reticulum (ER) lumen through introducing KDEL sequence in the TurboID (TurboID-ER) and generating Cre-dependent TurboID-ER knock-in mouse (LSL-TurboID-ER mouse). The LSL-TurboID-ER mouse were crossed with the skeletal muscle-specific Cre driver mouse (Acta1-Cre) resulting in the ACTuR (Acta1-Cre:: TurboID-ER) model mouse, to label myokines released from skeletal muscles. Using this mouse tool, we could validate exercise-induced secretion of biotinylated myokines and detect increases in biotinylated myokines in blood plasma after the aerobic exercise using activity wheel for 4 weeks. Furthermore, we show that biotinylated myokines could directly localize to the several brain areas, and such direct transmission of the myokines to the brain was significantly enhanced after the 4-week exercise. Our study provides evidence for exercise-induced myokine directly transmitted to the brain and modulation of cognitive function by these muscle-derived factors.

Disclosures: **H. Kim:** None. **H. Rhee:** None. **H. Park:** None.

Poster

162. Bioinformatics and Systems Biology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 162.09

Topic: I.02. Systems Biology and Bioinformatics

Title: In situ whole transcriptome profiling of FFPE brain using NanoString GeoMx®Digital Spatial Profiler

Authors: *M. VANDENBERG[1], N. HOLLAND[1], J. MUHLICH[2], J. HOFFER[2], A. VANSCHOIACK[1], J. REEVES[1], T. HETHER[1], Y. LIANG[1], A. HECK[1], J. GONG[1], E. PIAZZA[1], K. FUHRMAN[1], P. DANAHER[1], M. HOANG[1], S. RANADE[1], B. MUDDUKRISHNA[1], S. WARREN[1], N. CONFUORTO[1], M. RHODES[1], J. BEECHEM[1]; [1]NanoString Technologies, Inc., Seattle, WA; [2]Harvard Med. Sch., Boston, MA

Abstract: *In situ* whole transcriptome profiling of FFPE brain using NanoString GeoMx® Digital Spatial Profiler**Megan Vandenberg[1*]**, Natalie Holland[1,†], John Thomas Hoffer[2], Jeremy L. Muhlich[2], Alison Vanschoiack[1,†], Jason Reeves[1], Tyler Hether[1], Yan Liang[1], Ashley Heck[1], Jingjing Gong[1], Erin Piazza[1], Kit Fuhrman[1,†], Patrick Danaher[1], Margaret Hoang[1], Swati Ranade[1], Bhavana Muddukrishna[1], Sarah Warren[1,†], Nicholas Confuorto[1], Michael Rhodes[1], Joseph Beechem[1]
1. NanoString Technologies, Inc., Seattle, Washington, USA2. Laboratory of Systems Pharmacology, Harvard Medical School, Boston, Massachusetts, USA† Former association*Presenting author
Formalin-fixed, paraffin embedded (FFPE) brain tissue preserves detailed spatial, morphological, and molecular information of cells and their surrounding cellular environment. Here we demonstrate NanoString's GeoMx® Digital Spatial Profiler technical capabilities to quantitate whole transcriptome expression on specific cell types or distinct morphological regions within human or mouse FFPE brain sections. In five human brain samples, we profile over 250 areas across cortex and hippocampus. In four mouse brain samples, we profile over 350 areas across more than 10 distinct regions. In both species, spatial gene expression of over 18,000 targets are profiled using both geometric and cell type-enriched regions of interest, showing distinct biology across both histological structures and cell types. In human, we compare gene expression of neurons of the hippocampal CA1 region to densely packed neurons of the dentate gyrus and identify numerous differentially expressed genes, including *SEMA5A* and *MET*. Both genes have been identified as risk factors for autism spectrum disorders and are known to function in distinct regions of hippocampus (*SEMA5A* in dentate gyrus and *MET* in CA1). We make these rich and complex data accessible to the community for download and further analysis through our Spatial Organ Atlas and visualized using the Minerva Software Suite. Together, our results demonstrate the potential to unlock spatial, pathological, and genomic data types from archival brain samples

in one experiment, enabling new discoveries of diseased states.For research use only, not for use in diagnostics.

Disclosures: **M. Vandenberg:** None. **N. Holland:** None. **J. Muhlich:** None. **J. Hoffer:** None. **A. Vanschoiack:** None. **J. Reeves:** None. **T. Hether:** None. **Y. Liang:** None. **A. Heck:** None. **J. Gong:** None. **E. Piazza:** None. **K. Fuhrman:** None. **P. Danaher:** None. **M. Hoang:** None. **S. Ranade:** None. **B. Muddukrishna:** None. **S. Warren:** None. **N. Confuorto:** None. **M. Rhodes:** None. **J. Beechem:** None.

Poster

162. Bioinformatics and Systems Biology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 162.10

Title: WITHDRAWN

Poster

162. Bioinformatics and Systems Biology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 162.11

Topic: I.02. Systems Biology and Bioinformatics

Title: Mosaicneedles: a tool for biomarker analysis in plasma with high sensitivity and wide dynamic range

Authors: *Q. QUAN, J. RITCHEY, J. WILKINSON, A. KAISER, J. GEANACOPOULOS, J. BOYCE;
NanoMosaic, Woburn, MA

Abstract: Quantification of brain-related biomarkers in blood is challenging due to their low concentrations in plasma or serum. In addition, studies that compare the levels of biomarkers across plasma/serum, cerebrospinal fluid (CSF) and brain are insightful for establishing the pathological function of the biomarker. At present, no analytical method, known to us, can provide large dynamic range (>6 logs), high sensitivity (<1pg/ml) and high multiplex in a single test. We fabricated nanoneedle sensors on a planar substrate using complementary metal-oxide semiconductor (CMOS) compatible methods. 94,000 sensors with more than 2 billion total nanoneedles can be integrated on to a standard SBS plate, which can be configured into 96, 384 or 1536 well format. Each sensor contains an array of nanoneedles, dedicated to detecting one analyte of interest. All nanoneedles comprising the same sensor are functionalized with the same capture antibodies. At low analyte concentration, the binding of proteins to the nanoneedles

follows a Poisson distribution. Therefore, statistically, no more than one molecule is bound per nanoneedle. A subsequent addition of aptamers or antibodies will form a sandwich complex with the target analyte. Since each of the nanoneedles has an intrinsic optical resonance spectrum and will red-shift as the sandwich complex forms on its surface, the number of analytes can be quantitated by simply counting the number of nanoneedles that display a color change. At high analyte concentration, each nanoneedle has more than one analyte, so the number of analytes can be calculated by averaging the spectrum shifts of all nanoneedles. This combined single molecule counting (digital) and spectrum shift (analog) analysis allows the platform to detect both high abundance and low abundance protein analytes in one reaction. We demonstrated the single molecule nanoneedle array can detect Tau proteins from 50fg/ml to 1ug/ml. In conclusion, we demonstrated the detection of neuro-biomarkers with high sensitivity (fg/ml) and large dynamic range (7 logs), with densely integrated nanoneedle sensor array (MosaicNeedles). The scalability in manufacturing nanoneedles, the low sample requirement and free of fluorescent labeling combine to drive down the analysis cost per protein.

Disclosures: **Q. Quan:** A. Employment/Salary (full or part-time):; NanoMosaic. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); NanoMosaic. **J. Ritchey:** A. Employment/Salary (full or part-time):; NanoMosaic. **J. Wilkinson:** A. Employment/Salary (full or part-time):; NanoMosaic. **A. Kaiser:** A. Employment/Salary (full or part-time):; NanoMosaic. **J. Geanacopoulos:** A. Employment/Salary (full or part-time):; NanoMosaic. **J. Boyce:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); NanoMosaic, BrickBio.

Poster

162. Bioinformatics and Systems Biology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 162.12

Topic: I.02. Systems Biology and Bioinformatics

Support: DST-SERB
SRG

Title: Identification of small molecule modulators of class II transactivator-I to control the aggravation of neuroinflammation

Authors: *K. NAGASUBRAMANIAN, K. GUPTA, S. JHA, A. S. RATHORE;
Shanmugha Arts Sci. Technol. and Res. Acad., Sastra deemed Univ., THANJAVUR, India

Abstract: Neurodegenerative disorders like Alzheimer's, Parkinson's or traumatic brain injury depends on level of inflammation (Amor et al., 2010). Targeting proinflammatory pathways to hinder disease progression is already on focus especially in neurological disorders. In these conditions, T cells play crucial role to check out the inflammatory progression (Amor et al.,

2010). Interaction between the major histocompatibility complex II (MHCII) on antigen presenting cells (APCs) and T cell receptors play a major role in the adaptive immune system. Class II trans activator (CIITA) is a master regulator of MHCII expression following activation of helper T cells (Th cells) (Devaiah and Singer, 2013). CIITA has also been implicated in myocardial infarction, rheumatoid arthritis, multiple sclerosis (Reith and Mach, 2001) and other neuroinflammatory conditions. Antigen presentation acts as a toll-gate between innate and acquired immunity, in which CIITA plays a vital role. Targeting CIITA could be a novel strategy to regulate hyperinflammation in neurodegenerative conditions. Ligands for CIITA proteins have not been identified yet. Here, we predicted 3D structure of CIITA-I by phyre2, pocket identification by CASTp analysis, molecular docking (also ADME property of small molecules) using Schrödinger- Maestro followed by stability of the bound molecule using GROMACS molecular dynamics. From the analysis, 3D
structures of CIITA-I scored 83.4% in ERRAT after refinement which was used for docking studies to identify its potential modulators. The top candidates from the ligand library were taken for simulation studies and the ligand 4-(2-((6-oxo-4-phenyl-1,6-dihydropyrimidin-2-yl) thio) acetamido) benzamide (ZINC5154833) showed maximum glide score (-6.591) followed by N-[4-(3-oxo-3-{4-[3-(trifluoromethyl) phenyl] piperazin-1-yl} propyl)-1,3-thiazol-2-yl] benzamide (F5254-0161, glide score -6.41). Simulation studies showed F5254-0161 to have a more stable interaction with CIITA-I. Based on our analysis, we propose ZINC5154833 and F5254-0161 to be potential interactors for CIITA-I and neuroinflammation. Further studies to identify modulators of other isoforms of CIITA are underway.

Disclosures: K. Nagasubramanian: None. **K. Gupta:** None. **S. Jha:** None. **A.S. Rathore:** None.

Poster

162. Bioinformatics and Systems Biology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 162.13

Topic: I.02. Systems Biology and Bioinformatics

Support: NIH R01AG067025
NIH R03NS123969
NIH DP2MH122403
NIH R21DA051921
NIH R00MH113823
NIH U01MH122509
NIH U01MH116492

Title: Illuminating links between cis-regulators and trans-acting variants in the human prefrontal cortex

Authors: S. LIU[1], H. WON[2], D. CLARKE[3], N. MATOBA[2], S. KHULLAR[1], Y. MU[1], ***D. WANG**[4], M. GERSTEIN[3];
[1]Univ. of Wisconsin - Madison, Madison, WI; [2]Univ. of North Carolina at Chapel Hill, Chapel Hill, NC; [3]Yale Univ., New Haven, CT; [4]Univ. of Wisconsin Madison, Madison, WI

Abstract: Psychiatric and neurological disorders afflict large portions of the global population and constitute a significant source of disability worldwide. Although genome-wide association studies (GWAS) have identified many genomic variants that are significantly associated with psychiatric and neurological disorder risk, decades of research have led to only limited progress in our understanding of the precise mechanistic linkages between these variants and disorders of the brain. Expression quantitative trait loci (eQTLs) constitute a powerful means of providing this missing link. However, most current eQTL studies on the brain have focused exclusively on cis- eQTLs, which link a given variant to its nearby genes (i.e., those within 1 Mb of the variant). A complete understanding of disease etiology necessitates a fuller understanding trans-regulatory mechanism, which in turn entails a detailed analysis of the relationships between variants and expression changes in distant genes. We thus conducted a genome-wide survey for trans-eQTLs in the dorsolateral prefrontal cortex (DLPFC). By leveraging large datasets from the PsychENCODE consortium, we identified ~80,000 candidate trans-eQTLs (FDR<0.25) that influence the expression of ~10K target genes (i.e., "trans-eGenes"). We found that a significant number of the variants associated with these trans-eQTLs overlap with those known to be a part of cis-eQTLs; moreover, for >60% of these variants (by colocalization), the cis-eQTL's target gene acts as a mediator for the variant's effect on the trans-eGene, implicating cis-mediation as essential for trans-regulation. Furthermore, many of these colocalized variants fall into a discernable pattern wherein the trans-eQTL SNP is part of a cis-eQTL for a transcription factor or RNA-binding protein, the distal regulatory target of which is found to be the gene associated with the trans-eQTL. Finally, we show that trans-regulatory mechanisms provide valuable insights into psychiatric disorders. In particular, we conducted a colocalization analysis between candidate trans-eQTLs and schizophrenia GWAS loci to link 23 additional loci to genes beyond those that had been possible using only cis-eQTLs. This analysis also implicates 90 additional risk genes in schizophrenia, beyond those implicated by cis-eQTL analysis.

Disclosures: S. Liu: None. **H. Won:** None. **D. Clarke:** None. **N. Matoba:** None. **S. Khullar:** None. **Y. Mu:** None. **D. Wang:** None. **M. Gerstein:** None.

Poster

162. Bioinformatics and Systems Biology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 162.14

Topic: I.02. Systems Biology and Bioinformatics

Support: JST ERATO grant number JPMJER2001
the Science and Technology Platform Program for Advanced Biological Medicine
JSPS KAKENHI grant-in-aid for scientific research (S) (grant number

JP18H05270)
JSPS KAKENHI grant-in-aid for scientific research (C) (grant number 20K06885)
JSPS KAKENHI grant-in-aid for scientific research (B) (grant number 22H02824)
JSPS KAKENHI grant-in-aid for Early-Career Scientists (grant number 20K16498)
Grant-in-Aid from the Human Frontier Science Program

Title: Development of a parallel device for tissue clearing using a 6-well multi-plate.

Authors: *F. AKIYAMA[1,2], K. MATSUMOTO[1,3], H. R. UEDA[3];
[1]RIKEN Ctr. for Biosystems Dynamics Res., Osaka, Japan; [2]Grad. Sch. of Med., Nagasaki university,, Nagasaki, Japan; [3]Grad. Sch. of Med., The Univ. of Tokyo, Tokyo, Japan

Abstract: Development of a parallel device for tissue clearing using a 6-well multi-plate.
AuthorsF. Akiyama[1,2], K. Matsumoto[2,3], H. Ueda[2,31]Graduate School of Biomedical Sciences, Nagasaki University[2]RIKEN Center for Biosystems Dynamics Research[3]Department of Systems Pharmacology, University of Tokyo
DisclosuresF. Akiyama: None, K. Matsumoto: None, H. Ueda: None
AbstractThe tissue clearing technique allows biological samples to be made transparent by delipidating and adjusting the refractive index with multiple reagents. Although observation of deep tissue is limited by light scattering, tissue clearing methods suppress light scattering and allow biological relationships between structure and function to be investigated by light-sheet microscopy. CUBIC (Clear, Unobstructed Brain / Body Imaging Cocktails and Computational analysis) is a tissue clearing technique using water-soluble reagents, which enables the clearing of most organs in mice. Although CUBIC is better at preserving the fluorescence of fluorescent proteins, it requires a long delipidating period and frequent reagent exchanges compared to hydrophobic reagents (BABB, iDisco, etc.). To solve this problem, we have developed a device that simplifies complicated procedures such as reagent exchange and gel embedding. In the conventional tissue clearing method using a microtube, there are problems of the risk of damaging the sample and complicated procedures when exchanging the reagents. By using a protocol using a 6-well plate and the device we developed, it was possible to clear and stain a larger number of samples in parallel with fewer procedures. In addition, it was possible to obtain transparency comparable to that of the conventional method using a microtube. Compared with the conventional clearing method using micro tubes, it has become possible to clear and stain a larger amount of samples in parallel with a smaller number of procedures. In this presentation, we will introduce the flow of tissue clearing, staining, gel embedding, and imaging using the device we developed and the 6-well multi-plate.

Disclosures: F. Akiyama: None. **K. Matsumoto:** None. **H.R. Ueda:** None.

Poster

162. Bioinformatics and Systems Biology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 162.15

Topic: I.02. Systems Biology and Bioinformatics

Support: NIH Grant MH116492-03S1

Title: Structured polygenic scores for psychiatric disorders using single-cell genomics

Authors: *J. WARRELL, P. S. EMANI, A. YANG, X. ZHOU, C. DURSUN, G. WANG, M. GERSTEIN;
Yale Univ., New Haven, CT

Abstract: Most psychiatric disorders display high levels of missing heritability, suggesting that more accurate models of the genetic components of these disorders are possible. One route to learning such models is to combine genetic information with functional genomics to learn structured polygenic scores. We make use of the large amount of matched genetics and genomics data (transcriptomics, epigenomics, Hi-C and ATAC-seq) from the human prefrontal cortex from the PsychENCODE consortium, both at bulk and single-cell resolution, to learn structured polygenic scores to characterize the risk for psychiatric disorders (Schizophrenia, Bipolar, Autism). We develop an interpretable deep learning framework to integrate data from these sources, where all endophenotypes are combined in a joint energy function, representing the network dependencies both at the cellular and inter-cellular level. At the cellular level, we learn cell-type specific Gene Regulatory Networks and Gene Co-expression Networks, while at the bulk/inter-cellular level we additionally learn Cell-type Communication and Protein-Protein Interaction Networks as part of the energy function. These are linked to the genotype via bulk and cell-type specific Expression Quantitative Trait Loci (eQTL) SNP-gene linkages. We provide a unified framework, combining Boltzmann machine (discrete trait) and Gaussian Markov Random field (continuous trait) components for imputation of endophenotypes, and an interpretative deep-learning architecture for high-level trait prediction. We show our polygenic scores improve prediction over scores learned using just genetics, or genetics and bulk data only, providing state-of-the-art performance. Further, we can robustly deconvolve the genetic risk for each condition over 24 cell-types (including layer-specific neuronal types, and non-neuronal types), and we show consistency with GWAS analyses and the ability of our model to learn from rare variants.

Disclosures: J. Warrell: None. **P.S. Emani:** None. **A. Yang:** None. **X. Zhou:** None. **C. Dursun:** None. **G. Wang:** None. **M. Gerstein:** None.

Poster

162. Bioinformatics and Systems Biology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 162.16

Topic: I.02. Systems Biology and Bioinformatics

Support: RGPIN-2019-04133

Title: A novel mouse model to characterize the differential distribution and targets of Sumo paralogs in the mouse brain

Authors: *T. R. SUK, T. T. NGUYEN, Z. A. FISK, H. M. GEERTSMA, J.-L. A. PARMASAD, M. M. HEER, S. M. CALLAGHAN, M. W. C. ROUSSEAUX;
Cell. and Mol. Med., Univ. of Ottawa, Ottawa, ON, Canada

Abstract: SUMOylation is an evolutionarily conserved and essential mechanism whereby Small Ubiquitin Like Modifiers, or SUMO proteins, are covalently bound to protein substrates in a highly dynamic and reversible manner. SUMOylation is involved in a variety of basic neurological processes including learning and memory, and central nervous system development, but is also linked with neurological disorders. However, studying SUMOylation *in vivo* remains challenging due to limited tools to study SUMO proteins and their targets in their native context. Additionally, of the three SUMO paralogs (SUMO1 - SUMO3) shared and conserved between humans and mice, Sumo1 and Sumo2 are ~50% homologous, whereas mature Sumo2 and Sumo3 are nearly indistinguishable. To overcome these limitations, we generated a novel mouse model to study SUMOylation in the mouse brain via knock-in of a hemagglutinin (HA) tag into the endogenous *Sumo2* locus. Using this HA-Sumo2 mouse line to complement a previously established HA-Sumo1 knock-in mouse line (Tirard et al, 2012), we compared brain regions via whole brain imaging of HA for differential distribution of Sumo1 verses Sumo2. Moreover, we performed immunoprecipitation coupled with mass spectrometry to identify native substrates targeted by Sumo2 or Sumo1 in the mouse brain. Finally, we validated select hits using proximity ligation assays providing insight into the subcellular distribution of neuronal Sumo2-conjugates. This model thus serves as a valuable tool to study the cellular and biochemical roles of SUMOylation in the central nervous system. Future studies will leverage this model to facilitate the study of context specific SUMOylation in neurons to gain better insight into activity or stress dependent SUMOylation on protein function.

Disclosures: T.R. Suk: None. **T.T. Nguyen:** None. **Z.A. Fisk:** None. **H.M. Geertsma:** None. **J.A. Parmasad:** None. **M.M. Heer:** None. **S.M. Callaghan:** None. **M.W.C. Rousseaux:** None.

Poster

162. Bioinformatics and Systems Biology

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 162.17

Topic: I.02. Systems Biology and Bioinformatics

Support: JST ERATO grant number JPMJER2001
the Science and Technology Platform Program for Advanced Biological Medicine (AMED/MEXT to H.R.U.)

JSPS KAKENHI grant-in-aid for scientific research (S) (H.R.U., grant number JP18H05270)
JSPS KAKENHI grant-in-aid for scientific research (C) (to K.M., grant number 20K06885)
a Grant-in-Aid from the Human Frontier Science Program (to H.R.U.)
JST [Moonshot R&D] (to K.M., grant number JPMJMS2023)
MEXT Quantum Leap Flagship Program (MEXT QLEAP) (to H.R.U., grant number JPMXS0120330644)

Title: Theoretical study of synaptic plasticity during the sleep-wake cycle

Authors: *F. L. KINOSHITA[1,2], K. MATSUMOTO[3,2], K. ODE[3], F. TATSUKI[3], H. R. UEDA[3,2];
[1]Grad. Sch. of Med., Osaka Univ., Osaka, Japan; [2]RIKEN Ctr. for Biosystems Dynamics Res., Osaka, Japan; [3]Grad. Sch. of Med., the Univ. of Tokyo, Tokyo, Japan

Abstract: Much is still unknown about the learning rules and trends in the synaptic weight of cortical neuron networks during the sleep and wake cycle. The synaptic homeostasis hypothesis proposes that synaptic strength increases in the wake and decreases during sleep (G. Tononi et al., 2005), which can be one of the sources for slow dynamics observed in the sleep and wake cycle. However, such synaptic dynamics contradict the fast electrophysiological activity during sleep because increases in synaptic strength tend to induce the sleep-like synchronized activity of cortical neurons. We studied the synaptic plasticity and learning rules in network activity using multi-electrode array (MEA) and computational models of networks of neurons. We obtained the spike train data of wake-like desynchronized patterns and sleep-like synchronized patterns by drug administration to primary cultured neurons of ICR E16 mice cortex on MEA. We have sorted the records from electrodes to obtain spike trains of individual neurons and calculated the cross-correlation of each pair of them, by which we predicted 200 synapses per neuron. We have assigned the sleep-like and wake-like spike trains to a computational model of 200 pre-synaptic neurons connected to one post-synaptic neuron (Graupner et al., 2012), in which the intracellular Ca^{2+} concentration decides the synaptic learning rules. To investigate the relationship between network activity and synaptic plasticity in neural networks that fire autonomously, we have made a model of thousands of cortical neurons with five ion channels, one ion pump, and synaptic receptors including learning rules. By searching parameters of channels or receptors' activities and assuming different learning rules, we found that the synaptic weight decreased from baseline in the wake-like spike trains while it increased in the sleep-like spike trains at 0.1-0.6 Hz if classical spike-timing-dependent plasticity (STDP) works between neurons. The increasing trend in synaptic weight during sleep-like spike patterns than in wake-like spike patterns is conserved when we incorporated the different learning rules including Hebbian, STDP, and anti-STDP. The duration of bursts in synchronized states and the firing rate influenced the trends in synaptic weight. These results have contradicted the hypothesis suggesting that synaptic strength increases in the wake and decreases in sleep. We proposed an alternative prediction that may explain synaptic changes during the sleep-wake cycle, compatible with the electrophysiological neural activity during sleep.

Disclosures: F.L. Kinoshita: None. **K. Matsumoto:** None. **K. Ode:** None. **F. Tatsuki:** None. **H.R. Ueda:** None.

Poster

163. Affective Disorders and Schizophrenia: Biomarkers and Drug Discovery

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 163.01

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Support: Stanley Medical Research Institute grants 03-484 and 06T-797
NIH NIMH/FIC/NCCAM grant R21MH095644
NIH NIMH grant R21MH117776
Contract # HHSN-271-2013-00017-C and HHSN-271-2018-00023-C (NIMH - PDSP)

Title: Botanicals with modulatory activity on GPR88: potential interaction with biologically relevant receptors

Authors: *C. GALLO[1], G. POLETTI[1], R. ROJAS[1], J. ALBÁN[2], R. CONDORI[1], A. VAISBERG[1];
[1]Univ. Peruana Cayetano Heredia, Lima, Peru; [2]Univ. Nacional Mayor de San Marcos, Lima, Peru

Abstract: The orphan G protein-coupled receptor 88 (GPR88) is highly expressed in the striatum, being most abundant in both the D1 and D2/A2A receptor expressing medium spiny neurons (MSNs).
Although no endogenous ligand for GPR88 has been discovered yet, it is known that GPR88 has the highest sequence homology with the 5-HT1d (27%) and the β3 adrenergic (21%) receptors; and that, based on the alignment of 30 critical residues predicted to line the binding cavity of GPCRs, GPR88 clusters with metabotropic glutamate and GABAB receptors. GPR88 knockdown in mice has been associated to a increase in delta-opioid receptor expression. We have a repository of extracts from 87 plants used in Peruvian traditional medicine. Thirty-nine of these extracts were found active for GPR88 in a functional Tango-beta-arrestin assay performed at the NIMH Psychoactive Drug Screening Program (PDSP) - University of North Carolina, Chapel Hill. The reported traditional use of these extracts ranged diverse behavioral conditions defined either in formal (depression, insomnia) and informal (“nerves”, “madness”, “heartache”, “sadness”) terminology. These 39 extracts were further analyzed for binding of the following receptors: 5-HT1-d (ligand: [^{3}H]5-CT, reference: Ergotamine), β3 adrenergic, D1 (ligand: [^{3}H]-SCH23390, reference: (+)-Butaclamol), D2 (ligand: [^{3}H]-N-methylspiperone, reference: Haloperidol), metabotropic glutamate mGlu2, mGlu3 (ligand: [^{3}H]-LY341495, reference: L-Glutamate), mGlu5 (ligand: [^{3}H]-MPEP , reference: Fenobam), opioid delta (ligand: [^{3}H]-DADLE, reference: Naltrindole), kappa (ligand: [^{3}H]-U69593, reference: salvinorin A) and mu (ligand: [^{3}H]-DAMGO, reference: DAMGO). Also, the extracts were assayed for functional A2A agonist (control: 5'-N-Ethylcarboxamidoadenosine -NECA-) and antagonist activity (control: CGS15943).The association between the binding or functional activity values of the extracts was explored through multiple correlation. The presence of GPR88 agonist activity in the extract

correlated negatively with A2A agonist ($p<0.001$) and positively with A2A antagonist ($p<0.05$) activity and delta-opioid binding ($p<0.02$). Methanol-chloroform fractions of the selected botanical extracts show the highest GPR88 agonist activity whereas the highest inverse agonist activity is found mostly in aqueous fractions. This information is promising, regarding to the biological relevance of the activities found in these extracts, as well as their potential as source of novel GPR88 active molecules, that could help to a better understanding of this receptor mechanisms and eventually as therapeutics for neuropsychiatric disorders.

Disclosures: C. Gallo: None. **G. Poletti:** None. **R. Rojas:** None. **J. Albán:** None. **R. Condori:** None. **A. Vaisberg:** None.

Poster

163. Affective Disorders and Schizophrenia: Biomarkers and Drug Discovery

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 163.02

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Support: NIH R01NS112176
Minnesota Partnership MNP #19.13
NIH F31NS115202-01A1
NIH R25GM055252-23
NIH TL1TR002380-03
NIH T32GM065841-17
NHMRC 1156072

Title: Cocaine increases stimulation-evoked accumbal serotonin release

Authors: *J. YUEN[1], A. GOYAL[1], A. RUSHEEN[1], A. KOUZANI[3], M. BERK[3], J. KIM[3], S. J. TYE[4], C. D. BLAHA[1], K. E. BENNET[2], K. H. LEE[1], Y. OH[1], H. SHIN[1];
[2]Div. of Engin., [1]Mayo Clin., Rochester, MN; [3]Deakin Univ., Geelong, Australia; [4]Queensland Brain Inst., St Lucia, Australia

Abstract: Cocaine increases stimulation-evoked accumbal serotonin release
Background
Although dopamine is the most implicated neurotransmitter in the mediation of the pathophysiology of addiction, animal studies show serotonin also plays a vital role. Cocaine is one of the most common illicit drugs globally, but the role of serotonin in its mechanism of action is insufficiently characterized.
Methods
We investigated the acute effects of the psychomotor stimulant cocaine on electrical stimulation-evoked serotonin (phasic) release in the nucleus accumbens core (NAcc) of urethane-anesthetized (1.5 g/kg i.p.) male Sprague-Dawley rats using N-shaped fast-scan cyclic voltammetry (N-FSCV). A single carbon fiber microelectrode was first implanted in the NAcc.

Stimulation was applied to the medial forebrain bundle using 60 Hz, 2 ms, 0.2 mA, 2 s biphasic pulses before and after cocaine (2 mg/kg i.v.) was administered.

Results

Stimulation-evoked serotonin release significantly increased 5 minutes after cocaine injection compared to baseline (153±21 nM vs 257±12 nM; p = 0.0042; n = 5) but was unaffected by saline injection (1 ml/kg i.v.; n = 5). N-FSCV's selective measurement of serotonin release in vivo was confirmed pharmacologically via administration of the selective serotonin reuptake inhibitor escitalopram (10 mg/kg i.p.) which effectively increased the signal in a separate group of rats (n = 5). Selectivity to serotonin was further confirmed in vitro in which dopamine was minimally detected by N-FSCV with a serotonin to dopamine response ratio of 1:0.04 (200 nM of serotonin:1 micro-M dopamine ratio; p = 0.0048; n = 5 electrodes).

Conclusions

Our results not only reinforce the role of serotonin in the mechanism of action of cocaine but also confirm that N-FSCV can effectively and selectively measure phasic serotonin release in the NAcc. This helps to fill a gap in our knowledge and provide a baseline for future studies in cocaine addiction.

Disclosures: **J. Yuen:** None. **A. Goyal:** None. **A. Rusheen:** None. **A. Kouzani:** None. **M. Berk:** None. **J. Kim:** None. **S.J. Tye:** None. **C.D. Blaha:** None. **K.E. Bennet:** None. **K.H. Lee:** None. **Y. Oh:** None. **H. Shin:** None.

Poster

163. Affective Disorders and Schizophrenia: Biomarkers and Drug Discovery

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 163.03

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Title: Efficacy of CVL-042, a novel M4 receptor full agonist, and CV-0000071, a novel M4 receptor partial agonist in preclinical in vivo models of psychosis

Authors: *P. STOLYAR[1], J. LOCANTORE[2], G. SUIDAN[1], S. CHAKILAM[1], H. NGUYEN[1], P. IREDALE[1];
[1]Cerevel Therapeut., [2]Cerevel Therapeut., Cambridge, MA

Abstract: The M4 muscarinic acetylcholine receptor (mAchR) functions as an inhibitory autoreceptor for acetylcholine. Activation of M4 inhibits acetylcholine release and subsequently serves to regulate the transmission of dopamine (DA). More specifically, striatal M4 receptor activation inhibits D1-mediated increases in locomotor activity in rodents. Xanomeline, an M4/M1 preferring agonist, showed promising clinical activity in psychosis-related indications but was hindered by side effects such as nausea, vomiting and dyspepsia, likely driven by non-selective muscarinic agonism. To evaluate the antipsychotic properties of M4 agonism with the goal of avoiding the M1-mediated side effects, CVL-042 and CV-0000071, a full and partial (respectively) agonists were designed and evaluated in two preclinical models of psychosis:

amphetamine-stimulated locomotor activity (aLMA) and conditioned avoidance response test (CAR). Both compounds were shown to be efficacious in aLMA (in both rat and mouse), however only the full agonist was efficacious in the CAR assay. This lack of efficacy of the partial agonist may suggest differences in indirect dopamine modulation that needs further understanding to maximize the varied antipsychotic and cognitive effects that the M4 mechanism can provide. CVL-042 and CV-0000071 were also shown to decrease amphetamine-stimulated increases in striatal acetylcholine in a mouse microdialysis study. These data suggest that although full agonism may be needed for efficacy in the CAR assay, both compounds may have potential as antipsychotic agents.

Disclosures: **P. Stolyar:** A. Employment/Salary (full or part-time):; Cerevel Therapeutics. **J. Locantore:** A. Employment/Salary (full or part-time):; Cerevel Therapeutics. **G. Suidan:** A. Employment/Salary (full or part-time):; Cerevel Therapeutics. **S. Chakilam:** A. Employment/Salary (full or part-time):; Cerevel Therapeutics. **H. Nguyen:** A. Employment/Salary (full or part-time):; Cerevel Therapeutics. **P. Iredale:** A. Employment/Salary (full or part-time):; Cerevel Therapeutics.

Poster

163. Affective Disorders and Schizophrenia: Biomarkers and Drug Discovery

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 163.04

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Support: Stanley Medical Foundation

Title: Leveraging in silico and in vitro models to design a GluA3-selective positive allosteric modulator for the treatment of the cognitive disruptions in schizophrenia

Authors: *W. MARTENIS[1], K. PELHAM[2], S. NELSON[2], S. P. MORAN[1], E. P. LEBOIS[1], A. J. CAMPBELL[2], M. WEIWER[1], Y.-L. ZHANG[1], A. GULETSKY[2], J. C. H. HSU[2], A. SKEPNER[2], K. PEREZ DE ARCE[1], S. JO[1], P. GRI[2], F. CHEN[1], B. SAUVAGNAT[2], Z. FU[1], D. E. BAEZ-NIETO[1], J. M. MADISON[1], J. Q. PAN[1], F. F. WAGNER[2], M. H. SHENG[1]; [1]Stanley Ctr., [2]Ctr. for the Develop. of Therapeut., Broad Inst. of MIT and Harvard, Cambridge, MA

Abstract: A wealth of preclinical data suggests that α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) positive allosteric modulators (PAMs) may ameliorate the cognitive disruptions in patients with schizophrenia and are currently being evaluated in human clinical trials. However, clinical use of AMPAR PAMs are limited by their major on-target side effects, such as seizures, thereby limiting the therapeutic window of AMPAR PAMs. Recent analyses from the Schizophrenia Exome Sequencing Meta-Analysis (SCHEMA) consortium have implicated the GRIA3 subunit but not other subunits of AMPARs in schizophrenia. We hypothesize that a GRIA3-selective AMPAR PAM may retain the

cognitive benefits of an unbiased AMPAR PAM while potentially reducing on-target toxicity by decreasing activation of other AMPARs at a given dosage. AMPAR homology models based upon existing crystal structures revealed key amino acid differences in the interface between AMPAR subunits that can be exploited to create compounds that are selective for specific subunit combinations. Using a suite of human AMPAR overexpression cell lines expressing different permutations of AMPAR isoforms, we evaluated six previously disclosed AMPAR PAMs to characterize the subunit selectivity of AMPAR PAMs in the literature. We then performed iterative medicinal chemistry to identify derivatives selective for GRIA3-containing AMPARs. Fluorescent imaging plate reader (FLIPR) studies enabled high-throughput comparison of AMPAR PAM modulation of AMPAR subunit combinations. Followup *in vitro* mechanism of action studies were performed using automated patch clamp electrophysiology to gain further insight into PAM activity. Using our iterative approach, we suggest that it is possible to design a GRIA3-preferring AMPAR PAM and that this selectivity may prove to be beneficial in the treatment of the cognitive disruptions in patients with schizophrenia.

Disclosures: **W. Martenis:** None. **K. Pelham:** None. **S. Nelson:** None. **S.P. Moran:** None. **E.P. Lebois:** None. **A.J. Campbell:** None. **M. Weiwer:** None. **Y. Zhang:** None. **A. Guletsky:** None. **J.C.H. Hsu:** None. **A. Skepner:** None. **K. Perez De Arce:** None. **S. Jo:** None. **P. Gri:** None. **F. Chen:** None. **B. Sauvagnat:** None. **Z. Fu:** None. **D.E. Baez-Nieto:** None. **J.M. Madison:** None. **J.Q. Pan:** None. **F.F. Wagner:** None. **M.H. Sheng:** None.

Poster

163. Affective Disorders and Schizophrenia: Biomarkers and Drug Discovery

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 163.05

Topic: G.05. Mood Disorders

Support: NIMH Grant R01MH112729

Title: Select second generation antipsychotics signal through arrestin-3 at D3 dopamine receptors in mouse prefrontal cortex

Authors: *S. SCHAMILOGLU[1], E. LEWIS[2], A. C. HERGARDEN[2], K. BENDER[1], J. WHISTLER[2];
[1]Univ. of California, San Francisco, San Francisco, CA; [2]Univ. of California, Davis, Davis, CA

Abstract: Second generation antipsychotics (SGAs), including clozapine, quetiapine, and aripiprazole, are used to treat schizophrenia and bipolar disorder and show fewer extrapyramidal side effects than their earlier counterparts. SGAs bind with high affinity to G-protein-coupled receptors (GPCRs), including D2 and D3 dopamine receptors (D2R, D3R). Their utility is thought to rely on blockade of dopamine-mediated G-protein signaling; however, individual SGAs have different effect and side-effect profiles, suggesting that effectors other than G-protein may be important for their function. SGA pharmacology is well-studied at D2R but less-

characterized at D3R, which is expressed throughout brain regions implicated in psychiatric disorders, including prefrontal cortex (PFC). We found previously that D3R agonist modulation of Cav3.2 calcium channels at the axon initial segment (AIS) requires non-canonical signal transduction through arrestin-3. Here, we report that some clinically important SGAs function as arrestin-3 agonists at D3R, even in the absence of G-protein activation, and that they modulate neuronal activity in the PFC through this arrestin-3-dependent mechanism. These results highlight an acute mechanism of SGA action; however, the full therapeutic effect of SGAs often takes weeks to months of treatment. We further show that chronic treatment with an arrestin-3 agonist-SGA, but not an antagonist-SGA, abolishes D3R function in the PFC through post-endocytic receptor degradation by G-protein-coupled receptor associated sorting protein 1 (GASP1). These results implicate D3R-mediated arrestin-3 signaling as a source of SGA variability, highlight the importance of including arrestin-3 signaling in the characterization of drug action, and implicate post-endocytic D3R trafficking in the need for chronic SGA treatment for maximal treatment efficacy.

Disclosures: S. Schamiloglu: None. **E. Lewis:** None. **A.C. Hergarden:** None. **K. Bender:** None. **J. Whistler:** None.

Poster

163. Affective Disorders and Schizophrenia: Biomarkers and Drug Discovery

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 163.06

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Support: National Institute on Drug Abuse (DA029840)

Title: Evaluation of ^{125}I-HY-3-24, a selective ligand for the dopamine D3 receptor: pharmacological approach by in vitro binding studies

Authors: *J. LEE[1], H. KIM[2], P. MARTORANO[2], M. TAYLOR[3], R. R. LUEDTKE[3], R. H. MACH[2];
[1]Dept. of Radiology, Univ. of Pennsylvania, Philadelphia, PA; [2]Dept. of Radiology, Uiversity of Pennsylvania, philadelphia, PA; [3]Dept. of Pharmacol. and Neurosci., Univ. of North Texas Hlth. Sci. Ctr., Fort Worth, TX

Abstract: Dopamine D3 receptor (D3R) ligands have been studied for the possible treatment of neurological and neuropsychiatric disorders. However, selective D3R ligands have been challenging to identify due to the high structural similarity between the dopamine D2 (D2R) and D3R subtypes. In the present study, we developed a new conformationally-flexible benzamide scaffold having a) D3R vs D2R binding selectivity and b) high affinity binding at the D3R. We characterized the pharmacological properties and distribution pattern of binding sites using rat or non-human primate (NHP) brain tissue. HY-3-24 was designed based on the structure of the metoclopramide (Ki D2: 21 nM, Ki D3: 27 nM). To investigate the receptor binding selectivity

of HY-3-24, *in vitro* receptor binding profiles for sigma receptor, dopamine D2/D3/D4R were measured. Also, a β-arrestin recruitment assay was performed. HY-3-24 was also radiolabeled with [^{125}I]iodine for additional studies. The maximal binding capacity (B_{max}) and the equilibrium dissociation constant (K_d) of [^{125}I]HY-3-24 was obtained by saturation curve analysis using rat ventral striatum membrane homogenates. PD128907, quinpirole, SCH23390, and raclopride were used for competition binding assays with [^{125}I]HY-3-24 (n = 3) and Ki values were compared to previously reported values. *In vitro* autoradiography was performed to confirm specific distribution regions in rat and nonhuman primate (NHP) brains. Non-specific binding was determined using (+)-butaclamole. HY-3-24 showed high potency at dopamine D3R (K_i = 0.67±0.11 nM) compared to other D2-like dopamine receptor subtypes (D2R K_i = 86.7±11.9 nM and D4R K_i > 1000). Using an β-arrestin recruitment assay HY-3-24 was found to be an antagonist (IC_{50} = 1.5±0.58 nM). K_d value (0.34±.0.22 nM) and B_{max} (38.91±2.39 fmol/mg) of [^{125}I]HY-3-24 were determined. K_i values of known dopamine antagonists and agonists were defined using [^{125}I]HY-3-24 with rat ventral striatum tissue and the results were similar to previously reported studies; PD128907 (K_i = 6.41±.2.69 nM), quinpirole (K_i = 28.6±28.4 nM), SCH23390 (K_i = 182±82.7 nM), and raclopride (K_i = 2.56±.0.74 nM). Autoradiography results demonstrated that [^{125}I]HY-3-24 specifically binds to D3Rs in the nucleus accumbens, islands of Calleja, and caudate putamen using rat and NHP brains. The results of direct competitive binding suggest that HY-3-24 is a novel D3R selective ligand. Furthermore, [^{125}I]HY-3-24 appears to be a novel radioligand exhibiting high affinity binding at D3R, with binding selectivity compared to other D2-like dopamine receptors. It is anticipated that [^{125}I]HY-3-24 can be used as the specific D3R radioligand.

Disclosures: **J. Lee:** None. **H. Kim:** None. **P. Martorano:** None. **M. Taylor:** None. **R.R. Luedtke:** None. **R.H. Mach:** None.

Poster

163. Affective Disorders and Schizophrenia: Biomarkers and Drug Discovery

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 163.07

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Title: Efficacy of subtype-selective, full vs partial M4 muscarinic receptor agonists in modulating amphetamine-induced brain activity assessed by functional MRI (fMRI) in rat

Authors: *S. BARDEHLE[1], G. SUIDAN[1], H. NGUYEN[1], S. CHAKILAM[1], G. GOKULRANGAN[1], R. IMMONEN[2], A. SHATILLO[2], P. A. IREDALE[1];
[1]Cerevel Therapeut., Cerevel Therapeut., Cambridge, MA; [2]Charles River Discovery Services, Kuopio, Finland

Abstract: The M4 muscarinic acetylcholine receptor (mAchR) is one out of the 5 mAchR subtypes (M1-M5) in the G-protein coupled receptor (GPCR) superfamily. It is a transmembrane Gi-coupled protein that is expressed in neurons both, pre- and postsynaptically, in brain regions

associated with psychotic and cognitive functions, including the striatum, the cortex, and the hippocampus. Activation of M4 receptors negatively regulates acetylcholine release, the transmission of dopamine, and thereby potentially modulates neuronal activity underlying cognitive and motor behaviors. The unique brain expression profile of the M4 receptor, as well as its effects on neurotransmitter signaling makes it a compelling target for various psychiatric diseases. One such therapeutic opportunity is in the potential treatment of the psychosis symptoms observed in both schizophrenia, and neurodegenerative conditions like Alzheimer's disease. In both cases, striatal dopaminergic hyperactivity is believed to drive the positive symptoms. However, to date subtype selective and potent M4 molecules with anti-psychotic, clinical efficacy are limited. Here we present in vivo efficacy data comparing a partial versus a full M4 selective agonist. Modulation of brain activity was assessed by fMRI at 7 Tesla system to monitor amphetamine-induced increase in relative cerebral blood volume (rCBV) in relevant brain regions in medetomidine anesthetized, ventilated Sprague-Dawley rats. Acute dosing with either partial or full M4 agonist produced a dose-dependent and significant decrease in amphetamine-induced rCBV changes, most robustly in the cortex and striatal brain regions. The differential fMRI response profiles observed between compounds with different level of M4 agonism suggest that there is opportunity to dial in the most appropriate amount of intrinsic efficacy in a compound to match the desired down-stream effect. In summary, in vivo fMRI data presented here, supported by behavioral studies (not shown), showed the efficacy of two selective and potent M4 agonists in a preclinical model indicative of their anti-psychotic potential in the treatment of positive symptoms in schizophrenia and Alzheimer's disease.

Disclosures: S. Bardehle: None. **G. Suidan:** None. **H. Nguyen:** None. **S. Chakilam:** None. **G. Gokulrangan:** None. **R. Immonen:** None. **A. Shatillo:** None. **P.A. Iredale:** None.

Poster

163. Affective Disorders and Schizophrenia: Biomarkers and Drug Discovery

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 163.08

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Title: Oxytocin receptor binding in the substantia nigra in schizophrenia

Authors: *A. SNOWDEN[1], G. MOWER[2], S. M. FREEMAN[2];
[2]Biol., [1]Utah State Univ., Logan, UT

Abstract: Schizophrenia is a chronic, psychiatric disorder characterized by hallucinations, delusions, cognitive deficits, and social cognitive impairments. Although antipsychotic drugs are typically effective in treating psychotic symptoms in schizophrenia, the social cognitive symptoms often persist. As social cognitive functioning is predictive of successful life outcomes in schizophrenia, there is a critical need to determine the biological basis of social cognitive impairments. Due to its ability to affect social behaviors in animals and humans, the oxytocin (OXT) system has become a therapeutic target of interest for schizophrenia. Although several

studies examine the OXT system in schizophrenia in the periphery, it is currently unclear whether there is dysfunction of central OXT in schizophrenia. Using receptor autoradiography and postmortem specimens from the NIH NeuroBioBank, we examined oxytocin receptor (OXTR) binding in the substantia nigra between individuals who had schizophrenia (n=16) and unaffected controls (n=16). The Freeman Lab has identified the substantia nigra as a region of interest in the human brain, due to its high levels of OXTR. No differences in OXTR binding were observed between individuals who had schizophrenia and controls. We also observed no effects of sex on OXTR binding in the substantia nigra. We found a trend toward decreases in OXTR binding with advanced age in the schizophrenia group, a finding that was not observed in unaffected controls. Our findings suggest that OXTR functioning is preserved in the substantia nigra in schizophrenia. However, it is unclear whether variation in OXTR binding in SZ in the substantia nigra is masked by effects of antipsychotic medication on OXTR. In future work, we will determine whether OXTR binding varies with antipsychotic medication dosage and examine OXTR binding in the hypothalamus (oxytocin synthesis) and superior temporal sulcus, a region showing aberrant functioning during social perception in schizophrenia.

Disclosures: **A. Snowden:** None. **G. Mower:** None. **S.M. Freeman:** None.

Poster

163. Affective Disorders and Schizophrenia: Biomarkers and Drug Discovery

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 163.09

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Support: Grants-in-Aid for Young Scientists (grant numbers JP16K19790 and JP19K17101 to M.K.) and a Grant-in-Aid for Scientific Research (grant number JP19H01041 to Y.T.) from the Japan Society for the Promotion of Science
the Japan Agency for Medical Research and Development (grant numbers JP20dm0207072 and JP20dm0307105 to M.H)

Title: Positron emission tomography assessments of phosphodiesterase 10a in patients with schizophrenia

Authors: *M. KUBOTA[1,2], K. TAKAHATA[2], K. MATSUOKA[2], Y. SANO[2], Y. YAMAMOTO[2], K. TAGAI[2], R. TARUMI[3], H. SUZUKI[2], S. KUROSE[2], S. NAKAJIMA[3], H. SHIWAKU[4], C. SEKI[2], K. KAWAMURA[2], M.-R. ZHANG[2], H. TAKAHASHI[4], Y. TAKADO[2], M. HIGUCHI[2];
[1]Dept. of Psychiatry, Grad. Sch. of Med., Kyoto Univ., Kyoto, Japan; [2]Inst. for Quantum Med. Sci., Natl. Inst. for Quantum Sci. and Technol., Chiba, Japan; [3]Dept. of Neuropsychiatry, Keio Univ. Sch. of Med., Tokyo, Japan; [4]Dept. of Psychiatry and Behavioral Sciences, Grad. Sch. of Med. and Dent. Sci., Tokyo Med. and Dent. Univ., Tokyo, Japan

Abstract: Phosphodiesterase 10A (PDE10A) is an enzyme highly expressed in the basal ganglia, in which cortical glutamatergic and midbrain dopaminergic inputs are integrated. While therapeutic effects of PDE10A inhibition on schizophrenia have been previously reported, alterations in the amounts and ligand reactivity of this molecule in living patients with schizophrenia remain elusive. We aimed to investigate the central PDE10A status in patients with schizophrenia and to examine its relationship with psychopathology, cognition, and cortico-striatal glutamate levels. Twenty-seven patients with schizophrenia, including five antipsychotic-free cases, and 27 healthy controls were studied. We employed positron emission tomography (PET) with [^{18}F]MNI-659, a specific PDE10A radioligand, to quantify PDE10A availability by measuring non-displaceable binding potential (BP_{ND}) of the ligand in the limbic, executive, and sensorimotor striatal functional subregions and the pallidum. BP_{ND} estimates were compared between patients and controls while controlling for age and gender. We also examined correlations of BP_{ND} with behavioral and clinical measures, along with regional glutamate levels quantified by magnetic resonance spectroscopy (MRS). A multivariate analysis of covariance demonstrated a significant main effect of diagnosis on BP_{ND} ($p = 0.03$), and a post-hoc test showed a significantly higher sensorimotor striatal BP_{ND} of patients. In controls but not patients, BP_{ND} in this subregion was significantly and negatively correlated with the scores of Tower of London, a cognitive subtest. There was also a trend toward positive correlations between BP_{ND} in several striatal subregions with dorsolateral prefrontal glutamate levels. Our results suggest higher sensorimotor striatal PDE10A availability and associated local neural dysfunctions in patients with schizophrenia.

Disclosures: M. Kubota: None. **K. Takahata:** None. **K. Matsuoka:** None. **Y. Sano:** None. **Y. Yamamoto:** None. **K. Tagai:** None. **R. Tarumi:** None. **H. Suzuki:** None. **S. Kurose:** None. **S. Nakajima:** None. **H. Shiwaku:** None. **C. Seki:** None. **K. Kawamura:** None. **M. Zhang:** None. **H. Takahashi:** None. **Y. Takado:** None. **M. Higuchi:** None.

Poster

163. Affective Disorders and Schizophrenia: Biomarkers and Drug Discovery

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 163.10

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Support: Ministry of Science and Technology (MOST), Taiwan Grant 110-2321-B-A49A-502
Ministry of Science and Technology (MOST), Taiwan Grant 110-2628-B-A49A-509
Ministry of Science and Technology (MOST), Taiwan Grant 110-2634-F-075-001
Mt. Jade Young Scholarship Award from Ministry of Education, Taiwan
National Yang Ming Chiao Tung University and the Ministry of Education (Aim for the Top University Plan), Taipei, Taiwan
Ministry of Science and Technology (MOST), Taiwan Scholarship 108-2926-I-010-001-MY4

Ministry of Science and Technology (MOST), Taiwan Grant 110-2634-F-A49-005

Title: Using multimodal structural magnetic resonance imaging to differentiate brain aging trajectories in different brain regions of individuals with schizophrenia

Authors: *J.-D. ZHU[1], S.-J. TSAI[1,3], A. YANG[2,4];
[1]Inst. of Brain Sci., [2]Inst. of Brain Science/Digital Med. and Smart Healthcare Res. Ctr., Natl. Yang Ming Chiao Tung Univ., Taipei, Taiwan; [3]Dept. of Psychiatry, [4]Dept. of Med. Res., Taipei Veterans Gen. Hosp., Taipei, Taiwan

Abstract: Brain-age prediction studies have been widely applied in schizophrenia recently. However, no study has predicted brain age based on different neuroimaging modalities and different brain regions to investigate deviations of brain aging trajectories in schizophrenia. We aimed to construct brain-age prediction models for different brain regions based on T1-weighted MRI and diffusion tensor imaging, respectively, and examine the disease-related impacts on the deviation of aging trajectories in different brain regions of individuals with schizophrenia. A total of 230 healthy controls were collected as a training dataset. We also collected 194 individuals with schizophrenia and 100 healthy controls to test model performance and investigate differences in brain age gaps between the two groups. Gaussian process regression algorithm with five-fold cross-validation was performed to train 90 models for gray matter maps and 48 models for fractional anisotropy (FA) maps in the training dataset. The brain age gaps in different brain regions for individuals with schizophrenia and healthy controls were calculated, and differences in brain age gaps between the two groups were examined using ANCOVA with chronological age and sex as covariates. The results showed that 71 out of 90 gray matter regions in schizophrenia showed over-aging, particularly in the frontal lobe, temporal lobe, and insula. In addition, individuals with schizophrenia had larger brain age gaps than those of healthy controls in 15 out of 48 FA tracts, including the cerebrum and cerebellum. Our findings suggest that different brain regions in schizophrenia have dynamic deviations of brain aging trajectories. Meanwhile, by constructing the brain-age prediction models for different brain regions, we could examine the impacts of schizophrenia on the dynamics in different brain regions and provide comprehensive insights into the neuropathology of schizophrenia.

Disclosures: J. Zhu: None. **S. Tsai:** None. **A. Yang:** None.

Poster

163. Affective Disorders and Schizophrenia: Biomarkers and Drug Discovery

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 163.11

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Support: NIH F32DA052966
NIH R01DA038613
NIH R01MH106500

Title: Mood disorders and blood mitochondrial copy number: a preclinical model and a clinical meta-analysis

Authors: *C. A. CALARCO[1], S. M. KEPPETIPOLA[1], G. KUMAR[1], A. SHIPPER[2], D. FRANCO[1], R. CHANDRA[1], M. LOBO[1];
[2]Hlth. Sci. and Human Services Library, [1]Univ. of Maryland Sch. of Med., Baltimore, MD

Abstract: Mood disorders, such as major depressive disorder and bipolar disorder, are globally prevalent, contributing to significant disease burden and adverse health outcomes. Mood disorders are associated with changes in many aspects of brain reward pathways, yet many cellular and molecular changes in the brain are not readily available in clinical populations. Therefore, the use of biomarkers as proxies for changes in the brain are necessary. Recently, the proliferation of mitochondria in blood leukocytes has emerged as a potentially useful biomarker for mood disorders, with the added benefit that this metric can be remeasured over multiple stages of disease, recovery, or relapse. Experimentally, mitochondria and mitochondrial DNA copy number (mtDNAcn) play a significant role in signaling the effects of stress adaptation characteristic of mood disorders. Preclinical and clinical evidence suggests that chronic stress is linked to the development of mood disorders, and the chronic social defeat stress (CSDS) model in mice has moderately high construct validity for chronic stress in humans. In the current study we examined mitochondrial copy number in blood from animals that have undergone CSDS. Mitochondrial copy number is significantly increased in animals that have undergone CSDS, with the largest increases in animals observed to be susceptible to the stress, as determined by their behavior in a social interaction test. Further, blood mitochondrial copy number is significantly correlated with time spent interacting with the social target in this social interaction test.
To further explore the relationship between mtDNAcn and stress-related mood disorders in humans, a meta-analysis of current literature was performed. The analysis determined whether blood mtDNAcn is systematically altered by specific mood disorders (major depressive disorder or bipolar disorder I/II). The overall effect estimate (standardized mean difference) showed a trending increase in mtDNAcn in patients with major depressive disorder and trending decrease in bipolar populations, compared to controls. mtDNAcn may be a crude indicator of mood pathology, and clinical data for major depression follows the same pattern observed using CSDS in mice, while bipolar disorders show a different mitochondrial profile. Further study of blood mtDNAcn and other circulating immune factors could reveal relevant biomarkers that may predict downstream health outcomes for individuals with mood disorders.

Disclosures: C.A. Calarco: None. **S.M. Keppetipola:** None. **G. Kumar:** None. **A. Shipper:** None. **D. Franco:** None. **R. Chandra:** None. **M. Lobo:** None.

Poster

163. Affective Disorders and Schizophrenia: Biomarkers and Drug Discovery

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 163.12

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Support: Princeton Accelerator Fund 2021

Title: Smartphone-mediated neurobehavioral testing as a digital biomarker for neurodevelopmental disorders.

Authors: S. SHERRY[1], C. JUNG[1], L. ROGGEVEEN[2], J. ÖHMAN[3], R. TAM[1], E. ABRAHAM[1], A. UVAROV[4], P. BOELE[4], S. KOEKKOEK[2], C. DE ZEEUW[2], J. F. MEDINA[5], S. S.-H. WANG[6], *H.-J. BOELE[1];
[1]Princeton Neurosci. Inst., Princeton, NJ; [2]Erasmus MC, Rotterdam, Netherlands; [3]Lund Univ., Lund, Sweden; [4]BlinkLab PTY LTD, Sydney, Australia; [5]Dept. of Neurosci., Baylor Col. of Med., Houston, TX; [6]Princeton Neurosci. Inst., Princeton Univ., Princeton, NJ

Abstract: Neurobehavioral assays of brain function can reveal fundamental mechanisms underlying neuropsychiatric conditions, but typically require centrally located equipment in a test facility. We have developed a smartphone-based app to perform neurobehavioral testing in a wide variety of environments. This platform, termed BlinkLab, can perform eyeblink conditioning (EBC), a form of sensory-motor associative learning, and prepulse inhibition (PPI) of the acoustic startle, which measures the ability to filter out irrelevant information through sensorimotor gating. EBC and PPI do not require verbal or social interaction, allowing large-scale cross-cultural human studies and a foundation on cross-species research. Performance in both EBC and PPI are strongly correlated with neuropsychiatric disorders, and have been suggested as a potential biomarker to identify mechanistically-based subtypes of autism spectrum disorder (ASD). At present, EBC and PPI, which can be unpleasant for the participant and require in-lab testing, are not used as diagnostic instruments in daily clinical practice. BlinkLab can be used at home and in other environments, independently or with the help of a caregiver following user-friendly instructions from the app. Tasks do not require attachment of instruments to the participant. Using the native iOS programming language Swift, each individual audio and/or visual stimulus during the trials is controlled with precise control over timing, amplitude, frequency, and other parameters. Stimulus intensities are calibrated based on the participant's response, extracting facial landmarks in real time. Participant attention is held by showing movies during testing. The participant's responses are measured by the smartphone's camera and microphone, processed in real time using state-of-the art computer vision techniques, fully anonymized, and transferred securely to a cloud-based storage and analysis platform using a TLS 1.2 encrypted connection. For EBC, the unconditional stimulus is a flash of light which activates cerebellum-dependent learning mechanisms, and induces conditioning comparable with traditional stimuli such as airpuff. The success rate of EBC and PPI in BlinkLab are equal to or better than previous reports for humans using conventional lab-based methods. As a demonstration of this platform's usefulness for neurobehavioral testing, we have found that PPI can reliably separate neurotypical and ASD participants, and changes in response to methylphenidate treatment on the time scale of pharmacological efficacy. We are now testing the capacity of BlinkLab to characterize ASD and ADHD endophenotypes.

Disclosures: **S. Sherry:** A. Employment/Salary (full or part-time):; Salary. **C. Jung:** None. **L. Roggeveen:** None. **J. Öhman:** None. **R. Tam:** None. **E. Abraham:** None. **A. Uvarov:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Founder shares. **P. Boele:** A. Employment/Salary (full or part-time):; Salary. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Founder shares. **S. Koekkoek:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Founder shares. **C. De Zeeuw:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Founder shares. **J.F. Medina:** None. **S.S. Wang:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Founder shares. **H. Boele:** None.

Poster

163. Affective Disorders and Schizophrenia: Biomarkers and Drug Discovery

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 163.13

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Title: In-vivo pharmacological imaging of NMDAR-modulators in rodents: functional ultrasound and MRI.

Authors: A. SHATILLO, R. IMMONEN, H. VAHERTO, T. MIETTINEN, N. MARKOFF, S. HALONEN, P. HAKKARAINEN, D. MISZCZUK, ***A. J. NURMI**;
Charles River Discovery Services, Kuopio, Finland

Abstract: Functional ultrasound (fUS), a novel in vivo imaging technique has emerged as a powerful preclinical CNS research tool in recent years. Method utilizes latest technological breakthroughs for ultrafast high sensitivity imaging of relative cerebral blood volume (rCBV) with high spatial resolution. Performed in lightly anesthetized mice, fUS can be a powerful complementary alternative to pharmacological MRI (phMRI) - a well-established, translational technique for in-vivo mapping of the CNS-active pharmacological compounds in the brain, most used in rats.
Ketamine, a dissociative NMDAR antagonist is commonly used in subanasthetic doses as a model of psychosis in schizophrenia. Multiple phMRI studies demonstrated high utility of the ketamine model as imaging platform to study pharmacological modulation of BOLD or rCBV responses by various classes of test compounds in rodents (Shim et al., 2021, Chin et al, 2011). Aim of this work was to prove the utility and value of the fUS imaging in preclinical drug discovery in mice using the ketamine model with known positive control compound - LY379268, a selective agonist of the group II glutamate receptors (mGluR2/3) and compare it to phMRI in rats.
The fUS experiments were performed on total of 36 naïve C57Bl/6J males, 8-10 weeks old mice with dexmedetomidine anesthesia. Experiments were conducted using the Iconeus One fUS

imaging system, equipped with 128 elements linear receiver probe (Iconeus, Paris, France). Animals were pre-treated with vehicle or LY379268 (10 mg/kg, i.p.), followed by R/S ketamine 15 or 30 mg/kg s.c. dosing during the imaging. Data was collected with 0.6s temporal resolution at -1.7 mm from bregma.
In vehicle treated animals, both doses of ketamine produced robust, strong, and significant increase in rCBV signal of ~10% across measured brain regions, peaking at 5-6 min in cortical and hippocampal areas. However, no significant differences were observed between two doses of ketamine. The LY379268 fully and highly significantly ($p<0.01$, pointwise one-way ANOVA) reversed the 30 mg/kg ketamine effect in all brain regions, including amygdala.
In summary, our results show great applicability of fUS - ketamine platform for in vivo drug testing of novel psychoactive compounds, such as allosteric modulators, co-agonists and other pharmacological classes targeting glutamatergic system. Compared to phMRI, fUS imaging is a completely non-invasive, high-sensitivity measurement with shorter protocol, which increases success rate and enables repeated measurements in lightly anesthetized mice while producing similar deliverables (rCBV maps, response profile and its derivatives).

Disclosures: **A. Shatillo:** None. **R. Immonen:** None. **H. Vaherto:** None. **T. Miettinen:** None. **N. Markoff:** None. **S. Halonen:** None. **P. Hakkarainen:** None. **D. Miszczuk:** None. **A.J. Nurmi:** None.

Poster

163. Affective Disorders and Schizophrenia: Biomarkers and Drug Discovery

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 163.14

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Support: TUM Innovation Network Neurotech

Title: Transdiagnostic resting-state EEG biomarkers of pathological fatigue - a systematic review

Authors: *H. B. HEITMANN[1], P. T. ZEBHAUSER[2], V. D. HOHN[2], H. MACLAREN[3], P. HENNINGSEN[4], M. PLONER[2];
[1]Dept. of Neurology, Dept. of Psychosomatic Med. and Psychotherapy, [2]Dept. of Neurol., [3]Dept. of Neurology, Dept. of Psychiatry, [4]Dept. of Psychosomatic Med. and Psychotherapy, Tech. Univ. of Munich, Muenchen, Germany

Abstract: Fatigue, the feeling of extreme mental or physical exhaustion, is a highly prevalent and prominent feature of many neuropsychiatric and multisystemic disorders. However, it's underlying brain mechanisms remain to be elucidated. To this end a systematic literature review was performed using a transdiagnostic approach in line with the NIH Research Domain Criteria framework. Since EEG is a widely used and cost-effective method to assess functional brain alterations it might be particularly suitable for detecting potential transdiagnostic biomarkers.

Additionally, such neurophysiological biomarkers could even serve as treatment targets for neuromodulatory approaches including biofeedback and brain stimulation. A PROSPERO-preregistered systematic literature search of the databases PubMed, EMBASE and Web of Science Core Collection was performed for articles dating until April 2022. The publications included report on alterations of EEG power and functional connectivity measures in patients suffering from fatigue as a primary symptom of different disorders compared to healthy controls. Selection of publications was refined using specific exclusion and inclusion criteria. Risk of bias and quality of publications included was assessed using the adapted Newcastle-Ottawa scale.This systematic review included a total of 21 studies. Most frequent primary diagnoses of study populations included were Chronic fatigue syndrome (CFS, n=11) and Multiple Sclerosis (MS, n=5). Others included Fibromyalgia Syndrome (FMS, n=1), Cancer-related fatigue (CRF, n=1) and Burnout (n=2). Power was assessed in 12 studies, with increases as well as decreases in various frequency bands, predominately in frontal and temporo-parietal brain areas, being reported. Functional connectivity was assessed in 7 studies. These reported disruptions in various brain networks and frequency bands. Additionally, one study assessed the peak alpha frequency in CFS patients and one study assessed brain dynamics in MS patients using microstate analysis.The results obtained suggest widespread functional brain alterations related to fatigue across the different disorders. However, a consistent transdiagnostic EEG biomarker for fatigue could not be identified. Interpretation of results is largely limited by small sample sizes and methodological heterogeneity. Larger scale studies with standardized assessments across different disorders are needed to evaluate potential transdiagnostic EEG biomarkers of fatigue.

Disclosures: H.B. Heitmann: None. **P.T. Zebhauser:** None. **V.D. Hohn:** None. **H. MacLaren:** None. **P. Henningsen:** None. **M. Ploner:** None.

Poster

163. Affective Disorders and Schizophrenia: Biomarkers and Drug Discovery

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 163.15

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Title: The value of preclinical cohort stratification for drug discovery - can baseline EEG biomarker predict treatment responses?

Authors: *N. SCHUELERT, D. URSU, H. ROSENBROCK, R. WILLIAMS, A. CECI, J. DU HOFFMANN, D. SCHNELL, E. TUNBRIDGE;
Boehringer Ingelheim Pharma Gmbh & Co. KG, Boehringer Ingelheim Pharma Gmbh & Co. KG, Biberach, Germany

Abstract: Many psychiatric symptoms (e.g. anxiety, depression, impulsivity) represent extremes of normally distributed variation in healthy humans. New studies suggest that such traits can be correlated with specific electroencephalographic (EEG) biomarkers, such as auditory-event related potentials (AERP), in healthy volunteers and that these biomarkers are highly sensitive to

pharmacological treatment. Therefore, proof-of-concept studies might be more sensitive to drug effects when conducted in surrogate subpopulations stratified based on psychiatric traits rather than unselected healthy volunteers. Additionally, stratification would provide a better prediction of treatment success in psychiatric patients. We investigated whether a stratification approach can be conducted in an animal model by assessing the individual AERP profile across subgroups to determine if baseline values can predict differential sensitivity to pharmacological intervention. Male mice were administered a positive allosteric modulator of the muscarinic acetylcholine receptor 4 (m4PAM), which has been shown to restore cognitive deficits and improve learning in rodent models. AERPs were measured using a novel wireless recording technique. Epidural electrodes were implanted above the primary auditory cortex and medial prefrontal cortex. The m4PAM VU0467154 was tested in a 4-arm cross-over design at 3 different doses. Animals were placed in a sound attenuated cubicle for recordings. A white-noise double-click paradigm, a 40Hz auditory steady-state response (ASSR) paradigm and a mismatch negativity (MMN) paradigm were presented to obtain all readouts. A median split approach was used to stratify animals at baseline into two clusters for all readouts. The m4PAM VU0467154 significantly increased evoked theta and gamma, N1 gating and MMN selectively in the cluster of individuals with low respective values at baseline. As well, the compound decreased ASSR coherence and power selectively in the cluster with high ASSR values at baseline. VU0467154 also increased basal theta, basal gamma and N1 amplitude, but those effects were not dependent on baseline values. Other readouts (e.g. P1 amplitude and P1 gating) were not affected by the treatment. Our results suggest that preclinical cohort stratification using AERP baseline values can predict the probability of response to pharmacological treatment. This approach could increase the sensitivity of preclinical trials and offer translatable application for cohort stratification of healthy volunteers, with the ultimate benefit of increasing the success rate of future drug trials in psychiatric patients.

Disclosures: **N. Schuelert:** A. Employment/Salary (full or part-time):; Employment/Salary. **D. Ursu:** A. Employment/Salary (full or part-time):; Employment/Salary. **H. Rosenbrock:** A. Employment/Salary (full or part-time):; Employment/Salary. **R. Williams:** A. Employment/Salary (full or part-time):; Employment/Salary. **A. Ceci:** A. Employment/Salary (full or part-time):; Employment/Salary. **J. Du Hoffmann:** A. Employment/Salary (full or part-time):; Employment/Salary. **D. Schnell:** A. Employment/Salary (full or part-time):; Employment/Salary. **E. Tunbridge:** A. Employment/Salary (full or part-time):; Employment/Salary.

Poster

164. Tools and Resources for Human Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 164.01

Topic: I.06. Computation, Modeling, and Simulation

Support: NIH grant MH116492-03S1

Title: Harnessing the potential of quantum computing in human brain genomics and imaging

Authors: *P. EMANI[1], J. WARRELL[2], J. CHAPMAN[2], G. WANG[2], A. DONAGHEY[2], M. B. GERSTEIN[2];
[2]Mol. Biophysics and Biochemistry, Program in Computat. Biol. and Bioinformatics, [1]Yale Univ., New Haven, CT

Abstract: Imaging and genomics studies produce high-dimensional data whose structure may not reside in an easily discernible, low-dimensional manifold. This is especially likely in the context of the human brain, with its intricate interdependencies. While increasingly sophisticated classical models have been deployed, the fact that quantum computing (QC) hardware provides an exponential state space (of dimension 2^N for N quantum bits, or *qubits*) allows QC methods potentially faster pathways to solutions and more complex representations of data structure. Here, we employ several quantum machine learning (QML) methods to analyze human prefrontal cortex gene expression data from the PsychENCODE consortium, as well as neuroimaging data: logic-gate-based quantum embedding algorithms map classes of data (eg. schizophrenia cases and controls) to well-separated parts of state space, with quantum neural networks (QNNs) finding the classifying boundaries; in parallel, energy minimization-based QC models such as quantum Boltzmann machines (QBMs) are trained to represent the same data in an alternate hardware context. We thus comprehensively investigate QML on the two main hardware paradigms of QC, as applied to data from different experimental modalities. Some quantum embeddings are known to be inaccessible classically, and we show that QNNs perform on par with or better than classical counterparts in complex classification tasks. Leveraging the combined strength of these approaches has the power to parse subtle differences between classes in neuroscientific data. We also demonstrate that diverse architectures vary in their ability to probe relationships between biological features. Similarly, QBMs utilize uniquely-quantum tunable parameters (i.e. transverse magnetic fields) to better represent the influence of features on case versus control samples. Our hierarchical QBM model suggests relationships between genes that are correlated with schizophrenia status. While training is conducted in simulation (due to current QC resource limitations), we perform prediction tasks on the IBM Q (logic-gate) and D-Wave (energy-minimization) systems. Overall, we demonstrate complex classification tasks with brain genomics and imaging data, while laying out the foundation for the future application of these models.

Disclosures: P. Emani: None. **J. Warrell:** None. **J. Chapman:** None. **G. Wang:** None. **A. Donaghey:** None. **M.B. Gerstein:** None.

Poster

164. Tools and Resources for Human Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 164.02

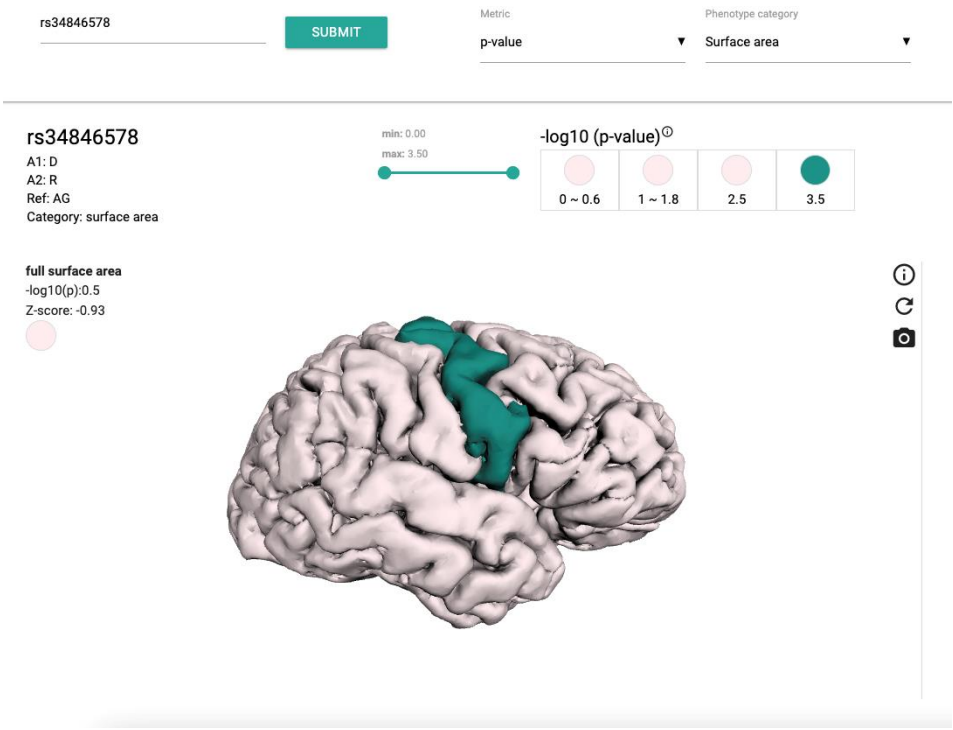
Topic: I.07. Data Analysis and Statistics

Support: U01AG068057

Title: Enigma-vis: a web portal to interact with international genome-wide association studies (gwas) of brain measures

Authors: *N. SHATOKHINA[1], F. PIZZAGALLI[2], R. M. BROUWER[3], H. E. HULSHOFF POL[4], N. JAHANSHAD[1], J. L. STEIN[5], S. E. MEDLAND[6], P. M. THOMPSON[1];
[1]Imaging Genet. Center, Mark and Mary Stevens Neuroimaging and Informatics Inst., USC, Marina del Rey, CA; [2]Dept. of Neurosci., Univ. of Turin, Piemonte, Italy; [3]Complex Trait Genet. Lab., Vrije Univ., Amsterdam, Netherlands; [4]Brain Ctr. Rudolf Magnus, Univ. Med. Ctr. Utrecht, Utrecht, Netherlands; [5]Dept of Genet. & Neurosci. Ctr., UNC-Chapel Hill, Chapel Hill, NC; [6]Psychiatric Genet. Group, QIMR Berghofer Med. Res. Inst., Brisbane, Australia

Abstract: We present an update on our ENIGMA Consortium GWAS visualization portal, ENIGMA-Vis (https://enigma-brain.org/enigmavis/). Our portal is a set of browser-based tools to visualize and navigate the GWAS results from the ENIGMA consortium. These GWAS have discovered over 500 common genetic variants associated with brain measures (cortical and subcortical morphometry, sulcal measures, and longitudinal rates of brain growth and atrophy). Users can query and visualize all datasets side by side - to make regional GWAS plots, perform PheWAS analyses, and enable LD data visualization. For cortical data visualization, the portal offers a tool for making 3D color-coded brain maps of SNP effects on the brain. To readily explore the datasets, a search bar is provided at the top of the page. It accepts query input data in the form of the Single Nucleotide Polymorphism Database (dbSNP) id, gene name, phenotype name, and study name. With the recent release of a new GWAS study of brain longitudinal changes (Brouwer et al., 2022), we updated the portal with the top findings from the age-independent meta-analysis. This new data prompted us to add several new features to improve usability. We enhanced the portal to accept a user query by genomic position and upgraded the underlying data reference source to a recent version 155 of dbSNP for the genome assembly GrCh37/hg19. To help with the case when a query SNP entered in the search bar cannot be found in the data reference source, we implemented an additional SNP lookup in the Ensembl API. For a smoother user experience, the PheWAS page was upgraded with an added option to sort data points by p-value.
The figure demonstrates a 3D brain map made with one of our tools, for a SNP rs34846578 associated with longitudinal changes in the caudate (Brouwer et al., 2022) and the surface area of the precentral region (Grasby et al., 2020).



Disclosures: **N. Shatokhina:** None. **F. Pizzagalli:** None. **R.M. Brouwer:** None. **H.E. Hulshoff Pol:** None. **N. Jahanshad:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Grant support from Biogen, Inc.. **J.L. Stein:** None. **S.E. Medland:** None. **P.M. Thompson:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Grant support from Biogen, Inc..

Poster

164. Tools and Resources for Human Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 164.03

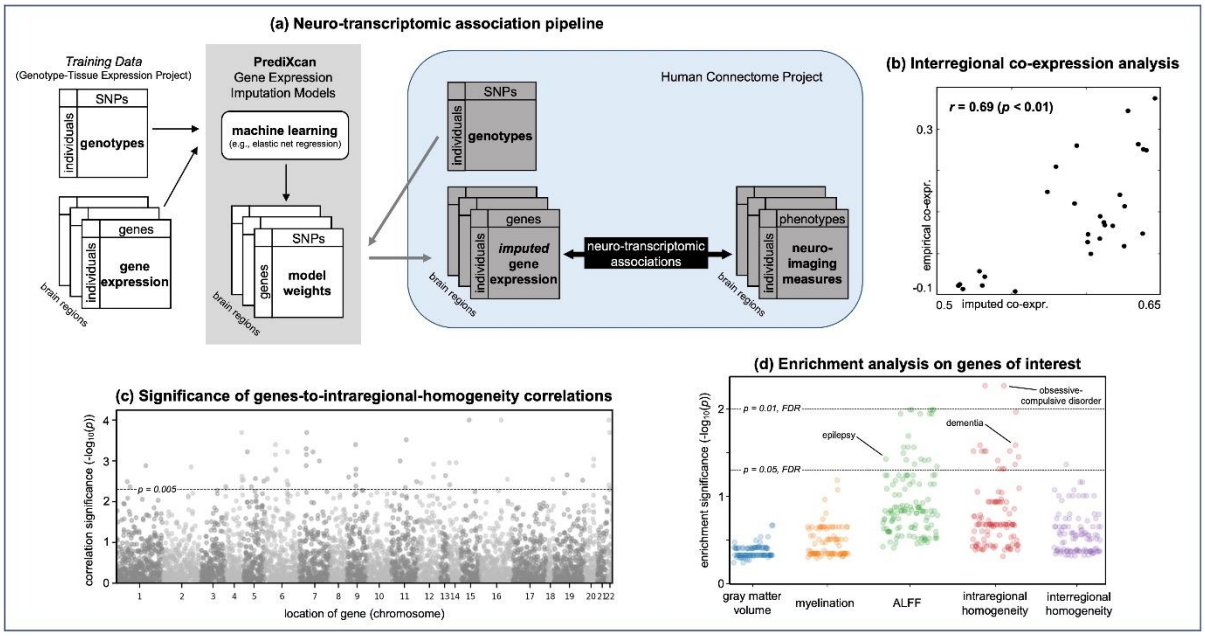
Topic: I.06. Computation, Modeling, and Simulation

Support: NIH Grant 1RF1MH125933-01A1

Title: Individual variability in heritable gene expression and neuroimaging phenotypes.

Authors: ***N. HOANG**[1], N. SARDARIPOUR[1], Y. CHEN[1], J. PARK[1], M. BENTON[2], J. CAPRA[3], M. RUBINOV[1];
[1]Vanderbilt Univ., Nashville, TN; [2]Baylor Univ., Waco, TX; [3]Univ. of California, San Francisco, San Francisco, CA

Abstract: Motivation: Recent studies have revealed mappings between brain-wide gene expression profiles and a range of brain structure, activity, and connectivity phenotypes. Most of these studies have used group-averaged expression data, such as data acquired by the Allen Human Brain Atlas (AHBA). While informative, this approach cannot capture the high degree of individual variability in brain phenotypes. The investigation of this variability to date has been limited by availability of corresponding gene expression and neuroimaging data for many individuals.
Methods: Here, we addressed this limitation by adopting PrediXcan, an established framework for imputing heritable gene expression using localized genetic variants. This framework has allowed us to study the otherwise inaccessible expression profiles for brain regions across many living individuals. We imputed heritable expression for several hundred genes in 10 brain regions for 890 individuals from the Human Connectome Project (HCP; 28.68 ± 3.73 mean age, 485 females) [figure, panel a].
Results and conclusions: We first found strong associations between interregional correlations of the imputed expression and assayed expression from the AHBA ($r = 0.69$, $p < 0.01$), demonstrating the validity of our approach [figure, panel b]. We then identified 37 - 46 genes whose imputed expression across brain regions of interest correlated with a range of phenotypes, most prominently intraregional homogeneity, in the HCP cohort [figure, panel c]. Finally, we performed enrichment analyses using a catalog of gene-to-medical-phenome mappings and found 16 neurological and psychiatric phenotypes associated with these genes ($p \leq 0.05$, FDR) [figure, panel d]. Our analyses bridge a gap in human neuroimaging by enabling the study of associations between individual-level gene expression and brain structure and activity. Ultimately, this approach can help reveal mechanistic pathways from gene expression to healthy or diseased brain function.



Disclosures: **N. Hoang:** None. **N. Sardaripour:** None. **Y. Chen:** None. **J. Park:** None. **M. Benton:** None. **J. Capra:** None. **M. Rubinov:** None.

Poster

164. Tools and Resources for Human Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 164.04

Topic: I.06. Computation, Modeling, and Simulation

Support: NIH Grant 1RF1MH125933-01A1

Title: Prediction of distributed cortical networks from local regional phenotypes

Authors: *N. SARDARIPOUR, N. HOANG, M. RUBINOV;
Vanderbilt Univ., Nashville, TN

Abstract: The wide availability of multimodal human neuroimaging data has enabled increasing investigations of the relationship between structural or functional brain imaging phenotypes and diverse aspects of cognition, development, aging, and disease. However, such investigations are typically conducted separately at the brain-regional and brain-network levels. The relatively little effort to bridge these parallel investigations can produce redundant explanations and obscure mechanisms.

To address this problem, we devised an interpretable model that predicted correlations between seven large-scale cortical networks from regional brain phenotypes. We extracted structural, diffusion, and functional MRI phenotypes from subsets of cortical and subcortical brain regions in 890 healthy subjects from the Human Connectome Project dataset (485 women, 28.7 ± 3.7 years). We computed a comprehensive set of regional features and trained linear regression models with L1-norm regularization in a nested cross-validation scheme to select features most predictive of network phenotypes. We found that regional features accurately predicted a large number of network correlations (figure). The most predictive features were regional homogeneity and gradient structure.

Collectively, our work introduces an interpretable model for linking local and distributed brain structures. Specifically, this model establishes a foundation for linking large-scale global network organization with other regional properties, including gene-expression patterns, across diverse conditions.

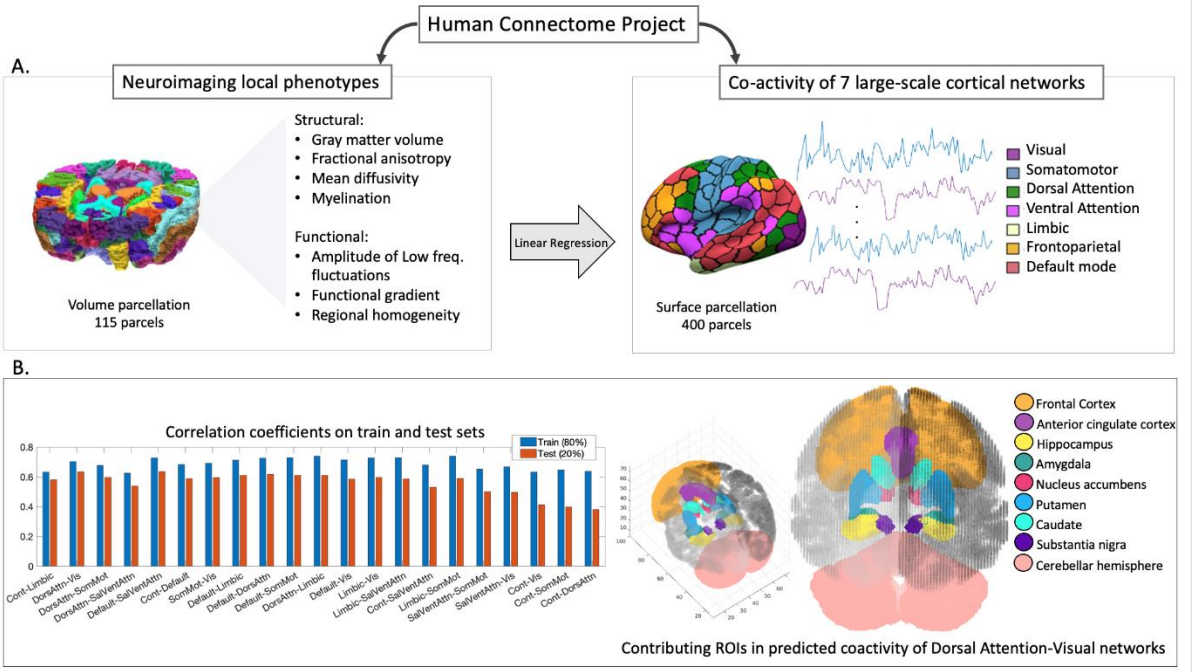


Figure. Our predictive model linked regional brain phenotypes to distributed network structure (A). A large number of network correlations were accurately predicted by regional features (R mean: 0.69 ±0.04, and 0.56 ±0.08 for train and test sets respectively) (B, left). Representative regions that contributed to predicted correlation between Dorsal Attention and Visual networks (B, right).

Disclosures: **N. Sardaripour:** None. **N. Hoang:** None. **M. Rubinov:** None.

Poster

164. Tools and Resources for Human Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 164.05

Topic: I.06. Computation, Modeling, and Simulation

Title: Uncertainty Assessment of Treatment Planning for Non-Invasive Brain Stimulation Techniques

Authors: *E. NEUFELD[1], **A. M. CASSARA**[2], N. KUSTER[3];
[1]IT'IS Fndn., Zurich, Switzerland; [2]Fndn. for Res. on Information Technol. in Society (IT'IS), Zurich, Switzerland; [3]Fndn. for Res. on Information Technologies in Society, Zurich, Switzerland

Abstract: Performance and safety of non-invasive brain stimulation (NIBS) techniques (e.g., transcranial electric stimulation (tES) and temporal interference stimulation (TIS)) rely on the precise delivery of stimulation dose (typically electric (E-)field related quantities) to targets. A systematic and standardized assessment of the predictions uncertainty associated with electromagnetic (EM) simulations - typically by finite-element methods (FEM) and detailed anatomical human head models - is lacking, with most computational studies not reporting uncertainty associated with dose predictions (e.g. E-field intensities) and performance metrics (e.g., focality). This fundamentally limits the interpretation of modelling predictions, may lead to erroneous estimation of experimental parameters, of safety and of performances, and limit the outcome of investigations. Here, we systematically investigated the impact of experimental and modelling sources of uncertainty/variability on tES exposure and on exposure-derived quantities (e.g., maximum amplitude modulation for TIS, focality of stimulation, etc.). We used simplified and anatomically detailed human head models (Virtual Population, IT'IS Foundation, Zurich, CH), and the calculation and the interpretation of the uncertainty contributions and of the combined uncertainty were performed according to the GUM Guidelines [JCGM100:2008]. The following sources of uncertainty were considered: (i) the biological variability/uncertainty in tissue electric conductivity; (ii) uncertainty in electrode placement (e.g., 10-10 International Electrode System); (iii) the number of segmented tissues; (iv) isotropy/anisotropy of tissues (e.g., white matter); (v) variability in tissue thicknesses (age-/sex- dependent); (vi) numerical approaches (e.g., discretization of model geometry); (vii) electrode models (e.g., ideal or resistive contacts). The combined uncertainty was calculated for a set of relevant electrode positions. First results have shown that the variability of the conductivities of cortical bone, gray and white matter contribute most to the combined uncertainty and that the impact of variability in conductivity of different tissues affects E-field exposure differently, due to their impact on how much current goes through the scalp, how much it is preferable to reroute or spread current to reduce overall path impedance, and how interfaces with dielectric contrast are oriented relative to the current. The result improves our understanding of the realistic performances of tES and helps estimate the realistic performances of TIS by providing insights on how to improve experiments.

Disclosures: **E. Neufeld:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); TI Solutions AG, ZMT Zurich MedTech AG. **A.M. Cassara:** None. **N. Kuster:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); ZMT Zurich MedTech AG, TI Solutions AG, NFT Holding AG.

Poster

164. Tools and Resources for Human Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 164.06

Topic: I.06. Computation, Modeling, and Simulation

Support: NIH Grant 1OT3OD025348-01

Title: Fully automated personalized head exposure modeling and application in a brain stimulation treatment modeling platform

Authors: *M. STEINER[1], E. NEUFELD[2], B. LLOYD[3], T. NEWTON[4], A. M. CASSARA[3], K. ZHUANG[1], P. CRESPO-VALERO[1], S. FARCITO[3], N. KUSTER[5];
[1]IT'IS Fndn., Zürich, Switzerland; [2]Computat. Life Sci., [3]IT'IS Fndn., Zurich, Switzerland; [4]Z43/IT'IS, Zuerich, Switzerland; [5]Fndn. for Res. on Information Technologies in Society, Zurich, Switzerland

Abstract: When the same transcranial brain stimulation conditions are applied to different persons, interindividual variability can have a large impact on outcomes. While this variability may be primarily due to physiological differences, recent results suggest that anatomical and dielectric differences and their impact on electromagnetic (EM) exposure explains an important part of the differences in blood-oxygen-level-dependent (BOLD) response.Hence, there is a need for image-based personalized brain stimulation modeling that reproduces the anatomy in sufficient detail (distinguished tissues, folding structure, heterogeneous/anisotropic brain conductivity). Existing solutions require manual work, distinguish too few tissue classes, or have other limitations. Here, we report about a fully automated head modeling pipeline that includes: i) a convolutional neural network (CNN, in combination with data augmentation and automatic segmentation clean-up) that predicts 16 tissue classes from T1/T2-weighted MRI; ii) DTI-based assignment of brain conductivity; iii) electrodes placement (10-10 system); iv) EM-exposure/EEG-lead-matrices simulation; and v) exposure quantification/optimization.The value of the developed pipeline was assessed by modeling the exposure of 15 volunteers to temporal interference stimulation in a motor learning study and correlating the exposure metrics defined prior to the analysis with functional and behavioral results. Compared to a state-of-the-art reference tool (Nielsen et al., 2018), the CNN-based approach provides segmentation in seconds (vs. 2-10 hours) and is able to distinguish more than twice the number of tissue classes. Combined with the automatic clean-up, superior segmentation quality is achieved. Data augmentation boosts robustness and facilitates generalization to other imaging modalities. The more detailed and realistic modeling positively impacts exposure predictions. Using the most detailed modeling, strong correlations (p=1-5%) were found between predicted stimulation selectivity
and intensity and the resulting effect on BOLD signal in the target region, and changes in motor learning performance, explaining up to 40% of the inter-subject variability. The results indicate that personalized modeling can improve stimulation quality.

Disclosures: **M. Steiner:** None. **E. Neufeld:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Shareholder of ZMT Zurich MedTech AG and Shareholder and Board Member of TI Solutions AG. **B. Lloyd:** None. **T. Newton:** None. **A.M. Cassara:** None. **K. Zhuang:** None. **P. Crespo-Valero:** None. **S. Farcito:** None. **N. Kuster:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Shareholder of NFT Holding AG and President of the Boards of NFT Holding AG, TI Solutions AG and ZMT Zurich MedTech AG.

Poster

164. Tools and Resources for Human Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 164.07

Topic: I.06. Computation, Modeling, and Simulation

Support: Swanson Fellowship in the Sciences and Engineering (K.A. Malaga)
Dean's Fund for Summer Undergraduate Research in STEM (X. Liu)

Title: Effect of patient-specific anisotropic brain conductivity on volume of tissue activation in deep brain stimulation for Parkinson disease

Authors: X. LIU[1], K. L. CHOU[2,3], P. G. PATIL[2,3,4], ***K. A. MALAGA**[1];
[1]Biomed. Engin., Bucknell Univ., Lewisburg, PA; [2]Neurol., [3]Neurosurg., [4]Biomed. Engin., Univ. of Michigan, Ann Arbor, MI

Abstract: Deep brain stimulation (DBS) modeling can be used to improve the understanding of how DBS elicits therapeutic effects by quantifying the spatial extent of stimulation relative to subcortical structures of interest. A certain degree of model complexity is required to obtain accurate predictions, particularly the complexity of the electrical properties of the tissue around DBS electrodes. The objective of this study was to evaluate the effect of anisotropy on the volume of tissue activation (VTA) in an individualized manner. Individualized tissue activation models incorporating patient-specific tissue conductivity derived from diffusion tensor imaging were built for 40 patients with Parkinson disease who had received bilateral subthalamic nucleus (STN) DBS. To assess the impact of local changes in tissue anisotropy on VTA predictions, one VTA was computed at each electrode contact using the same clinical stimulation parameters. For comparison, VTAs were also computed assuming isotropic tissue conductivity. Stimulation location was considered by classifying the VTAs as lateral/anterior/dorsal, centered, or medial/posterior/ventral relative to the STN. VTAs were characterized based on size and shape using volume, spread in the lateral-medial, anterior-posterior, and dorsal-ventral directions, sphericity, and Dice coefficient. The incorporation of anisotropy generated significantly larger and less spherical VTAs overall. However, its effect on VTA size and shape was variable and more nuanced at the individual patient and implantation levels. VTAs dorsal to the STN centroid had significantly higher sphericity, suggesting a more isotropic behavior than those ventral to the STN. In contrast, VTAs lateral and posterior to the STN had significantly larger and smaller lateral-medial spreads, respectively. VTA volume was negatively correlated with sphericity. The influence of anisotropy on VTA predictions is not negligible, and varies across patients and stimulation locations. This study highlights the importance of considering individualized factors in DBS modeling to accurately characterize the VTA.

Disclosures: X. Liu: None. **K.L. Chou:** F. Consulting Fees (e.g., advisory boards); Boston Scientific, Abbott. **P.G. Patil:** None. **K.A. Malaga:** None.

Poster

164. Tools and Resources for Human Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 164.08

Topic: I.06. Computation, Modeling, and Simulation

Title: Effect of STN-DBS induced artefacts on central auditory pathway recordings from HD-EEG in Parkinson's Disease patients

Authors: T. PIRENNE[1], M. F. HNAZAEE[2], P. SANTENS[3], *M. M. VAN HULLE[1]; [1]Dept. of Neurosciences, KU Leuven, Leuven, Belgium; [2]Queen Square Inst. of Neurol., Univ. Col. London, London, United Kingdom; [3]Dept. of Neurol., Ghent Univ. Hosp., Ghent, Belgium

Abstract: Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is a well-established therapeutic option for patients with advanced Parkinson's disease (PD). However, despite the evidence supporting its symptomatic efficacy, the physiological mechanism underlying DBS remains elusive. Simultaneous electroencephalography (EEG) could provide new insights, but this is challenged by the electrical artefacts induced by DBS. We investigated whether STN-DBS artefacts affect the detection of auditory steady state responses (ASSR) recorded with high-density EEG (HD-EEG). ASSRs are neural responses of central auditory pathway nuclei phase-locked to an auditory stimulus, which can serve to research altered auditory processing in PD patients. We recorded 128-channel EEGs at a 2000Hz sampling rate for lapses of 5 minutes in 6 PD patients in DBS *on* and *off-conditions* during auditory stimulation (white noise modulated at 20, 40, 80Hz) or resting state. We developed a classifier to discriminate between ASSR and resting state irrespective of DBS being *on* or *off*. The classifier leverages Canonical Correlation Analysis to maximise the correlation between the input EEG segment and the expected ASSR at the given modulation frequency. Using training data, a threshold for the returned correlation score was set and used to predict the presence or absence of ASSR. The classifier was trained on data collected while DBS was *off* and tested while it was *on*. The test data were cut into folds and the results confronted with chance results. The test performance of the classifier was far above chance level (using t-tests - $p < 0.01$) and consistent across a range of hyperparameter choices. These results support our claim that low-frequency ASSRs can be reliably detected from HD-EEG recordings despite the presence of STN-DBS artefacts. Future work is needed to investigate whether DBS modulates ASSR and, in the affirmative case, what the implications are for central auditory processing in PD.

Disclosures: **T. Pirenne:** None. **M.F. Hnazaee:** None. **P. Santens:** None. **M.M. Van Hulle:** None.

Poster

164. Tools and Resources for Human Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 164.09

Topic: D.03. Somatosensation – Touch

Support: NRF-2022R1I1A4063209
NRF-2022R1A2C2005062
National Research Foundation(NRF), Korea, under project BK21 FOUR

Title: Parameter Optimization of auricular Vagus Nerve Stimulation for Cognitive effects with Pupillometry

Authors: *J. LEE[1,2], K. MIN[5], J. SUNG[3], S. JUN[1,2,4];
[1]Electronic and Electrical Engin., Ewha Women's Univ., Seoul, Korea, Republic of; [2]Grad. Program in Smart Factory, [3]Communication Disorders, [4]Brain and Cognitive Sci., Ewha Womans Univ., Seoul, Korea, Republic of; [5]TODOC Co., Ltd., Seoul, Korea, Republic of

Abstract: Vagus Nerve Stimulation (VNS) activates the locus coeruleus-norepinephrine (LC-NE) system by modulating vagal afferent inputs to the brainstem nucleus of the solitary tract. Not only does VNS provide therapeutic potential for medical conditions like drug-resistant epilepsy or depression, but it also has been known to increase cognitive abilities. However, due to the surgical risks associated with device installation, the invasive VNS approach has limitations as a first-line treatment for humans. Thus, a method known as transcutaneous auricular vagus nerve stimulation (aVNS or tVNS) has been proposed, which stimulates the auricular branch of the vagus nerve at the cymba conchae of the ear. Our previous study confirmed that aVNS stimulates autonomic nerve system and mimics conventional invasive VNS. We suggest aVNS to investigate the impact of stimulating the vagus nerve on cognition. On this account, it is critical to establish precise stimulation parameters to maximize the efficacy of stimulation. Also, this study requires proper biomarkers to look forward optimal stimulation conditions and influence of aVNS on cognitive escalation. Given that pupil dilation is closely related with LC-NE activity which shares VNS transmission brain pathway, the Event-Related Pupil Response (ERPR) based on pupil size is selected. As a control, sham stimulation is applied to earlobe far from the vagus nerve branch. Except site, the same parameters for the electrical stimulation are used for both aVNS and sham stimuli. Prior to aVNS stimulation and pupil measurement, stimulus amplitude is identified just below the pain threshold for adjusted to each participant's different impedance. In this study, we change pulse width, frequency, duration, and on/off duty of stimulation, and compare each condition with ERPR. The current study develops a medium to monitor biological signals changed by "customized neural stimulation", and it helps the establishment of a next-generation neural control system with the concept of personalized therapy since pupil size can be easily monitored. Also, due to the variety of impacts on the overall nervous system of VNS, optimization of stimulation will serve as the platform for active future research.

Disclosures: **J. Lee:** None. **K. Min:** None. **J. Sung:** None. **S. Jun:** None.

Poster

164. Tools and Resources for Human Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 164.10

Topic: I.06. Computation, Modeling, and Simulation

Support: NIH Grant RF1AG057892

Title: Learning meaningful white matter tract representations from tractography using a deep generative model

Authors: *Y. FENG[1], B. Q. CHANDIO[2], T. CHATTOPADHYAY[1], S. I. THOMOPOULOS[1], C. OWENS-WALTON[1], N. JAHANSHAD[1], E. GARYFALLIDIS[3], P. M. THOMPSON[1]; [1]Imaging Genet. Center, Mark and Mary Stevens Neuroimaging and Informatics Inst., USC, Marina Del Rey, CA; [2]Dept. of Intelligent Systems Engin., Indiana Univ., Bloomington, IN; [3]Dept. of Intelligent Systems Engin., Indiana Univ. Bloomington, Bloomington, IN

Abstract: Diffusion MRI tractography can easily generate over 500,000 streamlines (3D curves tracking neural pathways), making downstream analysis challenging. This motivates work in dimensionality reduction methods using deep representation learning, which maps 3D streamlines to individual points in a latent space, where they can be partitioned, labeled, and aligned for population analyses. Meaningful embeddings should ideally preserve inter-bundle distance metrics and allow bundles to be distinguished in the latent space.
We tested an unsupervised Convolutional Variational Autoencoder (ConvVAE) to learn low dimensional streamline embeddings from 10 healthy controls (5F/5M) from the Alzheimer's Disease Neuroimaging Initiative Phase 3 (ADNI3) database. Whole brain tractograms were generated using a probabilistic particle filtering tracking algorithm and 30 white matter bundles per subject were extracted using auto-calibrated RecoBundles from the DIPY package.
To study the preservation of streamline distances in the low dimensional latent space, we calculate the correlation between Euclidean distance in the embedding space and the minimum average direct-flip (MDF) distance in the streamline space for models trained with various embedding dimensions (z). The Pearson correlation for 300 subsamples was 0.543 for z=2, 0.718 for z=3, 0.751 for z=4, 0.814 for z=6, 0.788 for z=8 and 0.701 for z=16. ConvVAE best preserved streamline distances when z=6, and such a relationship holds for streamlines far apart as well as those nearby each other.
To study the preservation of inter-bundle distance, we used the Mantel test to compare pairwise bundle distances between bundle centroids calculated from QuickBundles using MDF distances and embedding centroids (z=6) using Euclidean distances; they were strongly correlated ($r=0.980$, $p<0.01$). 3D visualization shows distinct embedding clusters corresponding to bundle labels, and hemispheric relationships are maintained, with commissural embeddings in between.
ConvVAEs can learn meaningful representations that preserve streamline distances in lower dimensions and spatial information of bundles, based on correlation analysis and visualizations. The generative nature of ConvVAE also makes it possible to generate embeddings from unseen data using a trained model, for downstream analyses such as inter-subject comparisons, abnormality and outlier detection, and to facilitate large-scale population analyses of brain diseases.

Disclosures: Y. Feng: None. **B.Q. Chandio:** None. **T. Chattopadhyay:** None. **S.I. Thomopoulos:** None. **C. Owens-Walton:** None. **N. Jahanshad:** None. **E. Garyfallidis:** None. **P.M. Thompson:** B. Contracted Research/Research Grant (principal investigator for a drug

study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; received a grant from Biogen, Inc., for research unrelated to this study..

Poster

164. Tools and Resources for Human Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

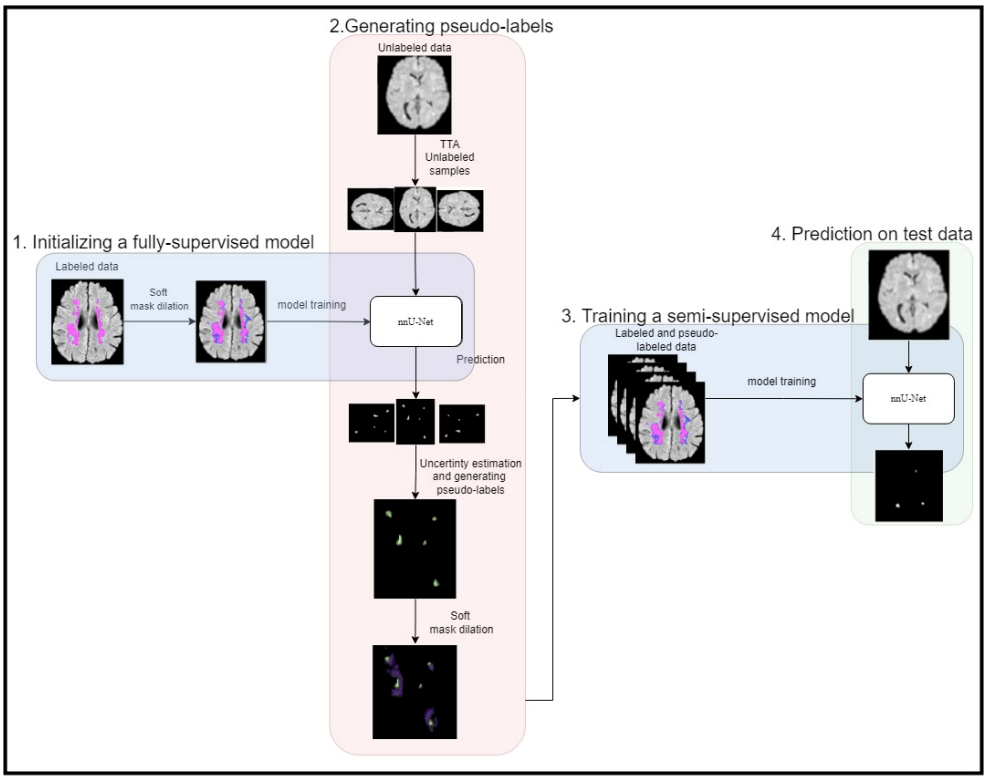
Program #/Poster #: 164.11

Topic: I.06. Computation, Modeling, and Simulation

Title: Segmentation of Multiple Sclerosis Lesionsusing Semi-supervised Learning and Soft Labeling

Authors: *Z. HANANIS[1], Y. HODAYA MOSHE[1], M. TEICHER[1], M. ARTZI[2];
[1]bar-ilan university, Bar-Ilan Univ., Tel Aviv, Israel; [2]Sagol Brain Inst., Tel aviv university, Tel Aviv, Israel

Abstract: Multiple Sclerosis (MS) is a chronic autoimmune disease of the central nervous system which affects more than 2.8 million people globally. The visual complexity of MS lesions makes the process of manual segmentation time and labor extensive, and to a lack in accuracy and agreement between different experts' annotations. Deep Learning approach is widely researched to overcome those issues and has outscaled others machine learning in MS lesion segmentation tasks. However, such deep learning approaches rely on large training datasets with high-quality manual annotations since the networks require tuning of a large number of parameters, which makes them limited in their adoption and application when trained on small datasets, as those available for MS.To tackle these issues we propose to incorporate semi-supervised learning with soft labeling and uncertainty estimation techniques for unlabeled data distillation into the state-of-the-art nnU-Net architecture. We hypothesize:1)Soft labeling will improve performance compared to baseline.2)Making use of unlabeled data with semi supervised learning will improve performance compared to baseline. For training and evaluation, we used ISBI2015 dataset with 21 labeled cases and Tel Aviv Sourasky Medical Center (TASMC) dataset with ~200 unlabeled cases of patients with MS. All cases contains T1WI+C, T2WI and FLAIR MR Images. The training and validation datasets were split into 80% training and 20% validation in a five-fold cross-validation manner. Evaluation was performed on the ISBI2015 test datasets using the competition's ranking method.Our results show an improvement using soft labels and semi-supervised learning compared to the fully-supervised baseline model.



Disclosures: **Z. hananis:** None. **Y. Hodaya Moshe:** None. **M. Teicher:** None. **M. Artzi:** None.

Poster

164. Tools and Resources for Human Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 164.12

Topic: I.06. Computation, Modeling, and Simulation

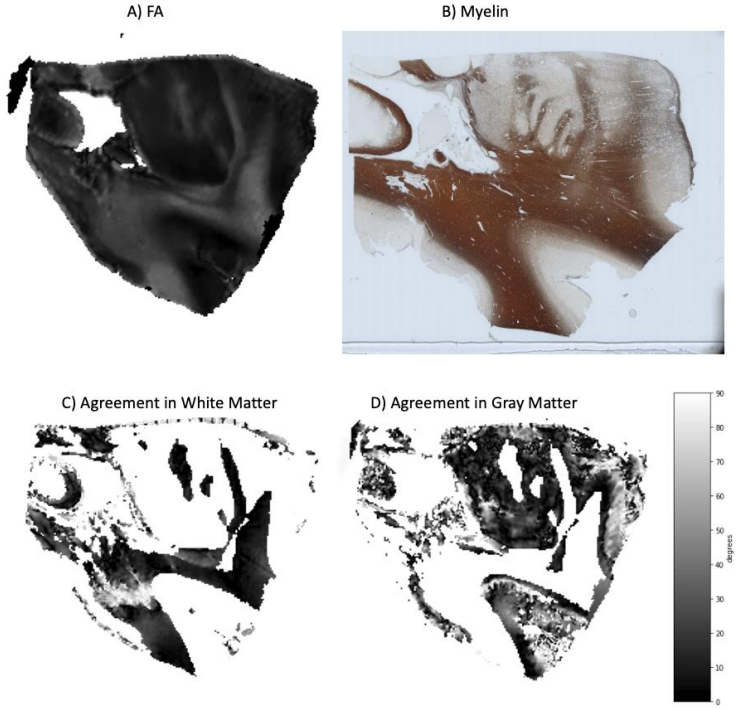
Support: NIH Grant RF1MH128875

Title: Histological validation of human post mortem amygdala DTI

Authors: ***B. GRAY**[1], C. MEZIAS[3], S. SAVOIA[3], R. CORONADO-LEIJA[4], D. NOVIKOV[4], E. FIEREMANS[4], J. ZHANG[5], D. NAUEN[6], P. P. MITRA[3], D. J. TWARD[2];
[1]UCLA, LOS ANGELES, CA; [2]Computat. Medicine, Neurol., UCLA, Los Angeles, CA; [3]Cold Spring Harbor Lab., Cold Spg Hbr, NY; [5]Radiology, [4]New York Univ. Sch. of Med., New York, NY; [6]Div. of Neuropathology, Johns Hopkins Hosp. and Hlth. Syst., Baltimore, MD

Abstract: The validation of diffusion-weighted MRI (dMRI) and diffusion tractography is difficult due to a scarcity of high-quality microstructural information for comparison. We aim to fill this gap by providing dense (20 μm) serial section histology of a whole human brain and

software tools to easily quantify accuracy and study the relationship between dMRI and brain microstructure. We developed a software pipeline to compare axonal orientations observed in myelin-stained histology sections with the white matter orientation information from diffusion tensor images (DTI). We first construct structure tensors from myelin-stained histology sections of a human amygdala, downsampling the tensors to match DTI resolution. Using a large deformation diffeomorphic metric mapping (LDDMM) algorithm with expectation maximization for multi-modality contrast matching, we compute transformations to co-register myelin histology slices, constructing a 3D volume. We then register DTI to the same coordinate space by trilinear interpolation of tensor components and rotation of tensors with the Preservation of Principal Directions method. We select white matter and gray matter regions for separate comparison using a fractional anisotropy (FA) threshold. We also select regions in which the out-of-plane angle of diffusion tensors is sufficiently small so that the tensor projected into the histology image plane is large enough for a valid comparison. The angle between principal eigenvectors of the diffusion tensors projected into the slice plane, and structure tensors is calculated and used to quantify agreement between orientation information from each modality. We observed closer agreement between DTI orientations and myelin in high FA regions, 22.2 +/- 20.6 degrees, and lower agreement in low FA regions, 29.8 +/- 21.9. This observed agreement may be complicated by complex crossing fiber pathways in both gray and white matter, and indicate a need for expanding our tool to employ comparisons of orientation distribution functions with histological data for analyzing complex fiber architectures.



Disclosures: **B. Gray:** None. **C. Mezias:** None. **S. Savoia:** None. **R. Coronado-Leija:** None. **D. Novikov:** None. **E. Fieremans:** None. **J. Zhang:** None. **D. Nauen:** None. **P.P. Mitra:** None. **D.J. Tward:** None.

Poster

164. Tools and Resources for Human Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 164.13

Topic: I.07. Data Analysis and Statistics

Support: RF1AG057892
U01AG068057

Title: Unsupervised White Matter Tract Filtering for Robust Tractometry

Authors: *B. Q. CHANDIO[1,2], T. CHATTOPADHYAY[3], C. OWENS-WALTON[4], J. VILLALON REINA[5], L. NABULSI[3], S. I. THOMOPOULOS[3], E. GARYFALLIDIS[6], P. M. THOMPSON[3];
[1]Intelligent Systems Engin., Indiana Univ., Bloomington, IN; [2]Mark and Mary Stevens Neuroimaging and Informatics Inst., USC, Marina Del Rey, CA; [3]USC, Los Angeles, CA; [4]USC, San Francisco, CA; [5]USC, USC, Los Angeles, CA; [6]Indiana Univ. Bloomington, Bloomington, IN

Abstract: The brain's white matter (WM) pathways are digitally reconstructed from diffusion MRI (dMRI) using tractography algorithms. dMRI and tractography provide crucial information about brain connectivity and microstructural changes due to underlying conditions such as Alzheimer's or Parkinson's disease. Often generated tractograms have millions of streamlines (3D curves following fiber pathways) with many false positives and anatomically implausible streamlines. To obtain anatomically relevant streamlines and tracts, supervised and unsupervised methods can be used for tractogram clustering and tract extraction. Tractometry tools are then applied to study microstructural changes along the length of WM tracts. These methods rely on bundle segmentation methods and false-positive streamlines could lead to errors in the statistical analysis of microstructural measures along the length of the tracts. We propose FiberNeat, an unsupervised WM tract filtering method. FiberNeat takes an input set of streamlines (either unlabeled clusters or labeled tracts). Individual clusters/tracts are projected into a latent space using nonlinear dimensionality reduction techniques, t-SNE and UMAP, to find spurious and outlier streamlines. Outlier streamline clusters detected using DBSCAN, are then removed from the tracts in streamline space. We use labels of small clusters given by DBSCAN in 2D space to remove corresponding clusters of streamlines in streamline-space. FiberNeat is an unsupervised data-driven algorithm that does not require any anatomical reference atlas or labeled training data. We performed qualitative and quantitative comparisons with expertly delineated tracts. We ran FiberNeat on 3,930 WM tracts from 131 participants' data (30 tracts each) from the ADNI3 dataset. We used BUAN (Bundle Analytics toolkit) to find group differences in FA measures along the length of tracts for 87 controls and 44 participants with mild cognitive impairment. We found that having spurious streamlines in input data can overestimate or underestimate the effects of the disease. Deploying FiberNeat into the BUAN tractometry pipeline improved the robustness of statistical analysis by removing spurious and false-positive streamlines that could create artifacts in the analysis. FiberNeat code and a tutorial are available at: https://github.com/BramshQamar/FiberNeat.

Disclosures: **B.Q. Chandio:** None. **T. Chattopadhyay:** None. **C. Owens-Walton:** None. **J. Villalon Reina:** None. **L. Nabulsi:** None. **S.I. Thomopoulos:** None. **E. Garyfallidis:** None. **P.M. Thompson:** Other; Biogen.

Poster

164. Tools and Resources for Human Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 164.14

Topic: I.06. Computation, Modeling, and Simulation

Support: NSF Grant IIS-1850102
NSF Grant CMMI-214412

Title: Cortical thickness consistently correlates with cortical morphology for both humans and non-humans

Authors: *N. DEMIRCI[1], M. E. HOFFMAN[2], O. KALLA[1], R. MASLAK[1], M. A. HOLLAND[1];
[1]Univ. of Notre Dame, Notre Dame, IN; [2]Univ. of Washington, Seattle, WA

Abstract: Gyri have been known to be thicker than sulci for almost a century, through earlier observations of histological sections and in recent decades by analysis of 3-D surfaces of the cortex obtained from magnetic resonance images (MRI). But these studies are limited by anatomical descriptions and more complex folds and shapes of the cortex are not thoroughly considered. To explore these patterns further, we have developed an open-source computational pipeline (https://github.com/mholla/curveball) that measures complex topological quantities, such as, thickness, curvature, depth, and shape index locally. Previously, we analyzed N=501, publicly available, typically developed human subjects from Autism Brain Imaging Data Exchange (ABIDE) repository and our results showed a strong correlation between cortical thickness and morphology; the cortex is consistently thickest at convex-shaped points, in the middle at saddle-shaped points, and thinnest at concave-shaped points. Therefore, the patterns of cortical thickness follow a spectrum throughout the folds of the cortex, which are both radially or tangentially oriented. In this study, we expanded our dataset and included more than a dozen primate cortices with varying shapes, sizes, and degrees of foldedness. The MRI data were collected from publicly available non-human primate databases, such as the Primate Data Exchange (PRIME-DE) and the National Chimpanzee Brain Resource (NCBR). We used multiple neuroimaging tools and pipelines to reconstruct 3-D surfaces if they weren't already available. Our findings from non-human primate species on patterns of cortical thickness closely follow our previous findings on humans. Additionally, we found a strong, allometric scaling of cortical thickness with total surface area; but, interestingly, the scaling exponent of average sulcal depth with total surface area was barely different from the predicted value. Moreover, the cortical thickness ratio (average thickness of all convex points to concave points) is positively correlated with size and thickness. All of our results point us to a universal physical law of

cortical folding. In the future, we aim to expand our data set to include more mammalian species and human fetal brains to better understand the growth and development of the brain through ontogeny and phylogeny. Our findings would also provide more insight into understanding the various aspects of cortical folding and its relationship to neurological diseases and health.

Disclosures: **N. Demirci:** None. **M.E. Hoffman:** None. **O. Kalla:** None. **R. Maslak:** None. **M.A. Holland:** None.

Poster

164. Tools and Resources for Human Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 164.15

Topic: I.06. Computation, Modeling, and Simulation

Title: An MR-Compatible Virtual Reality System for Assessing Activities of Mirror Neurons in the Motor Cortices

Authors: *X. WANG[1], D. DONG[2], D. MEKBIB[3], A. ROE[4], D. XU[5];
[1]Interdisciplinary Inst.of Neurosci. and Technol. & Sch. of Computer Sci. and Technol., [2]Sch. of Computer Sci. and Technol., [3]Biomed. Engr and Instru. Sci., [4]Interdisciplinary Inst. of Neurosci. and Technol. & Sch. of Med., Zhejiang Univ., Hangzhou, China; [5]Dept. of Psychiatry, Columbia Univ. & New York State Psychiatric Inst., New York, NY

Abstract: Virtual reality(VR)assisted rehabilitation systems are being used more commonly in supplementing upper extremities (UE) functional rehabilitation. Currently, most of such systems may only help to collect resting-state functional magnetic resonance imaging (rs-fMRI) to measure neuronal recovery status of motor cortex after patients receiving the VR therapy, because the systems cannot work in an MRI setting. However, rs-fMRI data may only evaluate a patient's motor functions indirectly as the data cannot assess neural activities in real-time tasking when a patient is executing the VR rehabilitation training. To address this challenge, we recently have implemented a novel VR-assisted system (MRVR: MR-compatible VR for assessment of UE motor functions) that is compatible with an MR environment, which involves mirror therapies for assessment of human motor functionalities. The system consists of both hardware and software. The hardware includes using a signal-response(S/R) controller for signal synchronization between the MR scanner and the software part running on a high-performance computer. The VR scene transmitted from the computer using fiber optics displays on an MR-compatible display. Meanwhile, an MR-compatible button box transmits real-time feedbacks from the participant back to the computer through the S/R controller. The VR was programmed to immerge the participant in a traditional Chinese styled room. Entering the room, the participant will see a table in the front against a wall with a white basket on top. Ball will show up at particular positions on the table, as designated ahead of the training. The patient should control the virtual limb to grasp one ball each time and put it into the white basket by operating the MR-compatible button box. Three different training modes are provided adapting to a

patient's appropriate level of sensorimotor cortex impairment, including a unilateral-contralateral mode (using the healthy-side arm to control the opposite virtual arm), a unilateral-ipsilateral mode, and a unilateral-bilateral mode. Twenty healthy participants were recruited to test the validity of the MRVR system. The system succeeded in running the tasks on a 3T Siemens MR scanner. Experiment data showed that the tasks were able to stimulate and activate the sensorimotor neurons as well as mirror neurons in the motor cortical regions effectively. The findings suggested that the MRVR system may be a novel alternative for assessing neurorehabilitation of stroke patients with UE motor impairment in a tasked MRI setting, which in turn may provide direct imaging evidence of activities of mirror neurons in the cortices related to UE motor functions.

Disclosures: X. wang: None. **D. Dong:** None. **D. Mekbib:** None. **A. Roe:** None. **D. Xu:** None.

Poster

164. Tools and Resources for Human Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 164.16

Topic: E.06. Posture and Gait

Support: NIH 5K01HD096047-02

Title: Neuroimaging Compatible Dual Task Screen elicits greater neural activation during dual versus single tasks in healthy contact sport athletes.

Authors: *J. A. STEPHENS[1], S. M. MINGILS[2], S. ORLANDI[3];
[1]Colorado State Univ., [2]Colorado State Univ., Fort Collins, CO; [3]Univ. of Bologna, Bologna, Italy

Abstract: Deciding when athletes are safe to return to play after sports-related concussion (SRC) can be difficult, as many SRC measures suffer from poor test-retest reliability, reliance on baseline testing, or insufficient difficulty. However, dual task assessments can detect subtle, but impactful, SRC deficits. Namely, athletes with SRC tend to have similar single task performance as healthy athletes, but significantly poorer dual task performance. Our lab leveraged this foundational work to create a Dual Task Screen (DTS) to quickly evaluate dual task performance with low-cost, portable instruments. Recently, we modified the DTS to support simultaneous neuroimaging using portal functional near-infrared spectroscopy (fNIRS). We sought to establish that our Neuroimaging-Compatible DTS (NC-DTS) could elicit greater neural activation during dual vs. single task conditions. We tested this in a pilot sample of 10 healthy, female contact-sport athletes (mean age 19.5) who completed the NC-DTS in a single laboratory visit. The NC-DTS is comprised of an upper and lower extremity subtask, and each subtask includes five blocks of single motor (e.g. gait), single cognitive (e.g. verbal fluency), and dual task conditions (e.g. gait + verbal fluency). FNIRS data were acquired with the NIRSport2, a portable device worn on participants' backs that wirelessly transmits optical density data to a laptop computer for

later conversion into hemoglobin metrics (e.g., oxygenated hemoglobin (HbO)). Data were acquired at a 4.65 Hz sampling rate using 15 LED sources (wavelengths 760 and 850 nm), 15 detectors, and 8 short-separator detectors. Sources and detectors were placed over bilateral primary motor cortex (M1) and primary sensory cortex (S1) and right lateralized prefrontal cortex (PFC) and posterior parietal cortex (PPC). Preprocessing and first-level analysis were completed using a Matlab toolbox, SPM-fNIRS. SPM 12 was used for second-level analysis to compare dual vs. single motor conditions with paired t-tests and family-wise error corrections. Significantly different neural activation was observed during dual vs. single motor conditions on the lower extremity subtask; specifically, there was significantly greater HbO concentration during the dual task condition in voxels originating in the right PFC (MNI coordinates: 38,59,1), $p = .038$. However, no significant differences were found in the upper extremity subtask. Collectively, these early findings illustrate that the NC-DTS can elicit greater neural activation during dual vs. single conditions, indicating it is a valid dual task assessment with potential for evaluating behavioral and neural outcomes after SRC.

Disclosures: **J.A. Stephens:** None. **S.M. Mingils:** None. **S. Orlandi:** None.

Poster

164. Tools and Resources for Human Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 164.17

Topic: I.06. Computation, Modeling, and Simulation

Support: NIH Grant P01HL040962
NIH Grant R01089850

Title: Niphlem: neuroimaging-oriented physiological log extraction for modeling

Authors: *A. I. SENTIS[1], J. RASERO[2], A. GERLACH[3], T. D. VERSTYNEN[1];
[2]Psychology, [1]Carnegie Mellon Univ., Pittsburgh, PA; [3]Univ. of Pittsburgh, Pittsburgh, PA

Abstract: niphlem is a pip-installable python toolbox that extracts physiological recordings from MRI sessions and performs quality control. niphlem can generate multiple models of physiological noise to include as regressors in future GLM models from either ECG, pneumatic breathing belt or pulse-oximetry data (Verstynen and Deshpande, 2011).
niphlem operates in three distinct stages: preprocessing, data cleansing, and artifact model generation. Input files are BIDS consistent data files for either 1) ECG channels, 2) pulse oximetry, or 3) pneumatic respiration belt. Preprocessing may include data transformations, such as demean, and filtering. In the case of ECG input files, additional preprocessing steps may include combining signals from multiple channels. Data cleansing consists of detection of signal peaks (e.g., R peaks within the QRS waveform for ECG signals) and removal of artifacts in the detected peaks. Artifacts are identified through two one-sided Grubb's tests for outliers and subsequently corrected. Text files of the mean filtered timeseries and timepoints of the detected

peaks are optionally saved as outputs. An html quality control report can also be generated and saved that includes filtered signal statistics and visualization of data preprocessing and cleansing steps. Finally, niphlem generates two classes of artifact models: RETROICOR or variability models. RETROICOR is a phasic decomposition method that isolates the fourier series that best describes the spectral properties of the input signal (Glover et al., 2000). The variability model for low frequency signals (such as respiration from pneumatic belt and low-pass filtered pulse-oximetry) computes the combined respiration variance and response function (Birn et al., 2008). The variability model for high frequency signals (such as ECG or high-pass filtered pulse-oximetry) generates the heart-rate variance and cardiac response function (Chang et al., 2009). Through preprocessing, analysis and quality control of ECG data collected alongside resting-state fMRI, we show that niphlem is effective at identifying and removing physiological noise artifacts for future use in neuroimaging analyses. Github repository with a link to the website can be found here: https://github.com/CoAxLab/niphlem.
Birn RM, et al. (2008), Neuroimage. 40(2):644-654.
Chang C, et al. (2009), Neuroimage. 1;44(3):857-69.
Glover GH, et al. (2000), Magn Reson Med. 44(1):162-7.
Verstynen TD, Deshpande V. (2011), Neuroimage. 15;55(4):1633-44.

Disclosures: **A.I. Sentis:** None. **J. Rasero:** None. **A. Gerlach:** None. **T.D. Verstynen:** None.

Poster

164. Tools and Resources for Human Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 164.18

Topic: I.06. Computation, Modeling, and Simulation

Support: FONDECT postdoctorado N°3200248

Title: 1/f slope is continuously dependent on frequency range in resting state intracortical recordings

Authors: *G. BONCOMPTE[1], V. MEDEL[3,4], M. IRANI[5], T. OSSANDON[2];
[1]Dept. of Anaesthesia, [2]Dept. of Psychiatry, Pontificia Univ. Catolica de Chile, Santiago, Chile; [3]Dept. de Neurociencia, Facultad de Medicina, Univ. de Chile, Santiago, Chile; [4]Brain and mind center, The university of Sydney, Sydney, Australia; [5]Dept. of Psychology, Univ. of Illinois Urbana-Champaign, Urbana, IL

Abstract: Neural activity from cortical electrophysiological field potentials can be separated into oscillatory and background or aperiodic activity. It has been proposed that the spectral power of background activity decays across frequency following a power-law behaviour, the so called 1/f, which is fully defined by two parameters: offset and slope. However, it has been shown that real electrophysiological data is usually better adjusted by 1/f behaviour that comprises either a "knee", i.e. an initial frequency at which the 1/f behaviour begins, or even two different 1/f

equations, each with its corresponding pair of parameters. The frequency ranges in which 1/f is fitted to data are highly variable in the literature, and are normally chosen on a case to case basis based on visual inspection of power spectral density plots. In this line, both scale invariance and the general power spectrum structure of background cortical activity have not been fully characterised. Here we systematically estimated 1/f slopes across different frequency ranges in resting-state intracortical recordings from 62 subjects using the FOOOF algorithm. We fitted 1/f across several central frequencies (CF) using a spectral span of 2 octaves, ranging from CF = 3 Hz (1.5 to 6Hz) to CF = 125 Hz (63 to 250Hz). We discarded poor fit results ($r2 < 0.98$). We found a strong and positive dependence between 1/f slope and CF at low to medium CFs (from 3 to ~40 Hz), e.g. 1/f slope was lower when calculated between 5 and 20 Hz compared to when calculated between 15 and 60 Hz. At higher CFs we found that, on average, subjects presented a relatively more constant 1/f slope. However, individual subjects did showcase both positive and negative dependences between 1/f slope and CF. Our results show that the range of frequencies in which 1/f slope is estimated systematically changes the obtained 1/f slope value, particularly in the frequency ranges available for scalp EEG recordings. This implies that electrophysiological field potential data does not present a strict scale invariance, and thus caution should be taken when interpreting 1/f results calculated in different frequency ranges.

Disclosures: **G. Boncompte:** None. **V. Medel:** None. **M. Irani:** None. **T. Ossandon:** None.

Poster

164. Tools and Resources for Human Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 164.19

Topic: I.06. Computation, Modeling, and Simulation

Support: NIH NINDS R01NS047293

Title: Plotting the EEG channel 'cortical receptive field map'

Authors: *Z. AKALIN ACAR[1], S. MAKEIG[2];
[1]Univ. of California San Diego, Univ. of California San Diego, San Diego, CA;
[2]UCSD/INC/SCCN, Univ. of California San Diego, La Jolla, CA

Abstract: We have created a Matlab app, EEG-RF, to show the 'receptive field' in a participant's cortex of a given scalp EEG channel - i.e., to show the relative contribution by volume conduction of each cortical area to the recorded channel signal. To do this we first generated a 4-layer electrical head model of the participant from their MRI head image using the NFT toolbox [1]. We then segmented scalp, skull, CSF, and brain layers and used Freesurfer to generate a high-resolution cortical source space mesh of 80,000 dipoles oriented normal to the cortical surface. We used 128-channel electrode positions obtained using a Polhemus digitizer to calculate the lead field matrix from the 80k cortical voxel source space to the 128 electrode locations read in from an EEGLAB [2] channel locations matrix. The lead field matrix then

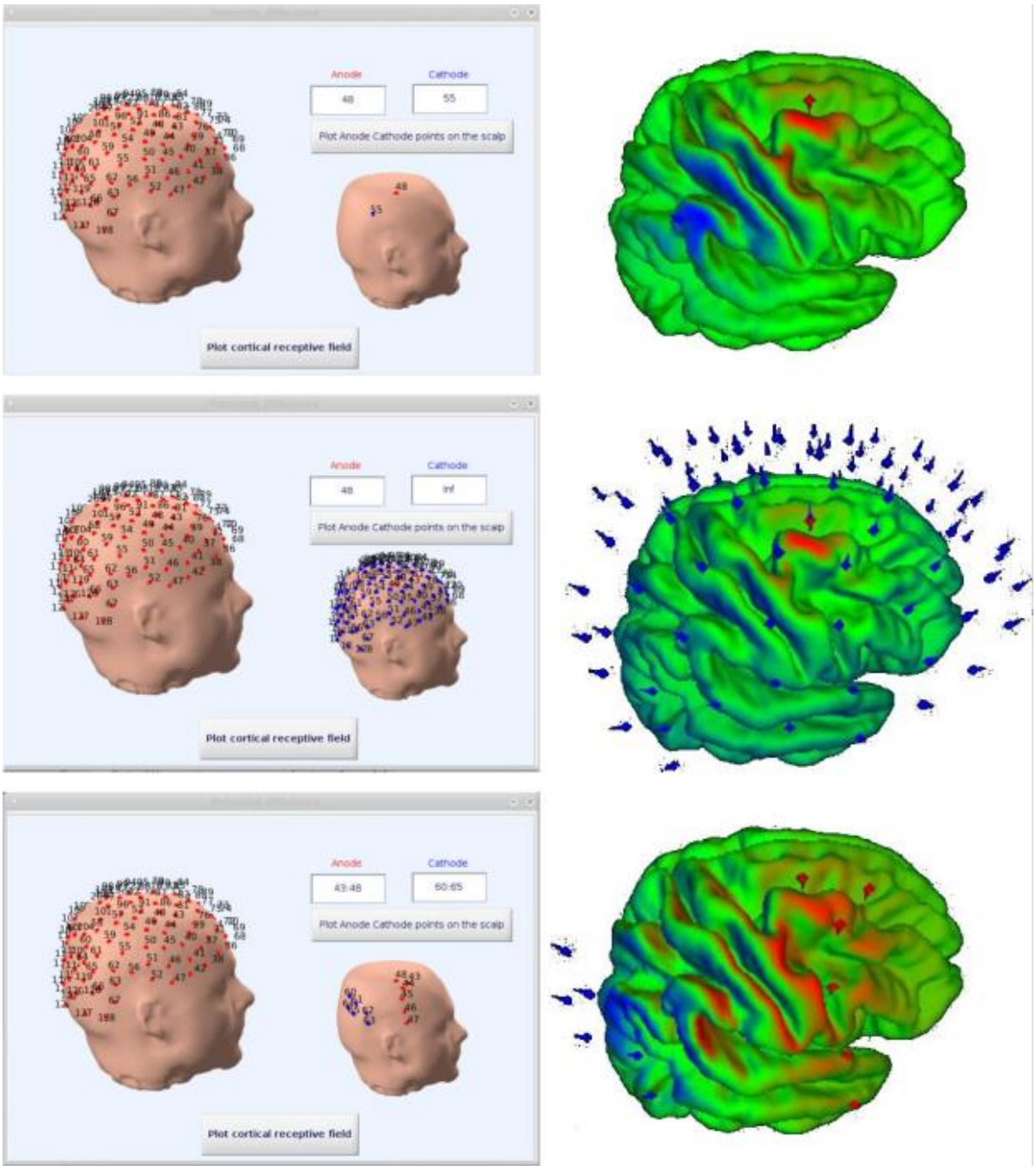
describes the relative contribution of each dipole source to the potential between an electrode and the reference electrode. Our app helps us visualize this for any input (anode) and output (cathode) electrode combination.

The figure shows the App's user interface (left column), and the cortical 'receptive field' image (right column) for different anode-cathode combinations (top: for the indicated right central scalp channel; middle: for all channels; bottom: multiple anode and cathode electrodes). The App helps users understand how each EEG channel (scalp electrode voltage difference) aggregates data from many cortical areas and is available at https://github.com/sccn/EEG_RF.

References

1. Akalin Acar, Z., Makeig, S., 2010. Neuroelectromagnetic forward head modeling toolbox. J. Neurosci. Methods 190, 258-270.

2. Delorme A, Makeig S., 2004. EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. Journal of Neuroscience Methods. Volume 134, Issue 1, Pages 9-21



Disclosures: **Z. Akalin Acar:** None. **S. Makeig:** None.

Poster

164. Tools and Resources for Human Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 164.20

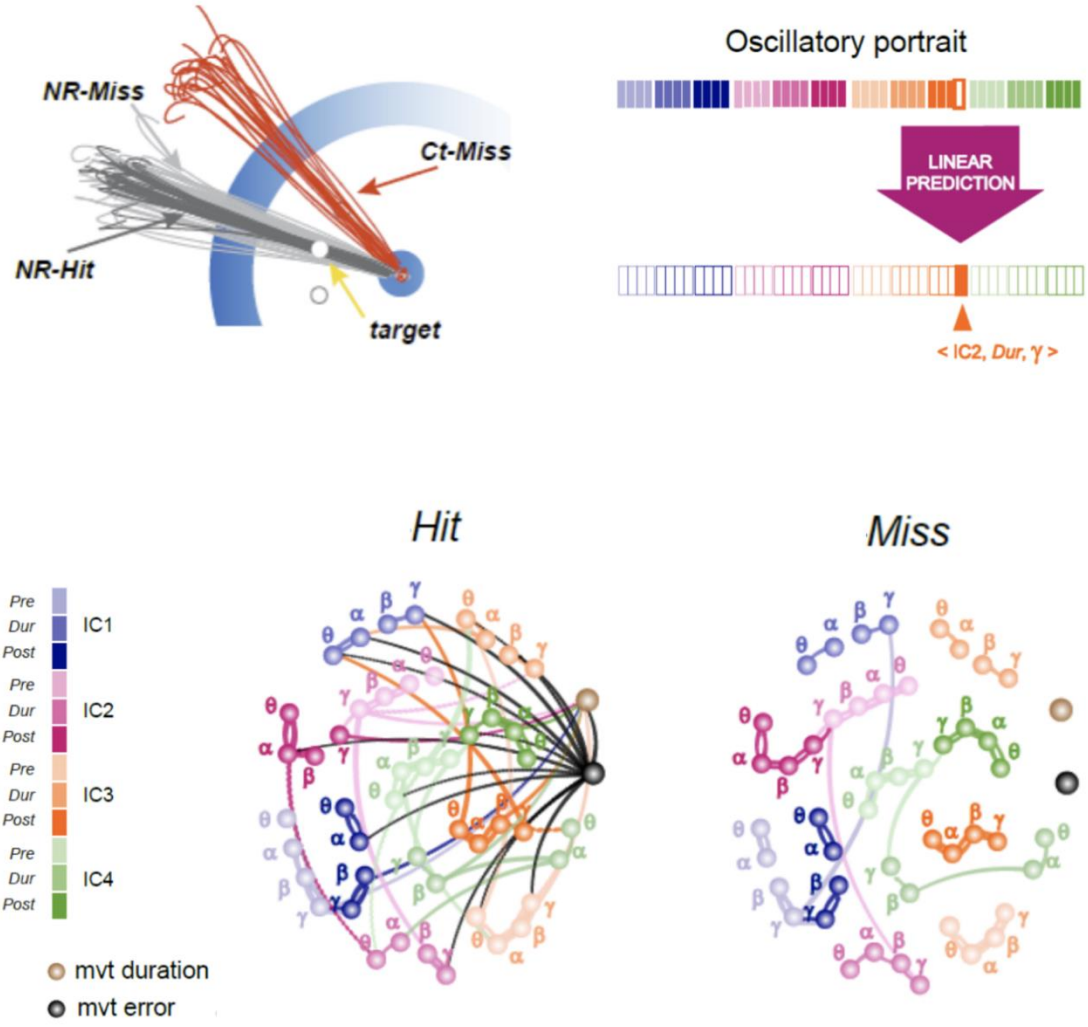
Topic: I.06. Computation, Modeling, and Simulation

Support: ANR-18-CE37-0018 SENCE

Title: Effective connectivity between spatiotemporal multi-frequency elements predict visuomotor behavior

Authors: *A. SCHWEY[1], D. BATTAGLIA[2,3], N. MALFAIT[1], J. BAHUGUNA[4];
[1]Inst. de Neurosciences de la Timone, Unité Mixte de Recherche 7289, Ctr. Natl. de la Recherche Scientifique/Aix-Marseille Univ., Marseille, France; [2]INS, Univ. Aix-Marseille, Marseille, France; [3]Inst. for Advanced Studies (USIAS), Univ. of Strasbourg, Strasbourg, France; [4]Psychology, Carnegie Mellon Univ., Pittsburgh, PA

Abstract: Numerous studies have described frequency specific event-related desynchronization/synchronization (ERD/ERS) calculated by averaging across single-trial absolute power time-series. However, there are two main limitations of this approach. First, searching for univocal correspondences between specific sensory, motor or cognitive processes and specific space-frequency-time oscillatory activities gives only a fragmentary description. Second, these oscillatory features may not even exist in the individual trials.
Here, we use a combination of graph visualization and mixed models to show that the single-trial activities in a 48 dimensional spatial-temporal-spectral space across four cortical areas (frontal medial, parietal medial, and sensorimotor cortices), three movement phases (pre, during and post), and four frequency bands (θ, α, β, γ) are tightly coordinated with each other. The structure of their interdependence network (effective connectivity) for the different task conditions (e.g. without or with an unexpected or expected visual perturbation) were very similar (high cross prediction among task conditions), yet unique as the task conditions could be discriminated with above chance level accuracy.
Furthermore, the single-trial activities are predictive of fine trial-to-trial variations in behavioral features such as movement error and duration. Remarkably, when movement error and duration are included as nodes in the effective connectivity network, the causal direction of the influence was from EEG oscillatory elements to movement duration ("control") whereas "regulatory" connections from movement error to EEG oscillatory elements.
Altogether, our findings suggest that visuomotor cognition and behavior are supported by collective brain states regulating distributed sub-systems in an integrated manner, rather than by a multitude of segregated spatio-temporal-spectral regions, each undergoing independent oscillatory processes.



Disclosures: **A. Schwey:** None. **D. Battaglia:** None. **N. Malfait:** None. **J. Bahuguna:** None.

Poster

164. Tools and Resources for Human Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 164.21

Topic: I.07. Data Analysis and Statistics

Support: US DEVCOM ARL Cooperative Agreement Number W911NF-20-2-0067
US DEVCOM ARL Cooperative Agreement Number W911NF-17-2-0158

Title: Automating the resolution parameter search in the Louvain algorithm to avoid scale biases and optimize temporal range.

Authors: *I. LIMA DIAS PINTO[1], K. BANSAL[2,3], J. O. GARCIA[4];
[1]Humans in Complex Systems Div., US DEVCOM Army Res. Laboratory, Human Res. and Engin. Directorate, San Francisco, CA; [2]Humans in Complex Systems Div., US DEVCOM Army Res. Laboratory, Human Res. and Engin. Directorate, New York, NY; [3]Dept. of Biomed. Engin., Columbia Univ., New York, NY; [4]Humans in Complex Systems Div., US DEVCOM Army Res. Lab., San Francisco, CA

Abstract: The use of network representations to describe brain states during a variety of tasks and special populations has proven fruitful, resulting in the emergence of the field of network neuroscience. As numerous efforts aim to uncover the dynamics that unfold in static network structures, how the networks in the brain change over time has gained traction. Temporal reconfigurations of networks can be viewed as outcomes of dynamical processes that change the interaction between different areas of the brain over time. To study these temporal reconfigurations and access the information contained in the changing network structure, community detection algorithms have been used. These methods are specialized clustering algorithms designed to group nodes in communities based on the structure and strength of the network links as a function of time. One of the most common of these algorithms is the Louvain algorithm used for static networks and the generalized Louvain algorithm used for dynamic and multilayer networks. These are greedy clustering algorithms and their performance can be significantly affected by the choice of the resolution parameters which drive the output community structure. These parameters define the community sizes and temporal resolution of the dynamic community structure detected by the algorithm. However, the choice of these parameters sometimes requires subjective choices and certainly depends on the nature of the data used to generate the network structure. We propose a method to more objectively determine the values of the resolution parameters based on the following criteria: first we choose the spatial resolution parameter based on the distribution of community sizes, in order to avoid scale biases we search for the parameter value that minimizes the skewness of the community size distribution. To determine the temporal resolution parameter we optimize the range of temporal scales captured by the algorithm, such that the temporal windows between each community hop demonstrate a distribution that is scale-free, denoted by a fitted power-law. In order to evaluate the effectiveness of this method, we test our results against benchmark network structures as well as multimodal neuroimaging data. We argue that this automatized parameter search could be used across a large variety of complex systems, beyond the brain, as long as the scale-free optimization is appropriate.

Disclosures: **I. Lima Dias Pinto:** None. **K. Bansal:** None. **J.O. Garcia:** None.

Poster

164. Tools and Resources for Human Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 164.22

Topic: I.06. Computation, Modeling, and Simulation

Support: T32 EY025187
DGE-1734815
R25 NS117356

Title: A New Method for Measuring Visual Snow Symptoms

Authors: *S. A. MONTOYA[1], M. S. LEE[2], S. A. ENGEL[3], M.-P. SCHALLMO[4];
[1]Grad. Program In Neurosci., [2]Ophthalmology and Visual Neurosciences, [3]Psychology, [4]Psychiatry and Behavioral Sci., Univ. of Minnesota, Minneapolis, MN

Abstract: The primary symptom of Visual Snow Syndrome (VSS) is a veil of dots/static flickering across the entire visual field. VSS is a serious but poorly understood disorder estimated to affect 1.4-3.3% of the population. The symptoms of VSS can interfere with daily tasks such as driving and reading. Despite its prevalence and impact, relatively few studies have examined VSS, and quantitative measurements of symptoms are lacking. To address this gap, we developed a matching task in which participants with VSS adjusted parameters of simulated visual snow on a computer screen to match their internal visual snow percept. Participants could modify the contrast, density, speed, and size of flickering dots to match it with their visual snow. The simulated snow was generated by random independent draws from a binary distribution controlled by the contrast parameter. The density of the snow was adjusted by setting a proportion of pixels equal to the background luminance. The speed parameter determined the lifetime of each snow element, after which it was replaced with a new random draw. Dot size was adjusted simply by moving closer or further from the display and the viewing distance was recorded, as snow percepts were generally as small or smaller than pixels viewed from 0.5 m. The dots were presented in a 10 by 10 degree region on one side of the display with an equally sized mean gray region on the other. Participants freely viewed the stimuli while adjusting the parameters with button presses until the simulated snow resembled their perceived snow. Individuals with VSS reported that simulated snow closely resembled their spontaneous snow percept, and parameter settings were consistent across trials. Simulated snow contrast was generally set relatively low and dot size was set relatively small. This task provides a quantitative assessment of visual snow percepts, enabling testing of hypotheses about underlying mechanisms, and may facilitate assessment of treatments/therapies.

Disclosures: S.A. Montoya: None. **M.S. Lee:** None. **S.A. Engel:** None. **M. Schallmo:** None.

Poster

164. Tools and Resources for Human Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 164.23

Topic: H.05. Working Memory

Support: Weizmann-UCLA Joint Research Program
NSF GRFP Grant No. DGE-2034835

Title: Inadequate reliability when measuring cognitive traits obscures investigation of complex behavioral tasks

Authors: C. WALSH[1], J. KADLEC[2], M. RAMOT[2], J. RISSMAN[1];
[1]Psychology, UCLA, Los Angeles, CA; [2]Brain Sci., Weizmann Inst. of Sci., Rehovot, Israel

Abstract: A longstanding goal of cognitive neuroscience is to uncover the nature of brain-behavior relationships. Recent work has shown that these correlations are often small and can require data from thousands of people to reliably detect. Some have suggested using approaches designed to find larger effects or optimizing experimental design to increase the relative amount of signal versus noise to help mitigate the need for such large samples. In this study, we propose that a third approach might lie in improving the reliability of the behavioral tasks themselves, such that the core cognitive traits we seek to measure are more robustly estimated. To do so, we collected data (n = 83) from multiple versions ('forms') of 13 different behavioral tasks spanning executive function, memory, face processing, general perception, and social/emotional cognition. Our core goal was to examine the degree to which individual differences in face memory ability can be explained by a weighted combination of cognitive factors. We used multiple forms of each task to identify the number of trials needed to reliably measure performance by iteratively selecting varying sizes of random subsets of trials and calculating test-retest reliability for each sample. Once we identified the requisite number of trials to reliably capture performance on each task, we conducted separate exploratory factor analyses on data from a single form of each task and on data pooled across multiple forms of each task. We used the resulting factors to explain performance on the Cambridge Face Memory Test, as well as on our newly developed Personal Identity Memory (PIM) task. The PIM task aims to capture face memory ability in a more ecologically valid manner by introducing identities using dynamic video montages and associating each with personally relevant semantic information; it probes both face recognition and recall of the associated semantic attributes. We show that when using an insufficient amount of data to reliably measure cognitive performance, factors reflecting domain-general executive function and visuospatial memory predict performance across all three outcome measures, whereas using additional data uncovers distinct patterns of relationships across tasks. Moreover, while using reliable measures of cognitive performance reduces residual error, less variance can be explained overall, suggesting that using unreliable measures might provide inflated estimates of the relationships between predictors and outcomes. These findings suggest that optimizing the trial counts and reliability of behavioral tasks will be a critical step for finding veridical relationships between brain and behavior.

Disclosures: C. Walsh: None. **J. Kadlec:** None. **M. Ramot:** None. **J. Rissman:** None.

Poster

164. Tools and Resources for Human Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 164.24

Topic: I.06. Computation, Modeling, and Simulation

Support: National Health and Medical Research Principal Research Fellowship GNT1120615
Discovery Project 210101712 from the Australian Research Council

Title: Neurocog.js; A new tool for running cognitive experiments in both lab and online environments.

Authors: *H. BURGESS[1,2], J. BARNBY[3,2], R. DEAN[1,2], L. MACKENZIE[1,2], R. N. THOMAS[4], P. DAYAN[5], L. J. RICHARDS[1,2];
[1]Neurosci., Washington Univ. in St. Louis, Saint Louis, MO; [2]Queensland Brain Institute, The Univ. of Queensland, Brisbane, Australia; [3]Psychology, Royal Holloway, London, United Kingdom; [4]Sch. of Information Technol. and Electrical Engin., The Univ. of Queensland, Brisbane, Australia; [5]Max Planck institute for Biol. Cybernetcs, Tuebingen, Germany

Abstract: Historically, neurocognitive experimental tasks have been administered to participants within a controlled laboratory environment. In recent years it has become popular also to administer such tasks remotely to reach a broader segment of the population and to increase sample size substantially. This movement has been accelerated by the ongoing COVID-19 pandemic. Due to current uncertainty in how changing the testing environment, i.e., in-person vs online, may potentially affect participant performance, there is a pressing need to test participants across multiple environments in order to conduct a comparative analysis on at least a subsample of a larger cohort to identify any online biases. Operating across multiple environments presents an engineering challenge to guarantee consistent and replicable experimental task behavior. Each environment presents a set of unique operational requirements that must be addressed to ensure complete data collection and task completion. There is a currently unfulfilled need for tools that enable neurocognitive tasks to be easily administered across multiple environments. We present Neurocog.js, a JavaScript library that enables jsPsych experiments to operate across three unique experimental environments: over the internet via the Gorilla behavioral experiment builder platform, in-lab within an MRI spectrometer, and in-lab in a standard psychophysics/decision-making environment. Additional features are introduced including support for button-boxes and alternate input configurations, seeded random number generation, global experiment state and state management, and error handling with data preservation. Neurocog.js is an open-source project designed to easily integrate with existing jsPsych experiments while remaining extensible; the project is freely available online via GitHub at https://github.com/Brain-Development-and-Disorders-Lab/Neurocog.js.

Disclosures: H. Burgess: None. **J. Barnby:** None. **R. Dean:** None. **L. Mackenzie:** None. **R.N. Thomas:** None. **P. Dayan:** None. **L.J. Richards:** None.

Poster

164. Tools and Resources for Human Studies

Location: SDCC Halls B-H

Time: Sunday, November 13, 2022, 8:00 AM - 12:00 PM

Program #/Poster #: 164.25

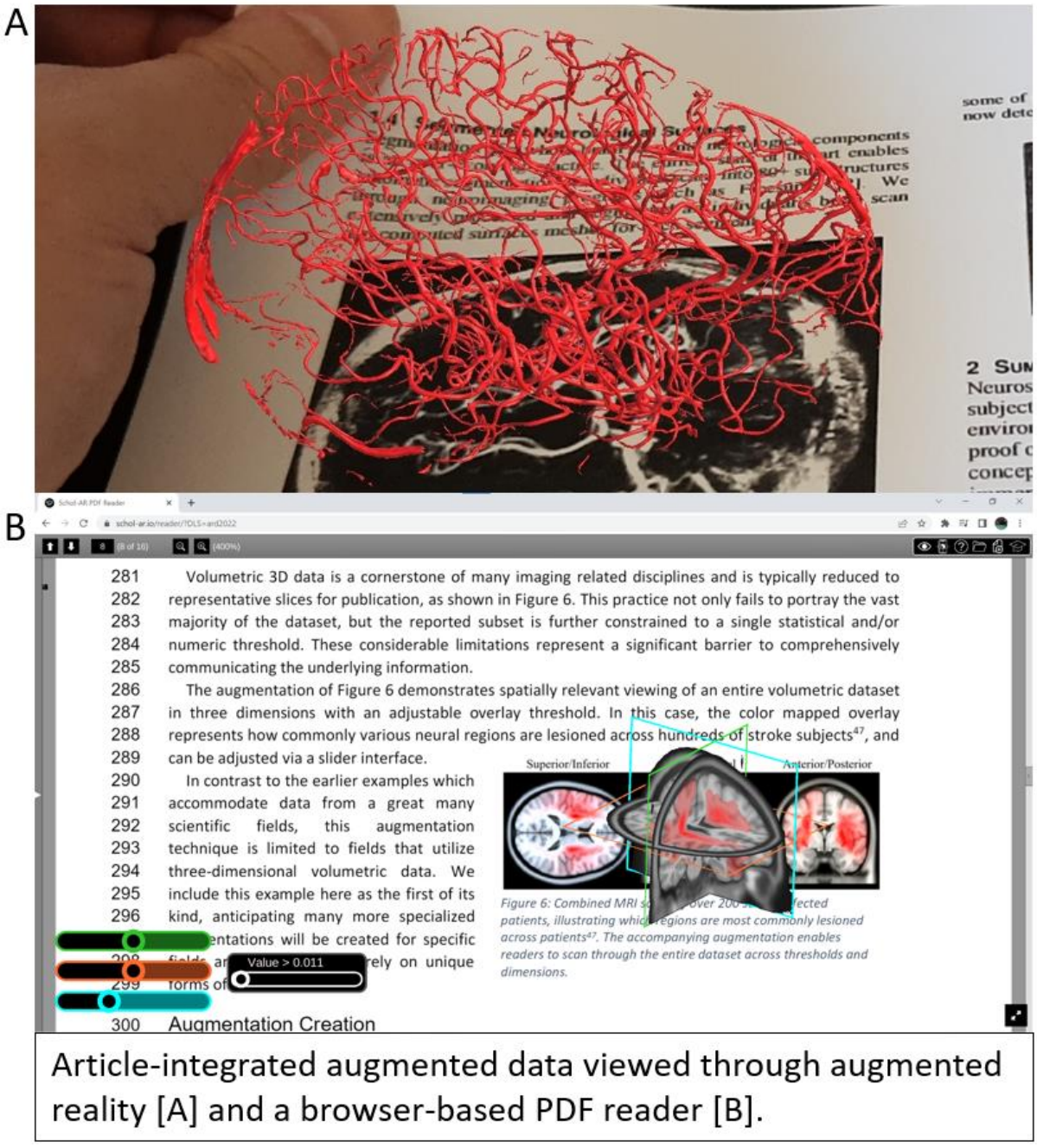
Topic: I.07. Data Analysis and Statistics

Support: NIH Grant P41EB015922
NIH Grant U54EB020406
Michael J. Fox Foundation's Parkinson's Progression Markers Initiative (PPMI – award # 8283.03)

Title: Web Browser and Augmented Reality Integration of Data into Publications - Schol-AR

Authors: *T. D. ARD[1], M. S. BIENKOWSKI[1], S.-L. LIEW[2], A. W. TOGA[1];
[1]Stevens Neuroimaging and Informatics Inst., [2]Chan Div. of Occup. Sci. and Occup. Therapy, USC, Los Angeles, CA

Abstract: Neuroscience research is heavily reliant on many forms of data, such as microscopic image stacks, volumetric MRI scans, 3D models, and numerous other digital formats. However, the articles we use to communicate neuroscience remain based on the centuries-old standard of printable text and static images, which can be inadequate for the communication of modern data. Here, we expand on our previous work and demonstrate how 'layering' data onto figures can be achieved through augmented reality technologies as well as browser-based interfaces. This technique provides access to digital data regardless if articles are electronically viewed or physically printed. Furthermore, these augmentations function within the standard PDF format and do not require any technical infrastructure from individual publishers. As such augmented figures are now automatically compatible with every journal, submission system, and publisher. Our framework, termed 'Schol-AR', provides the scientific community the capabilities to both create and view augmentations. Overall, this project aims to modernize the way data is represented in scientific publications, ultimately improving the state of scientific communication.



Article-integrated augmented data viewed through augmented reality [A] and a browser-based PDF reader [B].

Disclosures: **T.D. Ard:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Ownership Interest in Ardist Inc., which contributes to development of this project. **M.S. Bienkowski:** None. **S. Liew:** None. **A.W. Toga:** None.