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Poster

729. Neuron-Glia Interactions

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 729.01/A1

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grant NS104994
NIH Grant R25GM119973-02

Title: Pathological changes in microglia during cerebellar postnatal development in a mouse model of Niemann Pick type-C disease

Authors: R. S. ALTRECHE, B. R. BOYLE, *I. SOTO;
Rowan Univ., Glassboro, NJ

Abstract: Niemann Pick Type-C disease (NPC) is a lysosomal storage disease that is acquired by autosomal recessive inheritance. It is mostly caused by deficiency of the NPC1 protein, which transports cholesterol out of the lysosomes, therefore abnormal accumulation of cholesterol and other lipids in endosomes and lysosomes is a hallmark of NPC. Purkinje cells (PCs) in the cerebellum are hypersensitive to NPC1 deficiency, degenerating earlier and to a larger degree than other neurons in the brain. Previously, we found that in *Npc1^{nmf164}*mice activation of microglia is already detected at post-weaning age and precedes PCs degeneration, suggesting that NPC1 deficiency could alter microglia during cerebellar postnatal development. To determine the effects of NPC1 deficiency in cerebellar microglia during postnatal development, the migration, proliferation and maturation of developing microglia was studied using immunofluorescence and 3D image reconstruction analysis. It is known that during normal cerebellar postnatal development, microglia precursors migrate from the white matter region into the internal granule layer (IGL), then into the molecular (ML) and external granule layers (EGL). The location and number of microglia in the developing cerebellum was quantified; the number of microglia at the IGL, ML (where the dendrites of Purkinje cells reside) and the EGL was determined. We have found that in the first days of postnatal development there is a decreased number of microglia in the *Npc1^{nmf164}* mutant mice when compared to age-matched wild type (WT) mice. In contrast, we have found that overtime, there is an increase in the number of microglia in the ML of *Npc1^{nmf164}*mice when compared to age-matched WT mice. At 9-10 days, the number of microglia was remarkably higher in the ML of *Npc1^{nmf164}*mice than in WT mice. Similarly, at 14-15 days, the number of microglia was also higher in the ML of *Npc1^{nmf164}*mice than in the WT mice. Significant morphological differences between WT and *Npc1^{nmf164}*microglia were found, specifically shorter processes in the mutant microglia. Our findings suggest that microglia migration and/or proliferation may be delayed in *Npc1^{nmf164}* mice

during early postnatal days, however proliferative activity seems to be increased overtime in these mice when compared to WT.

Disclosures: **R.S. Altreche:** None. **B.R. Boyle:** None. **I. Soto:** None.

Poster

729. Neuron-Glia Interactions

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 729.02/A2

Topic: A.01. Neurogenesis and Gliogenesis

Support: 2011CBA00404 to X-h.Z
2015CB964501
2018YFA0108003, to L-p.C
XDA16010311, to L-p.C.
31371096, to L-p.C.
31871037, to L-p.C.

Title: Precise integration of direct cell reprogramming - induced neuronal cells into adult neocortical circuits

Authors: *F. WANG[1], Y. LIU[2], X. LI[1], L. CHENG[2], X. ZHANG[1];
[1]State Key Lab. of Cognitive Neurosci. and Learning, Beijing Normal Univ., Beijing, China;
[2]Inst. of Neurosci. and State Key Lab. of Neurosci., Chinese Acad. of Sci., Shanghai, China

Abstract: Recent discovery of *in vivo* reprogramming of glia cells to neurons by defined neurogenic transcription factors in the adult brain has provided a new approach for neuronal replacement therapy. However, it remains completely unknown whether and how these direct cell reprogramming-induced neuronal cells (iNs) are functionally integrated into the existing neural circuits. We report here that in the adult mouse primary visual cortex (V1), the iNs, reprogrammed from astrocyte by a single transcription factor Ascl1, can develop proper distinct visual tuning functions and they are precisely integrated into the existing retinotopic map, compared to original counterparts. Matured iNs receive brain-wide afferent connections that are known to innervate the V1. They form fully-assembled structures of afferent and efferent synapses with pre-existing V1 neurons under electron microscopy. Thus, these *in vivo* findings strongly endorse promise for application of direct cell-reprogramming to the neural circuit reconstruction in a diseased or injured brain.

Disclosures: **F. Wang:** None. **Y. Liu:** None. **X. Li:** None. **L. Cheng:** None. **X. Zhang:** None.

Poster

729. Neuron-Glia Interactions

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 729.03/A3

Topic: A.01. Neurogenesis and Gliogenesis

Support: Burke Neurological Institute

Title: Promoting oligodendrocyte differentiation in adult neural stem and progenitor cells by targeting G-quadruplex nucleic acid secondary structures

Authors: D. GOLDBERG[1], L. FONES[1], A. L. VIVINETTO[1], J. CAUFIELD[1], R. R. RATAN[2], ***J. W. CAVE**[2];
[2]Weill Cornell Med., [1]Burke Neurolog. Inst., White Plains, NY

Abstract: Neural stem and progenitor cells in the adult subventricular zone (SVZ) are a potentially important source of endogenous neural repair. Several different pathological conditions can stimulate this neurogenic niche to generate progenitors that migrate towards afflicted regions. This endogenous repair response, however, is usually inadequate to provide meaningful neuroprotection or repair. Thus, exploiting the SVZ neurogenic niche as potential source of endogenous repair requires the development of efficient methods to manipulate the proliferation and differentiation of SVZ derived neural progenitors. G-quadruplexes are nucleic acid secondary structures that are pervasive in the genomic DNA and RNA transcriptomes of mammalian cells. These structures regulate numerous cellular processes associated with gene expression and genome duplication, but their role in controlling the proliferation and differentiation of neural stem and progenitor cells is unexplored. In this study, we show that targeting nucleic acid G-quadruplex stability with small molecules can modify adult SVZ neural stem and progenitor cell proliferation and promote oligodendrocyte differentiation. We show that two related small molecules (pyridostatin and carboxypyridostatin) that differentially target DNA and RNA G-quadruplex stability reduce proliferation in the SVZ in vivo of adult mice. Using in vitro neurosphere cultures, however, our analyses reveal that targeting DNA G-quadruplex stability reduces proliferation by inducing DNA damage and apoptosis. By contrast, exclusively targeting RNA G-quadruplex stability with carboxypyridostatin does not induce cell death, but rather facilitates the production oligodenodrocyte progenitors when EGF and FGF2 growth factors are present. We also find that interperitoneal administration of carboxypyridostatin increases the number of Olig2-expressing cells in the cortex and corpus callosum of adult mice. Together, these findings suggest that RNA G-quadruplexes are an important, new class of molecular target for neural stem and progenitor cell engineering.

Disclosures: J.W. Cave: None. **D. Goldberg:** None. **L. Fones:** None. **A.L. Vivinetto:** None. **J. Caufield:** None. **R.R. Ratan:** None.

Poster

729. Neuron-Glia Interactions

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 729.04/A4

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grant R37 NS096359
NIH Grant R01 NS075243

Title: A distinct role of polycomb group proteins in CNS myelination

Authors: *L. YANG, J. WANG, R. Q. LU;
Cancer and Blood Dis. Institute, EHCB, Cincinnati Children's Hosp. Med. Ctr., Cincinnati, OH

Abstract: Epigenetic regulation iscrucial for neural cell fate specification and maintaining proper cell identity. However, the epigenetic mechanisms that regulate oligodendrocyte lineage progression remain incompletely understood. The polycomb repressive complex 2 (PRC2) deposits the H3K27me3 mark on the promoters and enhancers of regulatory genes to silence their expression. Expression of H3K27me3 increases during the transition from oligodendrocyte precursors (OPC) to mature oligodendrocytes, while H3K4me3, which labels active chromatin, is enriched on OPCs. Eed and Ezh2, the core component of PRC2, are expressed in OPC and differentiated oligodendrocytes. Intriguingly, EED is detected in the nucleus of OPCs but in cytoplasm of mature oligodendrocytes. In vivo stage-specific conditional knockout indicates that Eed is necessary for maintaining OPC proliferation and differentiation, resulting in myelination defects, while deletion of Ezh2 impairs OPC differentiation but OPC proliferation. Though the mice with deletion of EED and EZH2 display oligodendrocyte differentiation defects at early developmental stages, EED knockout mice show sustained myelination defects in the developing CNS, while myelination defects in EZH2 knockout mice recovers at the adult stage, suggesting a non-redundant role of PRC2 complex components during oligodendrocyte development. Genomic occupancy analyses reveal thatEed targets Wnt and TGF-β signaling components, the negative regulators of OPC differentiation. Wnt and TGF-β signaling is upregulated in oligodendrocyte progenitors Eed mutant mice.Inhibition of Wnt and TGF-β signaling partially rescues oligodendrocyte differentiation defects caused by Eed loss. Furthermore, genetic deletion of Eed in OPCs impairs myelin repair after demyelinating injury. These data reveal a novel epigenetic regulated pathway and suggest an essential role for Eed in SVZ homeostasis and injury.Thus, our findings reveala distinct role of PRC2 complex proteins-mediated epigenetic regulation for myelination and maintenance of myelin homeostasis during CNS development and after injury.

Disclosures: **L. Yang:** None. **J. Wang:** None. **R.Q. Lu:** None.

Poster

729. Neuron-Glia Interactions

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 729.05/A5

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH grant P20GM121334

Title: Altered fetal microglia phenotypes are associated with abnormal neurogenesis following maternal immune activation

Authors: M. LOAYZA, K. CARTER, L.-W. FAN, Y. PANG, *A. J. BHATT;
Univ. of Mississippi Med. Ctr., Jackson, MS

Abstract: Maternal infection is a risk factor for Autism Spectrum Disorder (ASD). Although the underlying neuropathology remains largely unknown, neuroimaging studies consistently showed that there is a period of brain overgrowth in ASD infants, which may be caused by dysregulated neuronal growth. Given that microglia are critically involved in both neurogenesis and programmed neuronal death in homeostatic condition, whereas activated microglia are known to exhibit different phenotypes linked to either proinflammatory or anti-inflammatory functions, this study tested a hypothesis that lipopolysaccharide (*LPS)-activated fetal microglia altered neural development by promoting neurogenesis.* Time-pregnant C57BL/6J mice at E12.5 were injected with LPS (50 ug/kg body weight, i.p.) and controls received saline injection. On postnatal day 1 (P1) and P21, brain sections were prepared from mice pups for immunohistochemical analysis of microglia and neurons. Microglia phenotypes were assessed by flow cytometry on E15 and P4. We found that maternal LPS challenge significantly increased Iba1+ microglia in neurogenic regions including the subventricular zone (SVZ) of lateral ventricles and the dentate gyrus (DG) of hippocampus. The majority of microglia exhibited unique phenotype characterized with double positive immunostaining for CD86 and CD206 in the control E15 and P4 mice brain, which was significantly increased by LPS treatment. LPS exposure resulted in a marked increase of Ki67+ cells in the SVZ and DG, suggesting potential over-production of neurons. We also found that TGFb+ neurons, which were only observed in the deep (layer III-IV) but not the superficial layers (I-II) of control P1 mice, were distributed throughout cortical layers in LPS-treated pups. On P21, the total number of parvalbumin positive neurons in the medial prefrontal cortex was significantly lower in the LPS-exposed offspring mice than the controls. Overall, our data showed that a low dose maternal LPS exposure leads to enduring activation of fetal microglia, which is associated with increased neural progenitor cell proliferation and reduced PV+ neurons, and this may alter cytoarchitecture and local circuits in highly laminated structures such as the cerebral cortex and hippocampus.

Disclosures: **M. Loayza:** None. **K. Carter:** None. **L. Fan:** None. **Y. Pang:** None. **A.J. Bhatt:** None.

Poster

729. Neuron-Glia Interactions

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 729.06/A6

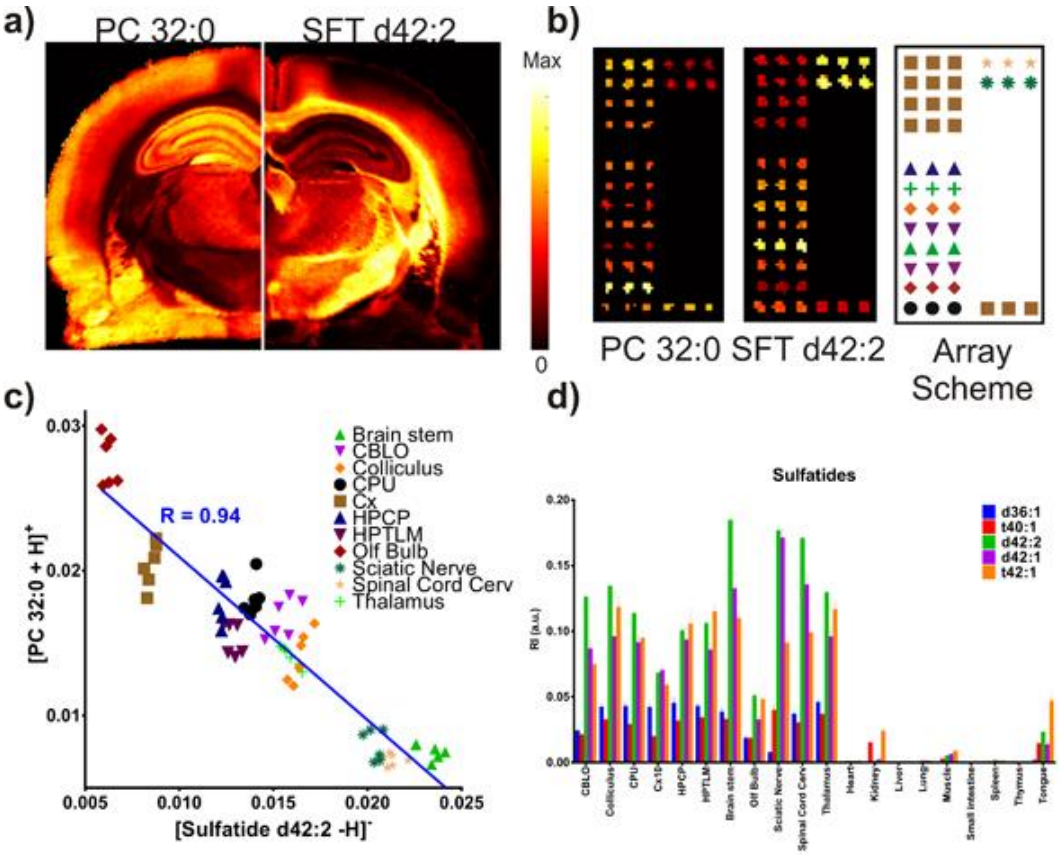
Topic: A.01. Neurogenesis and Gliogenesis

Support: Spanish Ministry of Economy and Competitiveness (RTC-2015-3693-1)

Title: Specific lipid biomarkers of neurons and glial cells in rat and monkey

Authors: R. FERNÁNDEZ[1,2], ***G. BARREDA-GÓMEZ**[1], T. TOLENTINO-CORTEZ[1], M. GULAK[3,4], J. FERNÁNDEZ[2], E. ASTIGARRAGA[1];
[1]IMG Pharma Biotech, Derio, Spain; [2]Univ. of the Basque Country (UPV/EHU), Leioa, Spain; [3]Cruz Roja Hosp., Bilbao, Spain; [4]Cruces Univ. Hosp., Barakaldo, Spain

Abstract: Recent developments have revealed the importance of lipids as biomarkers in different diseases and as indicators of the cell's homeostasis, in addition to their structural function. However, the limitations inherent to the assays used for lipidomic analysis hamper surfacing the complex relationships between lipid classes, lipid species and proteins. To overcome these handicaps, we developed cell membrane microarrays of different brain areas of non-human primate and rat to determine the lipid fingerprint of samples of different nature in a standardized and fast way, using MALDI mass spectrometry. Consecutive microarrays were also employed in enzymatic and immunohistochemical assays and the data obtained were analyzed together by supervised and unsupervised learning methods.
Several positive and negative correlations above 0.8 and below -0.8 were found between certain lipid species and even between some lipids and the expression of glyceraldehyde-3-phosphate dehydrogenase (GAPDH) and the activity of cholinesterases (ChE) and acetylcholinesterase (AChE). Some of these interactions between sulfatides, phosphatidylcholines (PC) and phosphatidylethanolamines (PE) or even ChE and AChE were equally high in rat and in non-human primate nervous system. In particular, an inverse relationship were determined in both species between [Sulfatide d42:2-H]- and [PC 32:0-H]-, characteristic lipids from white and grey matter respectively. Moreover, a good correlation was found between some sphingomyeline (SM) and sulfatide species and the GAPDH expression. Thus, these data indicate important relationships between cell membrane lipids and also proteins in the brain, although further research is required to determine the relevance of them in physiological and pathological conditions.



Disclosures: **R. Fernández:** None. **G. Barreda-Gómez:** None. **T. Tolentino-Cortez:** None. **M. Gulak:** None. **J. Fernández:** None. **E. Astigarraga:** None.

Poster

729. Neuron-Glia Interactions

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 729.07/A7

Topic: A.01. Neurogenesis and Gliogenesis

Support: NSF Fellowship DGE-0903443
Internal Grant RX2700 403
NMSS Grant RG5022A1/1

Title: Retinaldehyde dehydrogenase 2 is required for the production and maturation of oligodendrocyte precursors in the postnatal corpus callosum

Authors: *V. E. MORRISON, V. N. SMITH, J. K. HUANG;
Dept. of Biol., Georgetown Univ., Washington, DC

Abstract: Myelination of the central nervous system (CNS) relies on the production of oligodendrocytes (OLs) from oligodendrocyte precursor cells (OPCs). During the first month of postnatal life, OPCs that eventually populate the corpus callosum arise from neural stem cells (NSCs) in the dorsal subventricular zone (SVZ) of the lateral ventricle and then mature to generate myelinating OLs. However, the signals that regulate the production and maturation of OPCs in this region are not fully understood. In this study, we show that the retinoic acid (RA)-synthesizing enzyme retinaldehyde dehydrogenase 2 (RALDH2) is required for the production and maturation of postnatal OPCs in the corpus callosum. Deletion of RALDH2 in neural/glial antigen 2-positive ($NG2^+$) cells, including perivascular cells and OPCs, reduced total OL lineage cell number, disrupted OPC differentiation, and caused hypomyelination of the corpus callosum. Moreover, decreased OL lineage cell numbers coincided with reduced NSC survival and decreased sonic hedgehog (SHH) signaling in the SVZ. Additionally, astrocyte and cortical neuron numbers were reduced. Our work reveals a role for RALDH2-dependent RA synthesis by $NG2^+$ cells in regulating OPC development and myelination of the corpus callosum. Furthermore, we raise the possibility that paracrine RA signaling between $NG2^+$ cells and NSCs impacts neuro- and gliogenesis.

Disclosures: V.E. Morrison: None. **V.N. Smith:** None. **J.K. Huang:** None.

Poster

729. Neuron-Glia Interactions

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 729.08/A8

Topic: A.01. Neurogenesis and Gliogenesis

Support: Alana Foundation
LuMind RDS

Title: Glial cell dysfunction as a result of 3D genome architecture changes in Trisomy-21 in iPSC and Ts65Dn mouse models

Authors: *E. R. LOCKSHIN[1], G. KUFFNER[2], H. MEHARENA[3], L.-H. TSAI[2];
[1]Picower Inst. For Learning and Memory, Cambridge, MA; [3]Picower Inst. for Learning and Memory, [2]MIT, Cambridge, MA

Abstract: Trisomy 21(T21) is a genetic disorder that results from triplication of chromosome 21, which causes genome wide disruption. Some of the phenotypes of T21 include intellectual disability, craniofacial abnormalities, hypocellularity of the brain, deficits in neurodevelopment,

and early onset of Alzheimer's disease (AD). TS21 has been shown to cause dysfunction in gene expression in different cell types, and the implications of T21 on glial cell function has not been investigated. Proper glial cell function is necessary for neurodevelopment, homeostasis, and healthy aging. Our primary focus is on astrocyte and microglia function. Astrocytes maintain the environment of the CNS for neural function and GABAergic signaling. As the resident immune cells of the CNS, microglia are responsible for synaptic pruning, responding to injury and pathogens. Dysfunctional microglia are implicated in many age-related diseases, including AD. Initial RNA-seq analysis of iPSC derived microglia and astrocytes indicates down regulation in gene expression for migration, cell cycle, neurodevelopment, and other pathways. We used iPSC derived glial cells to further investigate this cellular dysfunction, and compare them to an in-vivo model of Ts65Dn mice. Additionally, we looked at the changes in the 3D genome architecture of these cell types using Hi-C analysis. Understanding the physiological differences of these cell types in TS21 will allow future development of therapies for individuals with TS21.

Disclosures: E.R. Lockshin: None. **G. Kuffner:** None. **H. Meharena:** None. **L. Tsai:** None.

Poster

729. Neuron-Glia Interactions

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 729.09/A9

Topic: A.01. Neurogenesis and Gliogenesis

Title: Using 3D brain organoids to model human astrocyte maturation and uncover the developmental origins of glioblastoma

Authors: *C. SOJKA[1], A. KING[1], A. TREVINO[2], G. CARSON[2], S. A. SLOAN[1];
[1]Emory Univ., Atlanta, GA; [2]Stanford Univ., Palo Alto, CA

Abstract: Astrocytes are the most abundant glial population in the human brain and yet we know little about their developmental origins and mechanisms of maturation. Further, although we are learning more about the role of astrocytes in guiding neural development, less is known about their own development and the implications of aberrant astrogenesis in neurodevelopmental disorders and oncogenesis. Human astrocytes undergo a profound maturation process during postnatal development that is evidenced by transcriptomic, morphological, and functional changes. In the case of glioblastoma (GBM), a brain cancer defined by uncontrolled astrocyte proliferation, astrocytes in the tumor core share a similar transcriptomic profile to that of fetal human astrocytes. We hypothesize that this similarity could either be a result of perturbed astrocyte development, abnormal astrocyte maturation, or aberrant astrocytic differentiation from other progenitor pools. Therefore, we sought to define the normal timeline of human astrocyte development, and to identify temporally-graded molecular drivers of astrocyte maturation and deviations of that process in instances of irregular astrocyte

development. One obstacle that has stymied attempts to study human astrocyte development has been lack of access to tissue samples at key developmental time points. To address this hurdle, we used 3D iPSC-derived brain organoids, supplemented with primary human fetal and adult cortical samples to define the genetic landscape throughout multiple stages of normal astrocyte maturation. Additionally, we analyzed the genetic landscapes of astrocytes purified from primary human GBM samples to determine the degree to which they deviate from normal astrocyte developmental trajectories and to pinpoint where on the maturation spectrum GBM astrocytes fall. Understanding the developmental origins of normal and neoplastic human astrocytes will help provide mechanistic insight into GBM formation and progression and uncover potential therapeutic targets for the treatment of GBM.

Disclosures: C. Sojka: None. **S.A. Sloan:** None. **A. King:** None. **A. Trevino:** None. **G. Carson:** None.

Poster

729. Neuron-Glia Interactions

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 729.10/A10

Topic: A.01. Neurogenesis and Gliogenesis

Support: Rahel Hirsch Fellowship Charite Berlin

Title: Serotonin and brain plasticity in the hippocampus: The role of microglial cells

Authors: A. TURKIN[1,2], M. SIDOROVA[2], N. ALENINA[1], ***F. KLEMPIN**[1,3];
[1]Max-Delbruck-Centrum (MDC), Berlin, Germany; [2]Inst. of Life Science, Immanuel Kant Baltic Federal Univ., Kaliningrad, Russian Federation; [3]Charité Univ. Med., Berlin, Germany

Abstract: Microglia are resident immune cells of the adult brain and become activated in response to stimuli. Among the various functions, microglial cells release neurotrophins and cytokines to maintain homeostasis of neural circuits, but also express neurotransmitter systems. Serotonin (5-hydroxytryptamine, 5-HT) is a crucial signal in the neurogenic niche microenvironment of the hippocampus, involved in antidepressant action, and has recently been shown to enhance microglial response to injury in acute mouse brain slices. Genetically modified animal models that differ in their availability of serotonin, constitute powerful tools to study neuroplasticity and drug development. We took advantage of tryptophan hydroxylase 2 deficient (*Tph2*$^{-/-}$) rats, selectively depleted of brain serotonin, to determine the expression profile of various 5-HT receptors on microglial cells in the hippocampus and prefrontal cortex at postnatal day (P)8 and P21. In the presence or absence of brain serotonin, microglia cells of female and male transgenic rats and their littermates were FACS-sorted by flow cytometry for qPCR analysis. Surprisingly, we observed a significant increase in the population of CD11b-expressing

microglia in the dissected brain areas of *Tph2*$^{-/-}$ rats at P21, suggesting reduced serotonin-induced suppression of microglia activation in the absence of the neurotransmitter. Our data show high expression of 5-HT2b and 5-HT5a receptor subtypes, weak expression of 5-HT1b and 5-HT7. Furthermore, we analyzed mRNA levels of the brain-derived neurotrophic factor, BDNF- since we had shown previously that complete lack of brain serotonin induces BDNF signaling- and also of interleukin-6 upon microglia activation in *Tph2*$^{-/-}$ rats at P21. Together, our data indicate an important link between microglial cells and signals of the neurogenic niche, e.g. serotonin and BDNF, that could be employed as therapeutic targets.

Disclosures: A. Turkin: None. **M. Sidorova:** None. **N. Alenina:** None. **F. Klempin:** None.

Poster

729. Neuron-Glia Interactions

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 729.11/A11

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH R15NS108234
NIH R01MH066084-03
SCU DeNardo Fellowship
SCU REAL Student Fellowship

Title: Examining the role of neuronal activity in the formation of neuronal-glial connections

Authors: *A. PARVATHANENI[1], A. SAHAGUN[1,2], J. GARCIA CASTILLO[3], L. HALLADAY[2], S. J. PLEASURE[3], L. A. COCAS[1,2,3];
[1]Biol., [2]Neurosci., Santa Clara Univ., Santa Clara, CA; [3]Dept Neurol, UCSF, San Francisco, CA

Abstract: The mechanisms that drive the timing and specificity of oligodendrocyte myelination during development, or remyelination after injury or immune attack are not well understood. Recent work has shown that oligodendrocyte progenitors receive synapses from neurons, providing a potential mechanism for neuronal-glial communication. We hypothesize that these connections are important both for correct myelination of neurons during development and for myelination during neuronal plasticity. We utilize chemogenetic tools and viral monosynaptic circuit tracing to analyze these neuroglial connections and to examine OPC proliferation, myelination and neuronal-glial connectivity after altering neural activity *in vivo*.

Disclosures: A. Parvathaneni: None. **A. Sahagun:** None. **J. Garcia Castillo:** None. **L. Halladay:** None. **S.J. Pleasure:** None. **L.A. Cocas:** None.

Poster

729. Neuron-Glia Interactions

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 729.12/A12

Topic: A.01. Neurogenesis and Gliogenesis

Title: Histological and ultrastructural evidence of planarian myelin

Authors: *L. THOMPSON[1], M. SCOTTO[1], S. GUARIGLIA[2];
[1]St. Joseph By the Sea High Sch., Staten Island, NY; [2]New York State Inst. for Basic Res., Staten Island, NY

Abstract: Planarians are a small invertebrate flatworm which belongs to the class *Turbellaria*. They are hardy organisms and can be found in many environments throughout the world. In a laboratory setting, planarians are inexpensive and easy to maintain. To date, it is thought that planarians lack myelin, like other invertebrates. Recently, some studies have demonstrated that invertebrates do have myelin, although it is often structurally different than vertebrate myelin. Using whole mount preparations of planarian stained with fluoromyelin, a fluorescent dye that is used to stain myelin, we found robust staining in the brain and ventral cords of planarians. To confirm our finding, we prepared samples to be stained using Luxol Blue, the dye that is traditionally used to visualize myelin. We found the same staining pattern in our Luxol Blue stained planarian sections. We also immunostained the planarians using an avian Schwann cell marker, which reacted with the structures thought to be myelin. We then investigated the ultrastructure of the planarian brain, and found cells that resemble *Drosophila* glia. Finally, we exposed the planarians to cuprizone, the agent that is typically used to pharmacologically induce demyelination in vertebrate models. The planarians completely lost all fluoromyelin positive regions of brain and the ventral nerve cords. This finding suggests that the fluoromyelin positive regions which we identified are indeed myelin, as they are absent after an animal is treated with the demyelinating agent cuprizone. Our findings also suggest that planarian myelin is affected by cuprizone in the same manner that is found in vertebrates, which suggests that studies performed in planarians are translational to other organisms, making planaria a potential high throughput model for studying demyelinating conditions.

Disclosures: **L. Thompson:** None. **M. Scotto:** None. **S. Guariglia:** None.

Poster

729. Neuron-Glia Interactions

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 729.13/A13

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH RO1 NS050674

Title: Characterization of peripheral glia using single cell RNA-seq approach

Authors: O. E. TASDEMIR YILMAZ[1], *L. V. GOODRICH[2], R. A. SEGAL[1];
[1]Dana-Farber Cancer Inst., Boston, MA; [2]Harvard Med. Sch., Boston, MA

Abstract: The peripheral nervous system is comprised of multiple distinct sensory and autonomic ganglia. In all types of peripheral ganglia and peripheral nerves, glial cells are closely associated with neurons, and the number of peripheral glial cells is higher than the number of peripheral neurons. Although we know much about the diversity and function of neurons in these ganglia, the genetic profile and differences of the glial cells that associate with those neurons are still a mystery. In order to investigate the similarities and differences among these peripheral glial cells, we profiled the developing peripheral glia from two sensory ganglia, dorsal root ganglion (DRG) and spiral ganglion of the cochlea, using single cell RNA-seq approaches. From our dataset, we uncovered unique markers for subtypes of glial cells. In particular, we found that the glial progenitors have different dynamics in these distinct ganglia. Glial progenitors persist in DRG from embryonic development through the postnatal period, while the progenitor cell population in cochlea can be seen in early embryonic development but decrease rapidly and are not detected in the postnatal setting. This finding could have implications on the glial renewal differences in the two sensory ganglia. Interestingly, while the Schwann cells of the DRG and sciatic nerve closely resemble those found in the cochlea, the gene signature of satellite glia from DRGs and cochlea are clearly distinct from one another, satellite glia may serve different functions in the two ganglia. As both sets of satellite glia express astrocyte-like patterns of gene expression, satellite glia may modulate the development and function of the associated peripheral neurons and thereby contribute to sensory transduction.

Disclosures: O.E. Tasdemir Yilmaz: None. **L.V. Goodrich:** None. **R.A. Segal:** F. Consulting Fees (e.g., advisory boards); Amgen, Decibel Therapeutics, Allergan.

Poster

730. Postnatal Neurogenesis: Environmental and Pharmacological Regulation

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 730.01/A14

Topic: A.02. Postnatal Neurogenesis

Support: Spanish Ministry of Economy and Competitiveness with FEDER funds (BFU2012-32089, RYC-2013-12817, BFU2015-66689)
Leonardo Award from the BBVA Foundation
Basque Government project (PI_2016_1_0011)
Hungarian Research and Development Fund Grant (K116654)
Hungarian Brain Research Program grant (2017-1.2.1-NKP-2017-00002)
Ikerbasque start-up funds
Predoctoral fellowship from the University of the Basque Country EHU/UPV

Title: Microglia actively remodels adult hippocampal neurogenesis through the phagocytosis secretome

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Abstract: During adult hippocampal neurogenesis, the majority of newborn cells undergo apoptosis and are rapidly phagocytosed by resident microglia in order to avoid disturbing the surrounding neurons. Here, we propose that phagocytosis is not merely a passive process of corpse removal but has an active role in maintaining adult hippocampal neurogenesis. First, we found that neurogenesis was disrupted in mice chronically deficient for two microglial phagocytosis pathways (P2Y12, MerTK/Axl), but was transiently increased in mice in which MerTK expression was conditionally downregulated. We then followed an in vitro approach to perform a transcriptomic analysis of microglial phagocytosis and identified genes involved in metabolism, chromatin remodeling, and neurogenesis-related functions. Finally, we determined that the phagocytic microglia secretome limits the production of new neurons both in vivo and in vitro. Our data suggest that reprogrammed phagocytic microglia acts as a sensor of local cell

death, modulating the balance between cell proliferation and cell survival in the neurogenic niche, supporting the long-term maintenance of adult hippocampal neurogenesis.

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Poster

730. Postnatal Neurogenesis: Environmental and Pharmacological Regulation

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 730.02/A15

Topic: A.02. Postnatal Neurogenesis

Support: NRF-2019R1A2C4004912

Title: Zinc is essential for adult hippocampal neurogenesis

Authors: ***B. CHOI**[1], D. HONG[1], J. JEONG[1], B. LEE[1], J.-Y. KOH[2], S. SUH[1];
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Abstract: Since the subgranular zone (SGZ) of the dentate gyrus (DG) is the most active neurogenic region and also the site where synaptic zinc is most highly concentrated in the mossy fiber terminals, we sought to explore the hypothesis that vesicular zinc is an important modulator for hippocampal neurogenesis. Our previous studies have demonstrated that chemical zinc chelation or dietary zinc deprivation both lead to reduced progenitor cell proliferation and impaired hippocampal neurogenesis. Both effects are reversed by zinc supplementation. To establish the role of zinc transporter 3 (*ZnT3*), a transporter of zinc ions from the cytoplasm into synaptic vesicles, in adult hippocampal neurogenesis, a genetic loss-of-function approach was employed using *ZnT3*$^{-/-}$ mice. Here we report that genetic deletion of *ZnT3* not only reduced progenitor cell proliferation and neuroblast production but also reduced neuronal maturation of newborn cells that survive in the DG. Furthermore, the present study also investigated the effects of zinc ($ZnCl_2$, 4 mg/kg), n-acetyl cysteine (NAC, 20 mg/kg) or $ZnCl_2$ plus 2NAC (ZN) supplement on hippocampal neurogenesis. Interestingly, compared to $ZnCl_2$ or NAC, administration of ZN was most effective in enhancing progenitor cell proliferation and neuroblast production. In addition, ZN supplementation reversed the *ZnT3* loss-associated reduction of neurogenesis via ERK and CREB activation. Therefore, the present study demonstrates for the first time that *ZnT3* and vesicular zinc are essential for adult hippocampal neurogenesis.

Disclosures: **B. Choi:** None. **D. Hong:** None. **J. Jeong:** None. **B. Lee:** None. **J. Koh:** None. **S. Suh:** None.

Poster

730. Postnatal Neurogenesis: Environmental and Pharmacological Regulation

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 730.03/A16

Topic: A.02. Postnatal Neurogenesis

Support: York College of Pennsylvania: Summer Research Grant

Title: Operant conditioning prevents the death of cells generated in the dentate gyrus of the adult rat

Authors: C. HUGGINS, *D. M. CURLIK, II;
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Abstract: Thousands of new neurons are produced each day in the dentate gyrus of the adult mammalian hippocampus. However, the majority of those cells die within weeks of their birth. The most effective way to prevent this cell death is through effortful and successful learning. Myriad studies have revealed that classical conditioning and spatial learning can prevent this cell death. However, little research has examined whether acquisition of an operant conditioning task with an appetitive reward also increases the number of surviving cells. Therefore, the current study was conducted to determine whether conditioning with an operant procedure would prevent the death of adult-born hippocampal cells. Adult male rats were trained with fifty trials of an operant discrimination procedure per day, for four consecutive days. In order to motivate animals to perform the task they were food restricted prior to conditioning, and food pellets were used as an appetitive reward during conditioning. Additional control animals were food restricted but not trained, or not food restricted and not trained. In order to ensure that exposure to food reward pellets did not alter neurogenesis, all animals received equal exposure to the pellets. Stereological analysis conducted approximately two weeks after training revealed that food restriction significantly decreased the number of surviving cells in the dentate gyrus ($p < 0.05$). However, training with the operant task prevented this decrease ($p < 0.05$). Together, these results indicate that food restriction decreased the number of surviving cells in the dentate gyrus, however training with an operant conditioning procedure was sufficient to attenuate that decrease.

Disclosures: **C. Huggins:** None. **D.M. Curlik:** None.

Poster

730. Postnatal Neurogenesis: Environmental and Pharmacological Regulation

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Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 730.04/A17

Topic: A.02. Postnatal Neurogenesis

Support: AA020024
AA020023
AA011605
AA019767
AA025713

Title: Galantamine prevents and reverses adolescent alcohol-induced deficits in hippocampal neurogenesis

Authors: *V. A. MACHT, R. P. VETRENO, F. T. CREWS;
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Abstract: Adolescent intermittent ethanol (AIE) exposure causes protracted reductions of hippocampal neurogenesis in adult rats. Previous studies have found AIE-induced reductions in neurogenesis are prevented by exercise, the non-steroidal anti-inflammatory drug indomethacin, and the HDAC inhibitor TSA, supporting the hypothesis that neurogenesis is reduced through long-lasting changes in proinflammatory/trophic gene expression in the hippocampal neurogenic niche. The current study expands on this hypothesis by testing whether the cholinesterase inhibitor galantamine (GAL), which has anti-inflammatory properties, can prevent and/or reverse decreases in hippocampal neurogenesis following AIE. In this study, we used a preclinical AIE model (5.0 g/kg/day i.g., 2-days on/2-days off from postnatal day [PND] 25-55) in male rats alone or combined with GAL. GAL (4.0mg/kg/day, i.p.) exposure was either 30 minutes before ethanol exposure (prevention) or daily following the cessation of AIE (reversal). On approximately PND 70, rats were euthanized and their brains were prepped for immunohistochemical staining for the neurogenesis marker doublecortin (DCX), the apoptotic marker cleaved caspase 3 (CC3), and the cell proliferation marker Ki-67. AIE reduced DCX+immunoreactivity (IR) by 37% and increased CC3+IR by 50% (p's < 0.05). GAL both prevented and reversed the AIE-induced reduction of DCX+IR (p's < 0.05). There was a main effect of GAL to increase Ki-67+IR by 56% (p < 0.05) indicating increased cell proliferation may contribute to restoration of AIE-induced reductions in hippocampal neurogenesis. Future studies will continue to probe mechanisms regulating AIE impaired neurogenesis. Supported by the Neurobiology of Adolescent Binge Drinking in Adulthood (NADIA) consortium of the NIAAA.

Disclosures: V.A. Macht: None. **R.P. Vetreno:** None. **F.T. Crews:** None.

Poster

730. Postnatal Neurogenesis: Environmental and Pharmacological Regulation

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Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 730.05/A18

Topic: A.02. Postnatal Neurogenesis

Support: NIH R21 Grant NS104293

Title: Electrically stimulated hind-limb muscle contractions increase adult hippocampal neurogenesis in anesthetized mice

Authors: *J. C. GARDNER[1], S. DVORETSKIY[2], Y.-Y. YANG[1], D. A. LANGE[1], S. VENKATARAMAN[1], A. KATWALA[3], C. RENDEIRO[4], M. D. BOPPART[2], J. S. RHODES[1]; [1]Dept. of Psychology, [2]Dept. of Kinesiology and Community Hlth., [3]Dept. of Chem. and Biomolecular Engin., Univ. of Illinois at Urbana-Champaign, Urbana, IL; [4]Sch. of Sport, Exercise & Rehabil. Sci., Univ. of Birmingham, Birmingham, United Kingdom

Abstract: Regular exercise is crucial for maintaining cognitive health throughout life. Many exercise-induced neurological adaptations have been identified, particularly in the hippocampus, including increased numbers of new neurons in the dentate gyrus (DG). However, how exercise enhances hippocampal neurogenesis whether through factors released from contracting muscles that travel to the brain via the blood, or in response to acute activation of the DG from the physical exertion remains a mystery. The goal of this study was to test the hypothesis that muscle contractions alone, in absence of DG activation, are sufficient to increase adult hippocampal neurogenesis. Adult male, C57BL/6J mice were anesthetized, and exposed to bilateral hind-limb muscle contractions (both concentric and eccentric) via electrical stimulation (e-stim) of the sciatic nerve twice a week for 8 wk. Another group was treated similarly except without e-stim (sham control; n=16/group). BrdU was injected during the first 4 weeks to measure survival of new neurons in the DG at 8 wk. A follow-up experiment explored acute effects of e-stim on neuronal activation of DG. A group experienced one session of e-stim or sham treatment (n=8/group) and then was euthanized 90 min later to measure numbers of c-Fos-positive cells in DG. The chronic e-stim produced muscle adaptations including decreased fatigue and increased capillary density. Relative to sham control, the e-stim increased total number of BrdU cells in the DG by 26% and total volume by 10%. The sham and e-stim group displayed similar numbers of c-Fos positive cells. Results demonstrate that muscle contractions alone are sufficient to increase adult hippocampal neurogenesis, in absence of activation of DG, and while the animal is anesthetized. We speculate that specific chemical signals are released from the contracting muscles which pass into the brain from the blood to exert their influence on the brain.

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Poster

730. Postnatal Neurogenesis: Environmental and Pharmacological Regulation

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Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 730.06/A19

Topic: A.02. Postnatal Neurogenesis

Support: Fulbright Scholarship
NYSTEM Einstein Training Grant

Title: Effects of environmental enrichment on hippocampal circuitry and function

Authors: *M. FRECHOU, K. MCDERMOTT, E. WOOD, R. FERGER, J. GONÇALVES; Neurosci., Albert Einstein Col. of Med., Bronx, NY

Abstract: Exposure to enriched environments (EE) improves performance in behavioral tasks that depend on the hippocampus, such as spatial memory and context discrimination. It also increases the number of newborn neurons added to the hippocampal dentate gyrus (DG) in the adult brain, which is thought to partly mediate its cognitive benefits. Conversely, decreasing adult neurogenesis results in cognitive deficits. Changes in connectivity patterns have been observed in the adult-born neurons (ABNs) of mice exposed to EE compared to mice housed in standard conditions. But overall, it is still unknown how the circuit properties of the DG change in EE, and which mechanisms underlie these changes. We hypothesize that exposure to behavioral experience during adult neuronal development results in changes in the functional patterns of ABN, resulting in altered spatial encoding and local network activity in the DG. To evaluate this, we use in vivo two-photon calcium imaging in head-fixed mice on a self-propelled treadmill to record the activity and spatial tuning of DG neurons, in mice exposed to EE compared to standard housing controls. Our goal is to parse out the effects of EE-dependent changes on the hippocampus and the contribution of ABNs to the observed effects. Understanding these changes and their underlying mechanisms will provide a novel framework for understanding how behavioral manipulations can have long-lasting effects on cognitive function.

Disclosures: **M. Frechou:** None. **K. McDermott:** None. **E. Wood:** None. **R. Ferger:** None. **J. Gonçalves:** None.

Poster

730. Postnatal Neurogenesis: Environmental and Pharmacological Regulation

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Program #/Poster #: 730.07/A20

Topic: A.02. Postnatal Neurogenesis

Support: NIH IRP ZIAMH002784

Title: The effects of anesthesia on adult hippocampal neurogenesis in adult rats

Authors: J. L. KIM, N. E. BULTHUIS, *H. A. CAMERON;
Section on Neuroplasticity, NIMH/NIH, Bethesda, MD

Abstract: Following anesthesia and surgery, some patients show symptoms of cognitive dysfunction that can last months after their procedure. While it is still debated whether these cognitive deficits result from anesthesia or other aspects of surgery, studies have recently shown that prolonged sedation of rats with isoflurane or propofol impair performance on memory tasks, like the radial arm maze and fear conditioning, days or even weeks later. One proposed mechanism by which anesthesia may alter memory is by decreasing hippocampal adult neurogenesis. Although several studies have seen a reduction in cell survival after anesthesia in rodents, most studies have focused on vulnerable populations, like neonates and aged rodents. Currently, it's still unclear to what extent sedation affects neurogenesis in young adults. We therefore examined the effects of sedation on proliferation and survival of new neurons in the adult dentate gyrus. In addition to isoflurane and propofol, we included two sedatives commonly used for moderate sedation, midazolam and dexmedetomidine. Because few studies has examined the effects of sedation on neurogenesis in females, we compared male and female rats. All animals were sedated for 4 hours and sacrificed 24 hours later. Control rats of both sexes remained in their home cages until time of sacrifice. Three different cell populations were analyzed: the permanent, distinguishable birthdate markers EdU and BrdU were administered one week and one month prior to anesthesia, respectively, to identify immature and mature neurons, while PCNA was used to identify dividing precursor cells and assess cell proliferation at time of sacrifice. None of the drugs altered cell proliferation or the number of immature neurons in the DG in either sex, and most had no effect on mature neurons. However, female rats treated with propofol (M=368.1, SE=50.1) had fewer BrdU+ cells than propofol males (M=608.5, SE=37.0) and control female (M=550.4, SE=34.5) and male (M=611.7,SE=37.0) rats (p<0.05). These findings suggest that there is no general effect of sedation on new neurons in the dentate gyrus but that propofol reduces adult neurogenesis, with greater effects in females than males. Future studies will include behavior to determine whether propofol-induced changes in neurogenesis have cognitive effects. Taken together, these studies will help elucidate possible

mechanisms by which sedation may alter ongoing production of new neurons to impair cognitive functions.

Disclosures: **J.L. Kim:** None. **N.E. Bulthuis:** None. **H.A. Cameron:** None.

Poster

730. Postnatal Neurogenesis: Environmental and Pharmacological Regulation

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Program #/Poster #: 730.08/A21

Topic: A.02. Postnatal Neurogenesis

Support: SNI 3491
CONACYT

Title: Chronic hypercaloric diet modifies the hippocampal neurogenesis and behavior in the adult rat

Authors: *V. VARGAS, C. VIVAR, I. JIMÉNEZ-ESTRADA;
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Abstract: Obesity is a public health problem around the world. Studies in humans and animal models suggest that high-calorie diets have negative effects on brain physiology, particularly in the hippocampus. This brain area is important for learning and memory, and it is one of the few regions of the brain where neurogenesis continues during postnatal life. The hippocampus and adult neurogenesis are susceptible to nutritional changes in early and later stages of development. However, the effect of chronic exposure, from perinatal to adulthood, to a high-calorie diet has not been evaluated. Here we evaluated the effects of chronic high-calorie diet on adult neurogenesis and hippocampus-mediated learning and memory. Adult female Wistar rats were fed either with a normal diet (standard chow diet, (3.8 Cal/g) or a high-calorie diet (5 Cal/g) before mating, throughout pregnancy and lactation. After weaning, all offspring male were fed under the same maternal diet until the end of the experimental procedure. At 23-weeks-old, the cognitive function of offspring rats was evaluated using hippocampus-dependent behavioral tasks. Additionally, in a separate group, adult neurogenesis was also evaluated using 5-bromo-2-deoxyuridine (BrdU; 50mg/kg, ip). Results showed that the chronic high-calorie diet increased energy intake, body weight gain, perivisceral adipose tissue, and modified the glycemic regulation compared to the control group. Quantification of BrdU-NeuN double-labeled cells showed that the chronic high-calorie diet significantly decreased the number of adult-born hippocampal neurons, which correlated with the impairment in spatial learning and memory in the Barnes maze task. Altogether suggests that the effects of chronic high-calorie diet, from the maternal environment to adulthood, induces a dysfunction in both hippocampal neurogenesis and learning and memory processes.

Disclosures: **V. Vargas:** None. **C. Vivar:** None. **I. Jiménez-Estrada:** None.

Poster

730. Postnatal Neurogenesis: Environmental and Pharmacological Regulation

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 730.09/A22

Topic: A.02. Postnatal Neurogenesis

Title: Functional recovery by enriched environment in neonatal white matter injury: Evidence from morphological and electrophysiological assessments

Authors: A. HATTORI, *N. TAJIRI, Y. UEDA, A. ISHIDA, T. SHIMIZU, H. HIDA;
Dept. of Neurophysiol. & Brain Sci., Nagoya City Univ., Nagoya-city, Aichi, Japan

Abstract: Hypoxia-ischemia (H-I) in preterm infants occasionally results in neonatal white matter injury (NWMI) associated with neurodevelopmental disabilities such as paralysis and cognitive dysfunction. Enriched environment (EE) that contains increased motor activity, social interaction and exploration is known as a good method to improve disturbed motor function. To investigate whether EE during the period of development effects on the recovery of disturbed motor function in NWMI, rat model of NWMI made by H-I at postnatal day 3 (P3) was grown in either condition of EE or standard environment (SE) for 5 weeks from P25 to P70. Four tests of hindlimb retraction, beam walk ability, horizontal ladder, and rotarod were performed at P25, P35, and P70, and immunohistochemical assessments and electrophysiological investigations were then carried out at P70. NWMI model exhibited significant deficits of four tests compared with sham-operated control at P25. EE for 5 weeks resulted in significant improvements of the behavior except for rotarod in NWMI at P70. However, NWMI-SE group did not show any improvements. The effects on EE was shown as early as P35 in NMMI. Although the sensorimotor cortex is thinner in the ipsilateral side of NWMI at P70, EE caused in the recovery of cortical thickness that is comparable to the opposite side and sham-control. To know if cortical motor map and electrical responsiveness in the sensorimotor cortex of the NWMI are changed by EE, intracoritical microstimulation was performed at P70. Although significant differences of the cortical maps and the responsiveness were detected in the NWMI, EE also caused in significant recovery of the cortical maps and the thresholds of the hip joint and hindlimb. These data suggest that EE during the period of development has significant effects on disturbed motor function in NWMI, accompanied with significant changes of the cortical motor map and the responsiveness in the sensorimotor cortex.

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Poster

730. Postnatal Neurogenesis: Environmental and Pharmacological Regulation

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 730.10/A23

Topic: A.02. Postnatal Neurogenesis

Title: The effect of environmental enrichment on hippocampal neuroplasticity-related genes in Hatano rats

Authors: *H. ASANO[1], H. OKAWA[1], A. NAKAYAMA[1], H. TOKUOKA[1], W. KASAI[1], R. OTA[2], M. KAWAGUCHI[1];
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Abstract: Low neuroplasticity in the hippocampus can be a factor in neuropsychiatric disorders, such as Alzheimer's disease, depression and anxiety disorder. It may be possible to treat these disorders by improving neuroplasticity, but first it is necessary to examine neuroplasticity-related genes and identify possible improvement factors. Environmental enrichment can improve neuroplasticity in rats' hippocampus, for example by introducing a running wheel, novel object, or a combination of these. Hatano low avoidance (LAA) and high avoidance (HAA) rats are inbred strains selected from Sprague-Dawley (SD) rats by active avoidance test. Studies have shown that environmental enrichment decreased anxiety-like behavior in LAA rats but not in HAA rats. Moreover, HAA have a smaller hippocampus than LAA, which suggests that there may be different neuroplasticity activity HAA and LAA rats. Therefore, investigating the relationship between environmental enrichment and neuroplasticity in the hippocampus of HAA and LAA Hatano rats could shed light on the treatment of neuropsychiatric disorders. Here, we investigated the effect of environmental enrichment on neuroplasticity-related genes in Hatano rats. At 4 weeks of age, the animals were introduced into either a standard environment cage (200×410×250mm) or a larger environmentally enriched cage (440×660×398mm) that contains a running wheel (350×170×370mm), a plastic tunnel (Φ77, length 163mm) and a wood house (200×170×300mm). Hippocampus were sampled at 15 weeks of age and the gene expressions levels of Brain-derived neurotrophic factor (Bdnf) exon9 and Wingless-type MMTV integration site family member 3a (Wnt3a) gene expression levels were measured by RT-qPCR. There was no significant difference in Wnt3a mRNA. Bdnf exon9 mRNA showed significantly higher gene expression in LAA than in SD and HAA, and only in SD showed significantly higher gene expression levels in environmental enrichment than in standard. These results suggest that the effects of environmental enrichment on neuroplasticity-related gene expression may affected by strain. Moreover, Bdnf forms eight mRNAs, so it is still possible that there could be differences in the expression levels in other exons and BDNF protein.

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Poster

730. Postnatal Neurogenesis: Environmental and Pharmacological Regulation

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Topic: A.02. Postnatal Neurogenesis

Support: NSERC
CFI

Title: Effect of voluntary running on aberrant seizure-induced neurogenesis and cognitive deficits associated with chronic pentylenetetrazole kindling in rats

Authors: K. POST, M. GILCHRIST, L. BRANDT, C. COLE, H. LEHMANN, *N. M. FOURNIER;
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Abstract: Chronic epileptic seizures are well known to increase levels of hippocampal neurogenesis. As these new neurons develop, they integrate abnormally within existing networks forming synaptic connections that enhance hippocampal excitability and contribute to cognitive dysfunction. Physical exercise is a robust stimulator of neurogenesis in rats and increases performance on behavioural tasks that require normal hippocampal function. It is also well known exercise can produce neuroprotective effects against seizures. In this study, we set out to investigate whether voluntary running could reduce aberrant hippocampus neurogenesis and cognitive deficits associated with repeated seizures induced by pentylenetetrazole (PTZ) kindling. Long-Evans male rats were individually housed in cages equipped with or without a running wheel for the entire duration of the study. Following a short habituation period, rats were repeatedly administered saline or the chemoconvulsant PTZ every two days for 24 days. After kindling, rats underwent a series of tests that measure cognitive and affective behaviours (e.g., open field test, elevated plus maze, forced swim test, object recognition, object location, context fear and trace fear learning). Our preliminary findings showed that both non-kindled controls and PTZ runners performed significantly better then the PTZ non-runners on trace fear learning and object location memory. Interestingly, PTZ runners also showed greater exploratory activity in the elevated plus maze and would venture further into the distal end of the open arms then non-kindled controls and PTZ non-runners. Finally, while PTZ kindled seizures increased doublecortin-positive immature neurons in the dentate gyrus of both runner and non-runner groups, running appeared to reduce the number of ectopic hilar cells and promoted greater dendritic growth and complexity in newborn neurons located in the granule cell layer. Together,

these findings provide evidence that physical exercise can improve cognitive outcome and reduce aberrant hippocampal neurogenesis that accompany repeated seizures.

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Poster

730. Postnatal Neurogenesis: Environmental and Pharmacological Regulation

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Program #/Poster #: 730.12/A25

Topic: A.02. Postnatal Neurogenesis

Support: NASA Grant 80NSSC17K0060
NIH Grant 5R37HD059288-15

Title: Mild traumatic brain injury in the mouse induces a transient increase in neurogenesis and sustained survival of newborn neurons

Authors: *L. R. CLARK[1,2], P. L. KUMAR[1,2], N. K. ACQUAH[1,2], R. C. COSTA PAIXAO[1,2], S. YUN[1,2], H. METHENY[1], A. S. COHEN[1,2], A. J. EISCH[1,2];
[1]Children's Hosp. of Philadelphia, Philadelphia, PA; [2]Univ. of Pennsylvania, Philadelphia, PA

Abstract: The majority of the 2.8 million traumatic brain injuries (TBIs) that occur annually in the US are classified as mild. Mild TBIs (mTBIs) can induce long-lasting impairment in memory and attention. Contextual memory is disrupted after mTBI, and is critically dependent on adult dentate gyrus neurogenesis. There are conflicting results about how TBI affects neurogenesis, with very little work examining the impact of a mild injury. We asked the question, how does a mouse model of mTBI influence the dynamic process of adult hippocampal neurogenesis? Male C57BL/6J mice (6-8 weeks) received either sham surgery or mTBI via lateral fluid percussion injury (LFPI), and dentate gyrus neurogenesis was measured via stereology at early (3 days post-injury, dpi), intermediate (7 dpi), and late (31 dpi) time points. Mice received a single injection of BrdU (150mg/kg i.p.) 3 dpi to label proliferating cells. Brains from each time point were assessed with markers for DG neurogenesis and reactive glia: proliferation [Ki67+, BrdU+ (2hr post-BrdU)], differentiation (DCX+), survival [BrdU+(4 wks post-BrdU)] and microglia (Iba1+). Additionally, GCL volume was assessed in brains from the early and late time points. At the early time point, GCL volume was not different between Sham and LFPI mice. LFPI mice had ~50% more Ki67+ SGZ cells relative to Sham mice, and the same number of DCX+ SGZ/GCL cells as Sham mice. In contrast, at the intermediate time point, LFPI mice had ~30% more DCX+ SGZ/GCL cells than Sham mice, but the same number of Ki67+ and BrdU+ cells. At the late time point, Ki67+ and DCX+ cell numbers were the same between LFPI and Sham mice, but LFPI mice had ~70% more BrdU+ SGZ cells than Sham mice. GCL volume was also not

different between Sham and LFPI mice at the late time point. These data suggest a transient increase in proliferation of neural precursor cells shortly after LFPI, which may relate to the subsequent transient increase in immature neurons and to a bolus of adult-born granule cell neurons that persist 1 month post-injury. Ongoing work is testing this hypothesis with additional immunohistochemical analyses (phenotyping of BrdU+ cells at intermediate and late time points; DCX+ cell morphological analyses), and exploring how these cells influence hippocampal anatomy and function on both the circuit and behavioral level.

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Poster

730. Postnatal Neurogenesis: Environmental and Pharmacological Regulation

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Program #/Poster #: 730.13/A26

Topic: A.02. Postnatal Neurogenesis

Title: Neuroanatomical correlates of socioeconomic status in infancy

Authors: L. M. BETANCOURT[1], H. HURT[1], T. NICHOLS[2], O. ELCI[1], B. AVANTS[2], ***M. J. FARAH**[3];
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Abstract: Socioeconomic status (SES) has long been associated with differences in mental health and cognitive ability. Understanding these differences is an important goal for public health and social equity. Given the brain's central position in causal pathways linking genes and experience to psychological outcomes, the neuroanatomical correlates of SES have become the subject of active study. Most such research focuses on people of school age and older. Our 2015 study analyzed brain structure in a group of 47 1-month-old healthy African American baby girls, whose family SES ranged from very low (sub-poverty line) to middle class (Betancourt et al., Developmental Science). We found cortical grey and white matter volume to correlate positively with SES, measured as a composite of family income-to-needs ratio and maternal educational attainment. Here we report the results of follow-up imaging, accomplished at least once at ages 1 and/or 2 years, using mixed model analyses to answer two questions: (1) Does the influence of SES grow, shrink or stay the same over the first two years of life? (2) Does brain volume differ globally or are differences regionally localized? Mixed model analysis, with variables SES, age and age^2 found significant effects of all three: higher SES brains had larger volumes, older brains had larger volumes, and the effect of age was nonlinear, with less growth in the second year. Regarding (1), the influence of SES neither grew nor shrank as tested by adding interactions SESxage and SESxage^2 to the model. (Interpretation is qualified by the low

power for testing interaction effects in this sample, and the possibility that rate of brain growth may differ across SES, such that 1 year and 2 year scans may assess volumes at different points in the developmental trajectory.) Regarding (2), SES predicted frontal and temporal lobe volumes. It also predicted overall white matter volume and cortical grey matter volume, with a borderline significant effect on parietal volume and no significant effect on occipital lobe volume or deep grey matter volume. Given SES differences in prenatal environment, and known effects of stress and toxins on fetal development, prenatal processes may be responsible for early SES brain differences.

Disclosures: L.M. Betancourt: None. **H. Hurt:** None. **T. Nichols:** None. **O. Elci:** None. **B. Avants:** None. **M.J. Farah:** None.

Poster

730. Postnatal Neurogenesis: Environmental and Pharmacological Regulation

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 730.14/A27

Topic: A.02. Postnatal Neurogenesis

Support: NIMH Grant MH104198

Title: Early-life iron deficiency anemia is associated with alterations in microbiome maturation and reduction of cortical volume in infant rhesus monkeys

Authors: *D. N. RENDINA[1], G. R. LUBACH[1], R. M. VLASOVA[2], M. LYTE[3], G. PHILLIPS[3], M. A. STYNER[2], C. L. COE[1];
[1]Harlow Ctr. for Biol. Psychology, Univ. of Wisconsin, Madison, WI; [2]Departments of Psychiatry and Computer Sci., Univ. of North Carolina at Chapel Hill, Chapel Hill, NC; [3]Dept. of Vet. Microbiology and Vet. Med., Iowa State Univ., Ames, IA

Abstract: Iron-deficiency anemia (ID) is the most common micronutrient deficiency, and young infants are especially vulnerable to negative neurodevelopmental, cognitive, and metabolic outcomes that can persist beyond infancy. While iron availability is known to dynamically modulate the intestinal microbiota, the extent to which host iron status influences microbial colonization, and the neurobehavioral consequences of the resulting dysbiosis, are not known. **Methods**: Twenty-nine infant rhesus monkeys (*Macaca mulatta*) were evaluated at 2-month intervals for the first year of life, and 12 naturally became iron deficient around the time of weaning (6-8 months of age). Blood was collected for hematology and iron indices, and fecal microbial community structure and diversity were determined by gene amplicon sequencing and taxonomic classification of the V4 region of the bacterial 16S rRNA gene. Mother-infant interactions were observed between 2-4 months to evaluate infant behavioral maturation. At 12 months, magnetic resonance imaging data were obtained on a 3T scanner. Gray matter (GM) and

white matter (WM) volumes were determined for major cortical regions using an automatic segmentation and parcellation pipeline, and volumes of several subcortical structures were evaluated. **Results:** The microbial colonization of the infant gut was distinct in ID infants with respect to bacterial phylogeny and abundance (p=0.044) and was characterized by decreased evenness (p=0.06), suggesting delayed microbiome maturation. In contrast to iron sufficient infants, the overall community structure in ID infants was stable between 4-6 months of age. However, the genera *Megasphaera* was consistently enriched in ID infants and its relative abundance at 4 and 6 months of age was predictive of low hemoglobin at 6-months. Despite subsequent iron treatment, the infants that were ID at 6 months of age had diminished total brain volumes (TBV) at one year. This impact on brain growth was most apparent in bilateral reductions in basal ganglia and amygdala volumes and decreased GM in the prefrontal cortex. ID infants also exhibited more motor activity and fewer behavioral interactions with the mothers during observations at 4 months of age. **Conclusion:** Differences in the gut microbiome preceded and were coincidental with infantile anemia, and associated with smaller brain volumes at one year of age. These findings highlight the importance of iron biology for understanding host-microbe interactions and indicate that ID during infancy can have enduring neurodevelopmental effects that were evident in spite of the administration of iron when anemia was detected.

Disclosures: D.N. Rendina: None. **G.R. Lubach:** None. **R.M. Vlasova:** None. **M. Lyte:** None. **G. Phillips:** None. **M.A. Styner:** None. **C.L. Coe:** None.

Poster

730. Postnatal Neurogenesis: Environmental and Pharmacological Regulation

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 730.15/A28

Topic: A.02. Postnatal Neurogenesis

Support: NSF Grant 1553667

Title: Changes in cultured adult neural stem cell physiology following sublethal exposure to silver nanoparticles

Authors: D. W. KIPPS, K.-C. K. PATTERSON, *N. SPITZER;
Dept. of Biol. Sci., Marshall Univ., Huntington, WV

Abstract: Silver nanoparticles (AgNPs) are an environmental contaminant of emerging concern due to their widespread use in the production of consumer goods including toothpaste, socks, and cosmetics. AgNPs released from these items could potentially be ingested or inhaled, crossing biological barriers due to their unique surface properties. Animal studies indicate that oral exposure to AgNPs leads to bioaccumulation in tissues including the brain. Although the efficacy

of AgNPs as antimicrobials and biosensors is well documented, their effects on mammalian cells at environmentally relevant low levels are unclear. We previously found that low-level (1μg/mL) AgNPs disrupt cytoskeletal function, leading to formation of f-actin inclusions and disrupting neurite dynamics in cultured adult neural stem cells. In addition, AgNPs disrupt β-catenin intracellular signaling mechanisms in these cells. Here, we investigated interactions of AgNPs with two other intracellular signaling pathways, MAPK/ERK and Akt, both of which are involved in regulation of neuronal cell differentiation. We exposed differentiating cells to AgNPs in combination with specific pharmacological agents to activate or inhibit the pathways, and then assessed cytoskeletal dysfunction. Neurite dynamics were examined with time-lapse microscopy where we found that the inhibition of Akt and MAPK/ERK stimulated neurite extension. However, pharmacological inhibition of these pathways was not able to rescue the neurite collapse resulting from low-level AgNPs exposure. Inhibition of MAPK/ERK signaling leads to an increase in f-actin inclusion formation that may be additive with AgNP-induced inclusions, while inhibition of Akt did not alter inclusion formation. Pharmacological activation of MAPK/ERK in combination with AgNPs indicated a more complex interaction of mechanisms regarding f-actin disruption. This was supported by immunoblot assessment of signal protein phosphorylation after AgNP exposure. These data suggest a more indirect or downstream connection between Akt or MAPK/ERK pathways and AgNPs. Finally, we investigated changes in electrical properties of cultured adult neural stem cells after exposure to sublethal AgNPs, measured by whole cell patch clamp electrophysiology. This work will help us to understand chronic effects of low-level AgNP exposure from consumer goods on brain cell function. Our work in neural stem cells is especially applicable to children, whose brains are still developing, and therefore depend significantly on neural stem cell function.

Disclosures: **D.W. Kipps:** None. **K.K. Patterson:** None. **N. Spitzer:** None.

Poster

730. Postnatal Neurogenesis: Environmental and Pharmacological Regulation

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 730.16/A29

Topic: A.02. Postnatal Neurogenesis

Support: NIH Grant MH117459-01
NIH Grant T32MH065214
National Science Foundation Graduate Research Fellowship under Grant No. DGE-1656466
C.V. Starr Fellowship Award (Sahana Murthy)

Title: Examining running-induced structural plasticity in the ventral hippocampus in relation to cognitive enhancement and anxiety regulation

Authors: *E. A. TAWA, B. A. BRIONES, E. C. COPE, E. J. DIETHORN, S. MURTHY, E. GOULD;
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Abstract: Previous findings of cognitive enhancement and anxiolysis after long term aerobic exercise raise the possibility that the neural mechanisms supporting exercise-induced cognitive improvement also operate in brain circuits involved in anxiety regulation. Because the rodent ventral hippocampus (vHIP) is important for anxiety regulation and has recently been found to contribute to some types of learning and memory, it is a likely candidate region for mediating these effects. Previous studies have shown that running stimulates widespread structural plasticity throughout the hippocampus, including the formation of large numbers of new neurons; however, it remains unresolved whether running-induced structural plasticity in the vHIP promotes cognition and dampens anxiety. Furthermore, a large number of parvalbumin-expressing (PV+) cells in the hippocampus are enwrapped in specialized extracellular matrix (ECM) structures, called perineuronal nets (PNNs), which are known to regulate plasticity. While there is some suggestive evidence that PNN formation can be affected by experience, no studies have investigated whether new neurons generated during running form microcircuits with PNN+ PV+ cells, thus inducing reduced anxiety/enhanced cognition states. Here, we study the potential roles of new neurons and PNNs in the optimizing effects of physical activity on anxiety and cognition in adolescent mice. By testing both males and females, we explore previously unaddressed questions regarding plasticity mechanisms underlying brain optimization during the transition into adulthood, when hormone levels are changing and sex differences may emerge. We replicated the anxiolytic effects of running in male mice on both the elevated plus maze and novelty suppressed feeding tasks, and also found a higher discrimination ratio on the object location test, suggesting cognitive improvement. We have also found anxiety reduction and cognitive improvement on the aforementioned tasks in group-housed mice using a vertical wheel in a larger home cage, compared to pair-housed mice using a disc wheel in a smaller home cage. These findings implicate that the home cage environment and running set-up play important roles in assessing behavioral differences. The relationship of these behavioral changes to alterations in new neurons, inhibitory interneurons, and PNNs is under investigation.

Disclosures: E.A. Tawa: None. **B.A. Briones:** None. **E.C. Cope:** None. **E.J. Diethorn:** None. **S. Murthy:** None. **E. Gould:** None.

Poster

730. Postnatal Neurogenesis: Environmental and Pharmacological Regulation

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 730.17/A30

Topic: A.02. Postnatal Neurogenesis

Support: NIMH R01 MH111604

Title: Sex-specific effects of early life stress on hippocampal neurogenesis in the pig

Authors: *K. DURGA[1], N. DUQUE-WILCKENS[2], A. MOESER[1], A. ROBISON[1];
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Abstract: Depression is a leading cause of disability worldwide, yet available treatments are ineffective for nearly half of treated patients. Mood disorders like depression have been linked to early life adversity and are exacerbated by chronic or traumatic stress, so uncovering how stress affects mood-related brain regions is critical to improve our understanding of depression etiology and potentially improving treatment. Depression patients often display reduced hippocampal volume, and many animal models of depression display a reduction in hippocampal neurogenesis that is reversed by chronic exposure to antidepressants like fluoxetine. Using a pig model, we assessed whether exposure to early life adversity affects hippocampal neurogenesis and gene expression. Early weaned (15 days post partum) or late weaned (28 days post partum) female, castrated male, and intact male pigs were euthanized at 20 weeks of age and brain tissue was immediately harvested. We performed immunohistochemistry in the dentate gyrus to detect the protein doublecortin, a marker of differentiating neurons. We found a significant reduction in doublecortin labeled cells in early weaned females compared to the late weaned females in the dentate gyrus, indicating a sex-specific reduction in neurogenesis not dependent on adult circulating testosterone. We also used western blot to detect expression of the *FosB* gene, which controls hippocampal gene expression and is necessary for neurogenesis in mice. We found that early weaned females had an increased level of hippocampal FosB and ΔFosB, while these *FosB* gene products were reduced in the early weaned castrated males. Ongoing studies are assessing FosB and ΔFosB in the prefrontal cortex and the nucleus accumbens, as well as examination of neuroinflammation throughout the brain. Together, these data suggest that early weaning has sex specific effects on hippocampal neurogenesis and gene expression later in life, perhaps driving susceptibility to mood disorders in adulthood.

Disclosures: K. Durga: None. **N. Duque-Wilckens:** None. **A. Moeser:** None. **A. Robison:** None.

Poster

730. Postnatal Neurogenesis: Environmental and Pharmacological Regulation

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 730.18/A31

Topic: A.02. Postnatal Neurogenesis

Support: NIH-NIAAA Grant 1F31AA027127
NIH-NIAAA Grant P50-AA022534

Title: Connectivity of adult-generated dentate granule cells in a mouse model of fetal alcohol spectrum disorder

Authors: *K. C. GUSTUS, L. LI, J. NEWVILLE, L. A. CUNNINGHAM;
Neurosciences, Univ. of New Mexico Sch. of Med., Albuquerque, NM

Abstract: Fetal Alcohol Spectrum Disorders (FASDs) are associated with impaired hippocampal function. Using a limited access voluntary drinking paradigm, we previously demonstrated that prenatal alcohol exposure (PAE) leads to impaired hippocampal neurogenesis in response to enriched environment (EE) in adult mice, which is associated with impaired performance on a neurogenesis-dependent contextual discrimination task, and increased excitatory synaptic input as assessed by patch clamp electrophysiological recordings in adult-generated dentate granule cells (aDGCs) (Choi et al., 2005; Kajimoto et al., 2013, 2016). Here, we test whether these structural, behavioral and electrophysiological parameters are associated with altered dendritic structure using a limited-access drinking-in-the-dark PAE paradigm for gestational alcohol exposure (maternal BEC=80-90mg/dl; Brady et al. 2012). PAE and Sac control Nestin-CreER^{T2}:tdTomato mice were used for sparse labeling of aDGCs by single tamoxifen injection (60mg/kg i.p.) on postnatal day (PD) 48. Mice were randomly assigned to standard housing (SH) or EE for 3 or 6 weeks post-tamoxifen. Confocal image stacks of tdTomato^{+} aDGCs were reconstructed using Imaris^{tm} 3-D software for Sholl analysis of dendritic complexity. Preliminary data (n=4 EE EtOH, 2 EE Sac) shows an interaction of treatment and Sholl intersections ($F_{27, 25} = 2.514$; $p=0.0116$ with increased basal dendrites (60-70μm) in 6 week old aDGCs of EE PAE mice, suggesting sustained increased connectivity of the inner molecular layer (IML). One method to explore this is through monosynaptic afferent connectivity studies. We performed a feasibility study on male C57Bl6 mice (n=7), in which each received stereotaxic injection of retrovirus conferring expression of an avian receptor TVA, rabies glycoprotein (G), and nuclear localized GFP at PD42 and a second injection of EnvA ΔG MCherry rabies with restricted infection to TVA^{+} hippocampal aDGCs at PD77. One week later mice were sacrificed and the distribution/quantification of MCherry^{+} cells relative to dual-labeled aDGCs was determined (hilus=0.9098±0.3617; granule cell layer= 0.3255±0.1451; molecular layer=0.2197±0.08522). The highest ratios are from populations that innervate aDGC proximal regions, making this technique useful for future determination by which EE-mediated dendritic morphology is modified in PAE. These data demonstrate an EE-mediated increase in proximal dendritic complexity of matured aDGCs, and further support subsequent elucidation utilizing the dual vector afferent tracing strategy.

Disclosures: K.C. Gustus: None. **L. Li:** None. **J. Newville:** None. **L.A. Cunningham:** None.

Poster

730. Postnatal Neurogenesis: Environmental and Pharmacological Regulation

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 730.19/A32

Topic: A.02. Postnatal Neurogenesis

Support: NIH R01 NS10742101

Title: Intermittent Hypoxia (IH) increases HIF1a signaling in TBR2+ intermediate progenitors through a reactive oxygen species mechanism

Authors: *C. SZUJEWSKI[1], M. A. KHUU[2], T. NALLAMOTHU[2], A. J. GARCIA, III[3]; [1]Neurobio., [2]Univ. of Chicago, Chicago, IL; [3]Emergency Med., The Univ. of Chicago, Chicago, IL

Abstract: Neurocognitive decline is a frequent consequence of sleep apnea, commonly associated with intermittent hypoxia (IH). Oxygenation is an important factor influencing adult neurogenesis. We have recently shown that IH disrupts this process in the dentate gyrus. Hypoxia inducible factor 1 (HIF1a), is a transcription factor regulated by the state of oxygenation and is important in stem cell development. However, the role of IH-dependent HIF1a signaling in neural stem cell (NSC) development and differentiation is unclear. This study examines how IH-dependent HIF1a signaling affects hippocampal adult neurogenesis. We tested the hypothesis that IH-dependent HIF1a signaling promotes survival of NSCs during IH. Immunohistochemical studies were performed on hippocampal tissue from young adult mice (>P36) exposed to room air (control) or 10 days of IH (IH_{10}). While IH_{10} did not change the number of proliferating NSCs ($KI67^+/SOX2^+$), the number of intermediate progenitors (INPs, $TBR2^+$) was reduced. IH_{10} also decreased the number of $HIF1a^+$ NSCs yet increased the number of $HIF1a^+$ INPs. Antioxidant administration during IH_{10} prevented both the loss of INPs and the upregulation of $HIF1a^+$ in this cell type. These findings suggest that IH-dependent HIF1a signaling does not promote NSC survival yet is upregulated through a reactive oxygen species-dependent mechanism in $TBR2^+$ INPs. Ongoing experiments are investigating the impact of IH-dependent HIF1a signaling INPs.

Disclosures: C. Szujewski: None. **M.A. Khuu:** None. **T. Nallamothu:** None. **A.J. Garcia:** None.

Poster

730. Postnatal Neurogenesis: Environmental and Pharmacological Regulation

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 730.20/A33

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH 5R21MH116681-02

Title: Mid-gestational poly(I: C)-mediated maternal immune activation causes aberrant cortical neurodevelopment in offspring

Authors: *C. P. CANALES[1], M. ESTES[1], K. CICHEWICZ[1], I. ZDILAR[1], E. J. KREUN[1], K. P. ANGARA[3], K. E. PRENDERGAST[1], J. J. ABOUBECHARA[1], K. FARRELLY[1], L. HAAPANEN[2], D. VOGT[3], J. VAN DE WATER[2], A. K. MCALLISTER[1], A. S. NORD[1];
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Abstract: Maternal immune activation (MIA) has emerged as an environmental risk factor for various neurodevelopmental disorders (NDDs), including autism and schizophrenia. Animal models of MIA provide the opportunity to identify the molecular signaling pathways that initiate the disease process and lead to NDD-related neuropathology and behavioral deficits. The preclinical polyinosinic-polycytidylic acid (polyI:C) model has become one of the most widely used approaches in MIA research, however the progression of pathological changes in the fetal brain remain uncharacterized. To identify changes in fetal mouse cortex across a time course following mid-gestational MIA via poly(I:C) injection, we applied transcriptional profiling and neuroanatomical characterization in MIA offspring across embryonic brain development. To reduce variability, we determined the effective dose of poly(I:C) to induce reproducible levels of immune response. Female mice were bred and injected with saline or poly(I:C) at E12.5. Cortices were dissected from E12.5 +6h, E14.5, E17.5 and P0 from MIA and control offspring and processed for RNA-seq, histology, and/or protein analysis. We identified strong transient transcriptional signatures in fetal cortex that included an initial acute signature suggesting activation of stress response pathways in the fetal brain, followed by alterations to proliferation and neuronal differentiation that emerged at E14.5 and peaked at E17.5. MIA-associated transcriptional changes were greatly diminished by birth (P0), though gene expression across several pathways remained elevated. We used immunohistochemistry and Western blot at E17.5 to examine dysregulated genes involved in a range of developmental processes. We validated proliferative populations, altered cortical lamination patterns, precocious astrogenesis and altered maturation on interneuron populations. In summary, the validated transcriptomic maps provide novel insights into the molecular and developmental processes linking MIA pathology and neurodevelopmental sequelae.

Disclosures: **C.P. Canales:** None. **M. Estes:** None. **K. Cichewicz:** None. **I. Zdilar:** None. **E.J. Kreun:** None. **K.P. Angara:** None. **K.E. Prendergast:** None. **J.J. Aboubechara:** None. **K. Farrelly:** None. **L. Haapanen:** None. **D. Vogt:** None. **J. Van De Water:** None. **A.K. McAllister:** None. **A.S. Nord:** None.

Poster

730. Postnatal Neurogenesis: Environmental and Pharmacological Regulation

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 730.21/A34

Topic: A.03. Stem Cells and Reprogramming

Support: NIH Grant EY024984
BrightFocus G201027
Indiana Department of Health 15779
Indiana Department of Health 26343

Title: Modeling glaucomatous neurodegeneration of human pluripotent stem cell-derived retinal ganglion cells

Authors: K. B. VANDERWALL[1], K.-C. HUANG[1], C. M. FLIGOR[1], S. S. LAVEKAR[2], Y. PAN[3], T. R. CUMMINS[4], ***J. S. MEYER**[5];
[1]Biol., IUPUI, Indianapolis, IN; [2]Biol., IUPUI, Indianapolis, MA; [3]Program in Med. Neuroscience, Paul and Carole Stark Neurosciences Res. In, Indiana Univ. Sch. of Med., Indianapolis, IN; [4]Dept Biol. SL306, Indiana University-Purdue Univ. Indianapolis, Indianapolis, IN; [5]Indiana Univ., Indianapolis, IN

Abstract: Human pluripotent stem cells (hPSCs) can serve as powerful tools for the *in vitro* analysis of human neurodegenerative diseases, as well as a platform for pharmacological screening of these diseased cells . Retinal ganglion cells (RGCs) serve as the essential connection between the eye and the brain, with this connection disrupted in blinding disorders such as glaucoma. As such, when derived from patients with inherited forms of the disease, the opportunity exists to study cellular phenotypes associated with glaucomatous neurodegeneration. However, in order to serve in this capacity, differentiated hPSCs must fully recapitulate the features of the affected *in vivo* cell type, including the ability to exhibit mature neuronal characteristics. Thus, efforts of the current study were initially focused upon the functional maturation of hPSC-derived RGCs based upon morphological and functional properties. Subsequently, the ability to derive RGCs from hPSCs was applied to an *in vitro* model of glaucoma using patient-derived cells. Using this system, it was hypothesized that when grown from hPSC-glaucomatous sources, RGCs would exhibit deficits in neuronal complexity and functional deficits, leading to increased apoptosis. hPSC-derived RGCs from healthy control sources demonstrated increased neurite complexity, functionality, and expression of synaptic

proteins over time in culture. These features were significantly enhanced and accelerated when grown in the presence of astrocytes, similar to what is observed in the retina and optic nerve. When grown from glaucomatous sources, hPSC-derived RGCs matured similarly during early stages but at later stages of development, they exhibited significant reductions in their morphology and neurite complexity. These morphological features were associated with an increased level of apoptosis exhibited specifically within the RGC population. Furthermore, RGCs derived from glaucomatous sources were found to be more highly excitable by patch clamp analysis, suggesting a potential role for excitotoxicity in the deficits observed in glaucomatous RGCS. The results of this study are the first of its kind to extensively study the functional and morphological maturation of RGCs *in vitro*, with important implications for the contributions of glial cells to RGC development and maturation. More so, glaucomatous hPSC-derived RGCs exhibited disease deficits, with the opportunity to explore the unknown mechanisms causing RGC death in glaucoma as well as explore areas of therapeutic intervention including pharmacological screening and cell replacement therapies.

Disclosures: K.B. VanderWall: None. **K. Huang:** None. **C.M. Fligor:** None. **S.S. Lavekar:** None. **Y. Pan:** None. **T.R. Cummins:** None. **J.S. Meyer:** None.

Poster

731. Stem Cell Neural Differentiation

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 731.01/A35

Topic: A.03. Stem Cells and Reprogramming

Title: Comparison of human iPSC-derived and rodent forebrain cultures reveals distinctive morphogenesis patterns of human neuronal development

Authors: M. ANDERSON[1], X. LU[1], S. TOUSEY[1], D. GALITZ[1], S. DEGESE[1], J. VAN ETTEN[1], C. HEGER[2], C. HAITJEMA[2], ***K. C. FLYNN**[1];
[1]Bio-Techne, Minneapolis, MN; [2]Protein Simple, San Jose, MN

Abstract: While embryonic rodent pyramidal neurons have been extensively used for modeling neuronal development, interspecies differences, including alterations in developmental timings, mean that not all results are readily recapitulated in human models. There is a pressing need for *in vitro* models to fully capture the mechanisms and molecular pathways specific to human neural development and disorders including cortical gyrification, autism, and schizophrenia. To meet this objective, we describe a protocol for generating low density human iPSC-derived forebrain neurons and compare the development of various morphological features in human versus rodent-derived neurons. Using specific markers for developmental milestones, such as Tau-1 to mark axon formation, in conjunction with high content imaging, we observe that human derived neurons follow a similar pattern of development to rodent neurons, but with a prolonged

time course. We use pharmacological treatments targeting the cytoskeleton to demonstrate that robust molecular mechanisms for neurite growth and polarization are preserved in human and rodent neurons. For example, myosin inhibition using Blebbistatin increased axon outgrowth and arborization in both rodent and in human neurons. Our findings indicate that while robust mechanisms for neuronal development are preserved, human iPSC-derived neurons follow a delayed growth pattern *in vitro* that can be used to explore nuanced mechanisms specific for human brain development.

Disclosures: **M. Anderson:** A. Employment/Salary (full or part-time):; Bio-Techne. **X. Lu:** A. Employment/Salary (full or part-time):; Bio-Techne. **S. Tousey:** A. Employment/Salary (full or part-time):; Bio-Techne. **D. Galitz:** A. Employment/Salary (full or part-time):; Bio-Techne. **S. Degese:** A. Employment/Salary (full or part-time):; Bio-Techne. **J. Van Etten:** A. Employment/Salary (full or part-time):; Bio-Techne. **C. Heger:** A. Employment/Salary (full or part-time):; Bio-Techne. **C. Haitjema:** A. Employment/Salary (full or part-time):; Bio-Techne. **K.C. Flynn:** A. Employment/Salary (full or part-time):; Bio-Techne.

Poster

731. Stem Cell Neural Differentiation

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 731.02/A36

Topic: A.03. Stem Cells and Reprogramming

Support: Regenerative Medicine Minnesota

Title: Medial induction accelerates neuroepithelial conversion of human pluripotent stem cells

Authors: *P. WALSH[1], V. TRUONG[1], J. R. DUTTON[2];
[1]Anatomi Corp, Minneapolis, MN; [2]Univ. of Minnesota, Minneapolis, MN

Abstract: Differentiation of human pluripotent stem cells (hPSCs) into ectoderm provides neurons and glia useful for research, disease modeling, drug discovery, and potential cell therapies. In current protocols, hPSCs are traditionally differentiated into ectoderm after 6 to 10 days *in vitro* when protected from mesendoderm inducers. This protracted timing has made ectoderm a difficult germ layer to access and manipulate, hindering development of efficient differentiation protocols for ectoderm-derived cell types. Here we report efficient and serum-free differentiation of hPSCs into ectoderm within 24 hours using specific pathway modulation. This method is greater than 70% efficient, is broadly applicable to a panel of five independent hPSC lines, and accelerates the emergence of downstream intermediate and terminal neurodevelopmental landmarks. Given its rapid and flexible nature, we expect this method to democratize the development and execution of significantly more efficient protocols for the differentiation of ectoderm-derived cell types from hPSCs.

Disclosures: **P. Walsh:** A. Employment/Salary (full or part-time):; Anatomi Corp. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Anatomi Corp. **V. Truong:** A. Employment/Salary (full or part-time):; Anatomi Corp. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Anatomi Corp. **J.R. Dutton:** None.

Poster

731. Stem Cell Neural Differentiation

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 731.03/A37

Topic: A.03. Stem Cells and Reprogramming

Title: Creation of inducible dCas9-effector iPSC-derived cortical organoids to study human astrocyte development

Authors: *S. N. LANJEWAR, A. T. KING, S. A. SLOAN;
Emory Univ., Atlanta, GA

Abstract: Astrocytes are the most numerous glial population within the central nervous system and play critical roles in neurodevelopment and maintenance of normal brain function. Due to their role as active choreographers of neural circuit formation, their own development, maturation, and function is critical to understand. However, limited access to human tissue at these key developmental stages makes this particularly challenging. Therefore, we utilize two approaches to study human astrocytes: primary astrocytes isolated from fetal and adult human brain tissue and human cortical organoids differentiated from induced pluripotent stem cells (iPSCs). Cortical organoids recapitulate key features of human cortical development, including the development and maturation of human astrocytes, which coexist alongside neurons in a complex 3D cytoarchitecture. An additional advantage of this platform is the ability to use the vast genetic toolset that is available to *in vitro* systems. We are particularly interested in developing new tools to artificially drive specific gene expression changes in human astrocytes to better understand the mechanisms that drive astrocyte development, maturation, and function. To accomplish this goal, we are using nuclease-dead Cas9 (dCas9) tethered to transcriptional activators (CRISPR activation) or inhibitors (CRISPR interference) to specifically modulate gene expression in our system. Our goal is to develop stable iPSC lines that contain tetracycline-inducible dCas9-effector systems with the intent of developing these into human cortical organoids. In the presence of specific guide RNAs, we plan to selectively modulate astrocyte gene expression to ask two fundamental questions: (1) what are the key regulators of astrocyte development, and (2) what are the functional roles of astrocytic genes in neurodevelopmental disorders? Additionally, this approach will allow us to determine how altering gene expression of

neurons and/or astrocytes affects developing neural circuits. Ultimately, these tools will help to study the roles of astrocytes in human brain development and how dysregulation of astrocytes contributes to the pathogenesis of neurodevelopmental disorders.

Disclosures: S.N. Lanjewar: None. **S.A. Sloan:** None. **A.T. King:** None.

Poster

731. Stem Cell Neural Differentiation

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 731.04/A38

Topic: A.03. Stem Cells and Reprogramming

Support: 5 F31 HD095583-02
5 T32 HD083185-02

Title: Neuroepigenetic regulation of the imprinted gene GRB10

Authors: *A. M. JUAN[1], M. BARTOLOMEI[2];
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Abstract: Imprinted genes are a subset of mammalian genes that are exclusively expressed from either the maternal or paternal chromosome. Dysregulation of imprinted gene expression is associated with various human disorders, including the stunted growth disorder Silver-Russell syndrome (**SRS**). This disorder is associated with the abnormal inheritance of two maternal copies or alleles of the imprinted gene Growth Factor Receptor Bound Protein-10 (**GRB10**). Although most somatic cells express *GRB10* exclusively from the maternal allele, alternative promoters on the paternal allele drive *GRB10* expression only in neurons. However, the regulatory elements that coordinate this remarkable epigenetic "switch" of *GRB10* expression in development are unknown. This proposal will test the requirement of (1) allele-specific DNA methylation sequences and (2) zinc-finger protein **CTCF** binding in normal neuronal *GRB10* expression using relevant mouse models and CRISPR-edited neurons. By analyzing these epigenetic elements in a neuronal differentiation system and *in vivo*, we are the first to demonstrate how *GRB10* is epigenetically regulated. These findings will elucidate the mechanisms for allele and tissue-specific gene expression in the brain. Our results may also provide insight into the molecular basis of SRS, which could prompt epigenetic etiology screening and therapeutic options.

Disclosures: A.M. Juan: None. **M. Bartolomei:** None.

Poster

731. Stem Cell Neural Differentiation

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 731.05/A39

Topic: A.03. Stem Cells and Reprogramming

Support: FAPESP - 2018/05006-0
FAPESP - 2015/26206-0

Title: Enhancement of human embryonic stem cells culturing conditions by the formation of spheroids in a three-dimensional microenvironment

Authors: M. VIDIGAL[1], M. C. DECARLI[2], M. H. T. NAGAHARA[2], P. R. G. KEMPE[1], S. KYRYLENKO[3], J. V. L. SILVA[4], A. M. MORAES[2], ***A. L. OLIVEIRA**[1];
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Abstract: Culturing of stem cells in two-dimensional (2D) conditions has become standard and widely used. It allows *in vitro* expansion of multi and pluripotent stem cells for various research and therapeutic purposes. Nevertheless, 2D culturing is considered highly artificial, since native cell physiology and behavior can be significantly altered, affecting many aspects of comparisons to the *in vivo* scenario. Over recent years, we have been studying neuroprotective and immunomodulatory effects of human embryonic stem cells (hESCs) following spinal cord injury by transplanting 2D cultured cells *in vivo*. Brain and glial-derived neurotrophic factors (BDNF and GDNF, respectively) are expressed by hESCs, particularly when engrafted nearby the lesion site, what is interpreted as a mechanism for rescuing axotomized motoneurons. With the perspective of enhancing the neuroprotective potential of cultured hESCs, we cultured cells in a 3D spheroid setup, using a micromolded nonadhesive hydrogel developed by our team. This method standardizes spheroid time frame formation and size. The cells were cultured in three different cell densities under standard conditions (mTeSR™1 feeder-free maintenance medium for human ES, STEMCELL Technologies), and evaluated at days 0, 2, 4 and 7 by phase contrast microscopy. 2D cultures were carried out as comparison counterparts. After seven days of culture, the formed spheroids were fixed in phosphate buffer containing 4% paraformaldehyde and processed for immunocytochemistry using anti-BDNF, GDNF, laminin, MHC I, β2-microglobulin and LILRB2 antibodies. Pluripotency was evaluated by flow cytometry with the BD Stemflow™ Analysis Kit. The results show that all three cell density conditions yielded the formation of spheroids, being those of 300μm in diameter the best, based on size, stability, and cell density. Immunolabeling (7 days of culturing) revealed striking BDNF staining, but not

GDNF, combined with robust laminin expression, which were detected in the extracellular matrix milieu. Undifferentiation state is suggested by the low levels of MHC I and β2-microglobulin, in line with high expression of Stage-specific embryonic antigen-4 (SSEA-4; 2D - 90.6%; 3D - 99.8%), obtained by flow cytometry. LILRB2 upregulation indicates that hESCs express MHC I ligand, what may in turn influence immunomodulatory processes and interaction with immune and glial cells as well as neurons. Overall, the present results indicate that 3D culturing of hESCs allows successful spheroid formation, providing potentially better neuroprotective support than the 2D counterpart when used for regenerative medicine approaches.

Disclosures: M. Vidigal: None. **M.C. Decarli:** None. **M.H.T. Nagahara:** None. **P.R.G. Kempe:** None. **S. Kyrylenko:** None. **J.V.L. Silva:** None. **A.M. Moraes:** None. **A.L. Oliveira:** None.

Poster

731. Stem Cell Neural Differentiation

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 731.06/A40

Topic: A.03. Stem Cells and Reprogramming

Title: Molecular and functional characterization of stem cells-derived neurons in support of drug discovery applications

Authors: *M. IOVINO[1], J. ANTON[1], S. DIJKSTRA[2], S. JAIN[2], J. KAMMONEN[1], V. LAZARI[1], I. WADDELL[1], D. F. FISCHER[3], P. MITCHELL[1];
[1]Charles River, Saffron Walden, United Kingdom; [2]Charles River, Leiden, Netherlands; [3]Discovery, Charles River, Saffron Walden, United Kingdom

Abstract: Central Nervous System (CNS) disorders are widely recognized as major economic, emotional and physical burden to patients, their families and society. Although progress has been made in the basic neuroscience research, there are still several challenges to overcome to find novel therapies and treatments for CNS diseases. One major limitation in current neurological research and drug discovery is the lack of human neuronal disease models which are biological relevant, scalable and reproducible. The advent of induced Pluripotent Stem Cells (iPSCs) technology has offered new opportunities for disease modeling and drug discovery as patient derived iPSCs and their derivatives represent more relevant disease models. Although methods for iPSCs generation have been well established, protocols for a highly consistent and scalable iPSCs neuronal differentiation still need further optimization to produce cost effective and reproducible neuronal cells. Charles River has performed molecular and functional characterization of human cortical, striatal and glutamatergic neurons differentiated from human stem cells using traditional differentiation protocols optimized from literature (Shi et al, Nat Prot

2012; Telezhkin et al., Am J Physiol Cell Physiol., 2016) or the forward reprogramming technology developed by Elpis BioMed (M Pawlowski et al. Stem Cell Rep, 2017) . Preliminary immunocytochemistry and branched DNA data showed expression of pan neuronal markers (betaIIItubulin and MAP2) in Elpis glutamatergic (eNeuron/glut) neurons already after 3 days in culture compared to the 23 days of neurons differentiated with traditional protocols. Moreover functional multi electrode array (MEA) data showed the presence of spontaneous activity in Elpis eNeuron/glut neurons at day 21 of differentiation compared to day 37 and 42 of striatal and cortical neurons. Finally when applying to high trough put (HTS) applications (TR-FRET assay) including cytotoxicity assay (Cell Titer Glo) Elpis eNeuron/glut neurons plated in 384 microplates and treated with tool compounds showed good assay statistic and higher suitability for HTS compared to neurons differentiated with traditional protocols.

Disclosures: **M. Iovino:** None. **J. Anton:** None. **S. Dijkstra:** None. **S. Jain:** None. **J. Kammonen:** None. **V. Lazari:** None. **I. Waddell:** None. **D.F. Fischer:** None. **P. Mitchell:** None.

Poster

731. Stem Cell Neural Differentiation

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 731.07/A41

Topic: A.03. Stem Cells and Reprogramming

Support: CONACYT 272968
INPER 212250-3230-21214-01-16

Title: Cortical neurons from human embryonic stem cells derived and maintained on the human amniotic epithelium

Authors: *D. AVILA-GONZÁLEZ[1], W. PORTILLO[2], A. MOLINA-HERNÁNDEZ[1], G. GARCÍA-LÓPEZ[1], N. F. DÍAZ[1];
[1]Inst. Nacional de Perinatología, Ciudad de México, Mexico; [2]Inst. de Neurobiología, Querétaro, Mexico

Abstract: Human embryonic stem cells (HESC) are derived from the epiblast and have a pluripotent potential (ability to differentiate into all the cell types that conform an organism). However, the conventional culture of HESC using a feeder layer of mouse embryonic fibroblasts (MEF) for their derivation and maintenance has several drawbacks, including the risk of xeno-contamination. Also, it has been suggested that culture of HESC in this standard condition is an artifact and does not correspond to the *in vitro* counterpart of the epiblast during human embryonic development. Besides, our previous studies demonstrated the use of an alternative feeder layer of human amniotic epithelial cells (HAEC) to derive and maintain HESC. In recent

years, different research groups have demonstrated that HAEC are specified from the epiblast prior to implantation, so the culture of HESC on HAEC could represent a different pluripotent stage, being more suitable to recapitulate development early processes, such as neural induction and formation of cortical layers of the forebrain. Here, we differentiated HESC on HAEC or standard conditions (on MEF) to derive cortical neurons. For neural induction, we used a dual SMAD signaling inhibition protocol during 12 days (D12); subsequently, the cells were detached and cultured in N2B27 medium. At the end of the neural induction stage, we found neural rosettes constituted by $SOX2^{+}$/$PAX6^{+}$ and $NESTIN^{+}$ neural stem cells (NSC). From D16 to D30, the first $TUJ1^{+}$ immature and $MAP2^{+}$ mature neurons were detected. Later, the cortical phenotypes of deep layers were identified at D40 using the specific markers CTIP2 and FOXP2; while from D50, $GAD67^{+}$ and $CALRETININ^{+}$ interneurons emerged. Interestingly, there was an increase in all the neural markers evaluated when HESC were induced to form neural lineage under the condition of HAEC as feeder layer, in contrast when were maintained on MEF. These data suggest that HESC maintained on the alternative feeder layer of HAEC are able to derive NSC and differentiate towards neuronal cortical phenotypes.

Disclosures: **D. Avila-González:** None. **W. Portillo:** None. **A. Molina-Hernández:** None. **G. García-López:** None. **N.F. Díaz:** None.

Poster

731. Stem Cell Neural Differentiation

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 731.08/A42

Topic: A.03. Stem Cells and Reprogramming

Support: NIH Grant 1R21DC016171-01A1

Title: Otic vesicle maturation into inner ear organoids requires extracellular matrix

Authors: *S. E. HOCEVAR[1], L. LIU[2], R. K. DUNCAN[2];
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Abstract: Inner ear organoids derived from pluripotent stem cells could be a useful model system to study disease and regeneration. However, there is heterogeneity in size, morphology, and efficiency of organoids derived from otic vesicles. Some of this may due to cues from non-otic cells in the surrounding cellular aggregate. Greater control of the microenvironment surrounding the otic vesicle could decrease heterogeneity and increase the yield of organoids. Animal-derived otic vesicles show some autonomy during development and can differentiate into cochlear and vestibular domains in mesenchyme-free ex vivo culture. Therefore, we investigated whether stem cell-derived otic vesicles can autonomously generate cyst-like

organoids. To accomplish this, R1/E mouse embryonic stem cells were treated with factors to induce the formation of non-neural ectoderm, otic placode, and then otic vesicles. Vesicles were isolated from the rest of the aggregate on day 10 (D10) to D14, when the Pax2+/Sox2+ vesicles are clearly defined from the rest of the aggregate. Isolated vesicles were embedded in 100% Matrigel and grown in organoid maturation media to test their ability to differentiate into organoids. The D10 isolated vesicles grew in diameter but their thickness decreased, giving them a cyst-like morphology. Some vesicles remained smaller and thicker, whereas approximately 60% became larger, thinner, and cyst-like. No matter when the vesicles were isolated, the same percentage became cyst-like. Cysts contained MyoVIIa+ cells with phalloidin-labeled hair bundles. Therefore, we concluded that the maturation of vesicles into inner ear organoids was autonomous and independent of the non-otic cells that remained in the aggregate. In order to further investigate cues from the microenvironment that could be impacting otic fate, we investigated whether hydrogel stiffness or composition impacted the ability of vesicles to mature into organoids. Vesicles were grown in maturation media containing only 2% v/v Matrigel. This concentration produced little polymerization while exposing vesicles to about 200 μg/ml of extracellular matrix. We found that isolated vesicles could still develop into cysts with MyoVIIa+ cells. In the absence of Matrigel, vesicles collapsed and failed to produce cysts. Additionally, further immunohistochemistry of aggregates revealed that vesicles stained positive for laminin and collagen IV, indicating that the presence of these proteins, which are major components of Matrigel, may influence the development of organoids. Together, our results may help to define factors that influence organoid maturation.

Disclosures: **S.E. Hocevar:** None. **L. Liu:** None. **R.K. Duncan:** None.

Poster

731. Stem Cell Neural Differentiation

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 731.09/A43

Topic: A.03. Stem Cells and Reprogramming

Title: BC box motif in Sox6 induced differentiation to GABAnergic neuron of somatic stem cell

Authors: *T. YOSHIZUMI, H. KANNO, M. SINONAGA;
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Abstract: Previously, we demonstrated BC-box motif-mediated neuronal differentiation. Neuronal differentiation of somatic stem cells is induced by intracellular delivery of a peptide composed of the amino acid sequences encoded by a neuronal differentiation domain (NDD), and the NDD contained the BC box motif corresponding to the binding site of elongin C of BC box protein like Von Hippel Lindau tumor suppressor protein or suppressor of cytokine signaling (SOCS) protains. Especially, the NDD containing the BC-box motif in SOCS-6 protain advances

selective differentiation into GABAnergic neuron of somatic stem cell. And, it is reported SOCS protains mediate Janus kinase-2(JAK2) ubiquitination. From this, we here propose the mechanism of the GABAnergic neuronal differentiation of somatic stem cell mediated by the peptide of the BC-box motif in SOCS-6 protain. Immunoprecipitation with anti-JAK2 followed by immunoblotting showed the compound that contained the peptide from SOCS-6 has activity as an E3 ubiquitin ligase and mediates JAK2 ubiquitination. According to the result of western blotting, JAK2 and STAT3 are degraded. These result suggests that the GABAnergic neuronal differentiation of somatic stem cell mediated by the peptide of the BC-box motif in SOCS-6 is related to JAK2 ubiquitination. This GABAnergic neuronal differentiation of somatic stem cell using the BC-box motif in SOX-6 might contribute to the treatment of neuropathic pain and spasticity following spinal cord injury.

Disclosures: T. Yoshizumi: None. **H. Kanno:** None. **M. Sinonaga:** None.

Poster

731. Stem Cell Neural Differentiation

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 731.10/A44

Topic: A.03. Stem Cells and Reprogramming

Support: NIH-NIAAA R01 AA023797
Collaborative Studies on the Genetics of Alcoholism/COGA 5U10AA008401-26

Title: Impact of OPRM1 A118G on ethanol sensitivity in stem cell derived human neurons

Authors: *M. S. SCARNATI[1], M. JOEL[1], M. SWERDEL[2], J. A. TISCHFIELD[3], R. P. HART[2], Z. P. PANG[1];
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Abstract: Alcohol use disorders (AUDs) are among the most prevalent mental disorders worldwide. Yet, the mechanism(s) that can promote dependence in humans, in addition to the synaptic basis of AUDs in the context of opioid signaling, remains poorly understood mainly due to the difficulty in obtaining and studying live human tissue. This is critical in the context of genetic variants, including single nucleotide polymorphism (SNP) rs1799971 (*OPRM1*A118G) in the μ-opioid receptor (MOR). This SNP results in an amino acid substitution in the MOR by replacing an Asparagine (N) with Aspartate (D) at position 40. While the involvement of N40D MOR variants in AUDs remains highly debatable, alcoholic individuals with D40 variants gained more therapeutic effects when administered naltrexone. Work performed in heterologous expression systems and in rodents found altered ligand binding affinities for MOR and decreased

N’-glycosylation in the D40 variant, resulting in altered receptor trafficking, signaling and expression. Unfortunately, these studies have not revealed the correlation of D40 with alcohol reinforcement, possibly due to species specific differences in MOR function in humans. This makes it particularly important to assay the cellular and molecular mechanisms responsible for MOR function in the D40 variant in the context of *human* neurons. The *objective* of this project is to utilize human neuronal cells generated from induced pluripotent stem (iPS) cell lines to study the molecular, cellular, and synaptic mechanism(s) of MOR N40D in a *human* neuronal context. We have discovered a defect in N’-glycosylation in human MOR N40D peptide. The *working hypothesis is that the D40 variant of MOR impairs MOR trafficking, ligand binding, and expression, resulting from defective N’-glycosylation ultimately altering opioid and alcohol sensitivity on synaptic regulation, increasing the likelihood to develop an AUD.*Acute application of EtOH caused a significant increase in sIPSC and mIPSC frequency for N40 harboring iNs, while only a modest increase was observed in D40 human iNs. Interestingly, application of the MOR agonist DAMGO, following acute EtOH treatment, reduced the frequency of inhibitory events to a greater extent in D40 containing iNs. These data in combination with paired pulse stimulations suggest that iNs containing D40 MOR allelic variants have a lower initial synaptic release probability, and a higher affinity for opioid agonists. Finally, EtOH treatment alone indicates a differential sensitivity to acute treatment between genotypes. These results may provide a more mechanistic understanding of the interaction between alcohol and opioid signaling in humans.

Disclosures: M.S. Scarnati: None. **M. Joel:** None. **M. Swerdel:** None. **J.A. Tischfield:** None. **R.P. Hart:** None. **Z.P. Pang:** None.

Poster

731. Stem Cell Neural Differentiation

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 731.11/A45

Topic: A.03. Stem Cells and Reprogramming

Support: Barrow Neurological Foundation

Title: Optimal culture conditions for human induced pluripotent stem cell neurons

Authors: *J. LEVY, I. LORENZINI, M. NAVARRETE, S. MOORE, B. RABICHOW, M. ROBERTS, C. BURCIU, R. SATTLER;
Barrow Neurolog. Inst. at St. Joseph's Hosp, Phoenix, AZ

Abstract: Human induced pluripotent stem cells (hiPSCs) have shown to be valuable models for neurodegeneration, neurodevelopmental or neuropsychiatric research. Co-culturing hiPSC derived neurons on top of primary cultured astrocytes support the maturation, functionality and

neural synchronization. Additionally, the neurons adhere better and spread out more evenly when astrocytes are present. Our laboratory utilizes hiPSC derived motor neurons and cortical neurons to study the mechanisms of neurodegeneration in both amyotrophic lateral sclerosis (ALS) and frontotemporal degeneration (FTD). Even though co-culturing human iPSC derived motor neurons on top of primary cultured mouse astrocytes is optimal for neuronal maturation and function, many times astrocytes obscure neuron specific data when performing image, biochemical and/or molecular analyses. However, plating hiPSC neurons without the astrocytes leads to clumped and less functional neurons that slightly attach to glass coverslips or detach from the glass coverslip over time. In an effort to decrease astrocyte background and improve the even adherence and neuronal function of these hiPSC neurons, we tested six different combinations of extracellular coatings and six different neuronal medias to see which would support the best neurite outgrowth, synapse formation, and electrical communication. Each of the six coating combinations were paired with each of the six media types. For coating materials onto coverslips we used the following: PEI/Laminin; PDL/Geltrex; PLL/Laminin; PLO/Laminin; PDL/Matrigel and Collagen/Astrocytes. For culture medias, we used astrocyte conditioned media (ACM) supplemented with fresh growth factors (GFs), neuronal differentiation media (NDM) or BrainPhys supplemented with freah GFs and a 1:1 mixture of fresh NDM or BrainPhys and ACM with fresh GFs. To determine which pair of coating and media was most effective in promoting cell adherence and development, hiPSCs neurons were assessed for dendritic arborization, synaptic protein expression, and electrical activity. Even though neurons show the best results when they are plated on top of a monolayer of astrocytes, our results suggest that hiPSCs neurons plated without astrocytes with an optimized combination of coating and media leads to improve cell morphology and function over time.

Disclosures: **J. Levy:** None. **I. Lorenzini:** None. **M. Navarrete:** None. **S. Moore:** None. **B. Rabichow:** None. **M. Roberts:** None. **C. Burciu:** None. **R. Sattler:** None.

Poster

731. Stem Cell Neural Differentiation

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 731.12/A46

Topic: A.03. Stem Cells and Reprogramming

Support: Agilent Grant

Title: Glycolytic suppression enhances iPSC differentiation to NPC

Authors: *E. SZABO[1], **Y. KAM**[1], N. JASTROMB[1], K. SINGH[2];
[1]Agilent Technologies, Lexington, MA; [2]McMaster Univ., Hamilton, ON, Canada

Abstract: Cellular metabolism is an emerging critical factor suggesting that the metabolic status of cells and the environment can alter the differentiation trajectory of stem cells. In this study, we performed sequential metabolic profiling during induced pluripotent stem cell (iPSC) differentiation toward neuronal progenitor cells (NPCs). We found that a simple replacement of glucose, as the major carbon source, with galactose in the differentiation media enhance emergence of NPC in both quality and yield. Cellular metabolic profiling enabled the early detection of the metabolic shifts as a result of the carbon source switch. In order to facilitate *in vitro* tracking of changes in the metabolic phenotype during the early differentiation, we exploited 2D-monolayer culture method using singularized iPSCs, which is highly compatible with the Agilent Seahorse XF analyzer system allowing real-time cellular metabolic profiling of the differentiation time course from an iPSC to a NPC. The singularized iPSCs successfully differentiated to NPCs within 10 days. Interestingly, the NPC differentiation and overall yield was significantly improved by glucose replacement with galactose, which promoted selective reduction in glycolytic activity without affecting mitochondrial respiration. More homogeneous and rapidly growing NPCs were obtained in the presence of galactose, while a significant amount of non-NPC-like cells remained in the presence of glucose. The XF analysis also revealed a significant difference in the metabolic profiles between the two groups, which showed more stable and persistent mitochondrial function in galactose supplemented condition. The difference in metabolic profile appeared as early as two days after the onset of differentiation, while the expression pattern of the NPC molecular marker, nestin, was already distinguishable after four days of differentiation. These results support the importance of the carbon sources during metabolically dynamic processes, such as lineage specification/differentiation of stem cells. The study demonstrates that alterations of mitochondrial function even early during the differentiation from iPSCs, which are highly glycolytic, can drive stem cell differentiation programs. In addition, the analysis suggests that a sequential or on-time metabolic profiling can be a useful readout for evaluating *in vitro* differentiation towards predicting trajectory and quality of the differentiation process.

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Poster

731. Stem Cell Neural Differentiation

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 731.13/A47

Topic: A.03. Stem Cells and Reprogramming

Support: NSF NRT Grant DGE-1633213
NIH Health Grant P20GM103620
NSF/EPSCoR Grant IIA – 1355423

Title: Multifunctional biodegradable porous microspheres to act as a delivery platform and three-dimensional model for neurological disease

Authors: *E. S. SANDHURST[1], D. ENGEBRETSON[1], K. R. FRANCIS[2];
[1]Univ. of South Dakota, Vermillion, SD; [2]Cell. Therapies and Stem Cell Biol. Group, Sanford Res., Sioux Falls, SD

Abstract: Optimization and improvement of stem cell survival and differentiation represent a critical barrier to both the modeling of nervous system development and utilization of stem cell derivatives for patient therapies. Our approach seeks to provide a 3D matrix that facilitates cell-cell interaction, differentiation, and functional activity within a chemically defined environment. To achieve this, we prepared 3D porous polymer microspheres to act as carriers that were seeded with human neural stem cells (NSCs) derived from induced pluripotent stem cell (iPSC) models. Using a double emulsion and porogen leaching technique, defined amounts of poly-(lactic-co-glycolic acid) (PLGA) and gelatin were combined to yield a highly porous microstructure capable of cell support. Techniques were optimized to generate microspheres with a diameter of 150 - 300 µm, average pore size of 20 µm and a porosity >90%. To demonstrate the feasibility of the 3D microspheres to act as a cell delivery vehicle, we cultured iPSC-derived NSCs for up to 28 days on microspheres. To define the impact of the substrate on NSC attachment and differentiation, we compared NSC response to culture on uncoated spheres versus spheres coated with Matrigel, poly-L-ornithine, or poly-L-ornithine/laminin. After 24 hours of culture on the 3D microsphere structure, NSCs exhibited high attachment and typical NSC morphology. After 7 days, NSCs exhibited a 5-fold increase in cell number, broad microsphere distribution, and cytoskeletal processes mediating cell-cell contacts. In addition to their ability to act as a cell delivery vehicle, we functionalized the surface of the microspheres with hydroxyapatite (HA) minerals by immersion in a simulated body fluid over various time periods. To validate their multifunctional capacity, we demonstrated the model protein bovine serum albumin could be loaded into the HA crystal matrix on the porous microspheres and released in a controlled manner over 10 days. Ongoing studies are defining the differentiation and functional maturation of neural lineages from NSCs within this model, evaluating other adult-derived stem cell models, including mesenchymal stem cells, within our microsphere model, and further defining the efficacy of our composite polymer/bioceramic microsphere model as a combined cellular and drug-delivery platform for additional neurologically-targeted proteins and small molecules. We have produced a promising biomaterial for combined local drug and cellular delivery for application in pharmacological analyses, developmental modeling, and regenerative techniques for neurological models.

Disclosures: E.S. Sandhurst: None. **K.R. Francis:** None. **D. Engebretson:** None.

Poster

731. Stem Cell Neural Differentiation

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 731.14/A48

Topic: A.03. Stem Cells and Reprogramming

Title: Reprogramming iPSCs into glutamatergic neurons, reconstruction of transcriptional events and cellular states using an integrated genomic approach

Authors: *M. ABDUL KARIM[1], K. BARANES[1], S. COOPER[3], E. BELLO[3], N. PATIKAS[2], E. METZAKOPIAN[2], A. BASSETT[3], M. KOTTER[1];
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Abstract: Direct cell reprogramming is a rapidly growing field that has challenged traditional concepts of cellular identity. The expression of Neurogenin 2 (NGN2) results in rapid reprogramming of human pluripotent stem cells (PSCs) into functional cortical glutamatergic neurons. This combines the advantage of the highly proliferative and epigenetically malleable PSC stage with the efficiency of direct reprogramming. We have previously demonstrated that gene targeting the components of a Tet-On system into two separate safe harbour sites overcome gene silencing and results in optimised transgene expression in hiPSCs (OptiOx), and consequently yields highly homogenous cultures of pure glutamatergic neurons within less than four days. The mechanisms that mediate this remarkable cellular metamorphosis remain poorly understood. To study the transcriptional events occurring as a result of NGN2 expression, three independent biological replicates were harvested at the iPSC stage (day 0), and 6h, 12h, 24h, 36h, day 2, day 3, day 4, day 14, and day 21 post induction. Cell extracts were subsequently processed for bulk RNA sequencing. This demonstrated distinct and highly reproducible transcriptional changes across each of the individual time points. To gain a more detailed insight into the distinct cellular states, we complemented our bulk-RNA-Seq approach with single cell RNA sequencing of cells harvested at the iPSC stage (day 0), as well as 12h, 24h, day 2, day 3, day 4, day 14, and day 21 post induction. Louvain network analysis demonstrated distinct cellular states through which cells synchronously progressed with little heterogeneity until attaining a distinct neuronal phenotype. In order to differentiate direct from indirect NGN2 down-stream effectors, an inducible hiPSC cell line in which NGN2 tagged with HA was constructed and validated as outlined above. CHiP-Seq data acquired on day 2 after induction was subsequently overlaid with bulk seq data and single cell seq data. This enabled identification of direct and indirect effectors of NGN2 with regards to gene regulatory networks as well as on peripheral genes over the time course of the experiment. In conclusion, we provide a detailed analysis of transcriptional events that govern the transition of iPSCs into mature glutamatergic neurons following NGN2 expression.

Disclosures: **M. Abdul Karim:** None. **K. Baranes:** None. **S. Cooper:** None. **E. Bello:** None. **N. Patikas:** None. **E. Metzakopian:** None. **A. Bassett:** None. **M. Kotter:** A. Employment/Salary (full or part-time):; Elpis Biomed Ltd.

Poster

731. Stem Cell Neural Differentiation

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 731.15/A49

Topic: A.08. Development of Motor/ Sensory/ and Limbic Systems

Support: NSF DGE 1735252
NSF STC CBET 0939511
P30 DA018310

Title: Neurotransmitter levels in spinal-organoids vs. rodent models during central nervous system development using capillary electrophoresis-mass spectrometry

Authors: ***S. E. MURPHY**, A. C. WEISS, K. P. RAMOS-CRUZ, C. D. KAUFMAN, H. KONG, J. V. SWEEDLER, M. U. GILLETTE;
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Abstract: Organoids have been used for disease modeling, drug testing, developmental studies, and transplantation. Spinal organoids are 3D aggregates of motor neurons and glia cultured from stem cells *in vitro*. The extent to which spinal organoids model spinal cords enables their utility in these studies. However, the extent to which ability of spinal organoids to accurately model neurotransmitter expression in rodent spinal cord development with regard to the profile of neurotransmitters expressed has not been studied. Therefore, the rationale behind this work is to determine how accurately spinal organoids model the cell-to-cell signaling molecule complement in rodent spinal cord explants. To accomplish this, we are growing spinal organoids and characterizing their chemical contents with mass spectrometry. More specifically, using capillary electrophoresis-electrospray ionization-mass spectrometry (CE-ESI-MS), we assay the neurotransmitters present during spinal organoid and rodent spinal cord explant development. Coupling these methods is significant, because there are no reports measuring neurotransmitters in organoids and rodent spinal cord explants using CE-ESI-MS. Here we present data showing our ability to generate spinal organoids that express neuronal and glial markers as well as qualitatively measure neurotransmitters in juvenile (P7) rodent spinal cord explants. Spinal organoids were cultured for up to 2 mo. After one mo., the spinal organoids expressed the neuronal marker NeuN and the glial marker GFAP. At 2 mo., the cells positive for GFAP displayed a star shape characteristic of astrocyte morphology. Explant samples from spinal cords of P7 rodents were collected, and neurotransmitters were extracted using an acidified methanol solution and sample homogenization by homogenizing samples. Three biological replicates were

analyzed in duplicate using a laboratory-built CE-ESI-MS. The neurotransmitters acetylcholine, γ-aminobutyric acid, glutamic acid, and aspartic acid were qualitatively measured in P7 rodent spinal cord explant samples. These results demonstrate the ability to measure neurotransmitters from rodent spinal cord explants using CE-ESI-MS. Future work aims to assess the emergence of neurotransmitters during the development of spinal organoids vs. rodent spinal cord explant development using CE-ESI-MS.

Disclosures: S.E. Murphy: None. **A.C. Weiss:** None. **K.P. Ramos-Cruz:** None. **C.D. Kaufman:** None. **H. Kong:** None. **J.V. Sweedler:** None. **M.U. Gillette:** None.

Poster

732. Synaptogenesis and Activity-Dependent Development IV

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 732.01/A50

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: National Natural Science Foundation of China (31530030)
Strategic Priority Research Program of Chinese Academy of Science (XDB32010000)

Title: Retinoid x receptoralpha mediates unesterified DHA-dependent spinogenesis and excitatory synapse formation *in vivo*

Authors: *H. CAO, M. LI, G. LI, S.-J. LI, B. WEN, X. YU;
Inst. of Neurosci., Shanghai City, China

Abstract: Neural circuit formation depends on synapse development, which is governed by coordinated interaction between extracellular cues and intracellular signaling. Nuclear receptors are ligand-activated transcription factors that play important roles in the development, homeostasis, and metabolism of the organism. They sense nonpolar regulatory molecules that diffuse across the plasma membrane, and directly transduce extracellular signals to regulate transcriptional programming. Retinoid X receptor α (*Rxra*) plays central roles in many physiological processes by forming homodimers or heterodimers with other nuclear receptors, although its role in the brain is largely unknown. As an endogenous ligand for RXRs, docosahexaenoic acid (DHA)—a brain-enriched polyunsaturated fatty acid and famous nutritional additive—has been associated with various neurological and psychiatric disorders. Here, we report that DHA and *Rxra* contribute to synapse development *in vivo* as a ligand-receptor pair. In NEX-Cre *Rxra* conditional knockout (*Rxra* cKO; *Rxra* conditionally removed from all excitatory neurons from the cerebral cortex and hippocampus) mice, we found significant reduction in dendritic spine density of layer 2/3 pyramidal neurons in both developing and adult cortices. We further showed the effect of *Rxra* in regulating dendritic spine density is

transcriptional, bidirectional and cell-autonomous. Correspondingly, we detected significant downregulation of excitatory synapse number and mEPSC frequency in *Rxra* knockout neurons. Moreover, intracerebroventricular (ICV) injection of unesterified DHA significantly upregulated spine density and synaptic transmission in control, but not in *Rxra* cKO mice. Blocking DHA release from brain phospholipids led to significant reduction in spine density, an effect rescued by unesterified DHA. Finally, we found that DHA and *Rxra* likely promote synapse development by upregulating immediate early genes (IEGs) expression. Together, these results dmonstrate that unesterified DHA promotes excitatory synapse development through *Rxra*-dependent signaling *in vivo*.

Disclosures: H. Cao: None. **M. Li:** None. **G. Li:** None. **S. Li:** None. **B. Wen:** None. **X. Yu:** None.

Poster

732. Synaptogenesis and Activity-Dependent Development IV

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 732.02/A51

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: NIH Grant 1R15AG045820-01A1

Title: Expression of chimeric GluN2 subunits in hippocampal NMDA receptors reveals mechanisms regulating the postnatal development of dendritic spines on area CA1 pyramidal neurons

Authors: *R. E. KEITH[1], M. J. KEITH[2], S. SINGH[2], S. K. PACK[4], R. BINOY[2], T. C. DUMAS[3];
[1]Interdepartmental Program in Neurosci., [2]Col. of Sci., [3]Psychology, George Mason Univ., Fairfax, VA; [4]Thomas Jefferson High Sch. for Sci. and Technol., Alexandria, VA

Abstract: During postnatal brain development, activity-dependent plasticity shapes dendritic spines; these activity-dependent changes in dendritic spines are regulated by N-methyl-D-aspartate receptors (NMDARs), a glutamate receptor at excitatory synapses. In the hippocampus, NMDARs are composed of two GluN1, and two GluN2 subunits, which can be sub classed as A, B, C, or D. At three weeks of age, there is a switch in NMDAR composition, from GluN2B-containing to GluN2A-containing and triheteromeric receptors. This switch in configuration has been associated with decreased spine density in hippocampal pyramidal cells and the emergence of spatial learning and memory.
Subunit composition affects the calcium-dependent and calcium-independent signaling properties of NMDARs significantly. Compared to NMDARs with GluN2A subunits, GluN2B-NMDARs conduct calcium for longer after activation and display affinity for CaMKII and Ras-

GRF1, while GluN2A-NMDARs interact more with Ras-GRF2 and PKA. Mice lacking GluN2B postnatally show reduced spine density and learning deficits; conversely, mice lacking GluN2A show an increase in density in dentate granule cells with no change in density in pyramidal cells. To dissociate the influences of calcium-dependent and calcium-independent signaling on dendritic spines, we created transgenic mice with the amino terminal domain (ATD) and transmembrane domains (TMDs) of GluN2A subunits coupled with the carboxy terminal domain (CTD) of GluN2B (termed ABc), and vice versa (termed BAc). We crossed these mice with mice expressing GFP in hippocampal pyramidal cells, allowing assessment of spine density through fluorescence microscopy. Slices were prepared during developmental stages just before (P17-P19) and just after (P22-P24) the switch in NMDAR composition, as well as in more mature animals (P30-P60). Spine segments were traced in hippocampal pyramidal cells by three independent investigators. The results demonstrated that, at P17-19, apical and basal dendrites showed lower spine density in ABc mice and a higher spine density in BAc mice compared to wildtype controls. At P22-24, BAc mice showed reduced spine density while ABc animals showed no change from wildtypes in the apical dendrite; the basal dendrite showed no genotype differences in density. The P30-P60 spine density results are more preliminary, but currently show reduced dendritic spine density in BAc mice compared to ABc and WTs. In summary, these results suggest that calcium-dependent and calcium-independent signaling streams act in opposing ways to regulate dendritic spines on hippocampal pyramidal neurons during postnatal development.

Disclosures: **R.E. Keith:** None. **M.J. Keith:** None. **S. Singh:** None. **S.K. Pack:** None. **R. Binoy:** None. **T.C. Dumas:** None.

Poster

732. Synaptogenesis and Activity-Dependent Development IV

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 732.03/A52

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: NIH-NINDS NS089791

Title: Astrocyte expression of synapse promoting genes is developmentally regulated by neuronal and astrocyte activity

Authors: *I. FARHY-TSELNICKER, C. DOWLING, N. J. ALLEN;
Mol. Neurobio. Lab., The Salk Inst., La Jolla, CA

Abstract: Astrocytes are crucial regulators of neuronal synapse development and function. In the rodent cortex neurons are arranged in 6 layers, each with stereotyped synaptic connectivity. Cortical astrocytes produce several synapse promoting factors, however, whether they

differentially regulate formation of synapses in different layers is unknown. Furthermore, the developmental expression pattern of astrocyte synaptogenic cues, and whether expression is regulated by neuronal or astrocyte activity, is unknown. Here we use mouse visual cortex to study the development of astrocytes and astrocyte-derived synapse promoting genes including glypicans, thrombospondins and Chordin like1. Using genetic mouse models, immunohistochemistry, and in situ hybridization we quantified the developmental changes in astrocyte numbers and expression levels of synapse promoting genes within each of the 6 neuronal layers. We observed differential developmental changes in expression of astrocyte-derived synapse promoting genes, which occurred mainly between post-natal days (P) 7 and 14, a time between synapse initiation and maturation. For example, glypican 4 (gpc4) expression is strongly reduced at P14 compared to P7 only in layer 1, while glypican 6 (gpc6) expression is increased in deeper layers. Next, perturbing glutamate release from thalamic neurons by knocking out VGlut2 resulted in significant increase in gpc4 expression in layer 1 at P14 compared to wild type controls, while expression of gpc6 was decreased in deep layers, thus preventing the developmental regulation. Moreover, perturbing astrocyte activity at P14 by knocking out IP3R2 resulted in a significant decrease in gpc4 expression, but had no effect on gpc6 expression. Our findings provide insight into neuron-astrocyte interaction as it occurs at the level of the distinct cortical connections during synapse development, and constitute an important frame work for future studies of astrocyte and synapse development in the cortex.

Disclosures: I. Farhy-Tselnicker: None. **C. Dowling:** None. **N.J. Allen:** None.

Poster

732. Synaptogenesis and Activity-Dependent Development IV

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 732.04/A53

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: NARSAD Young Investigator Grant 25248
William and Ella Owens Medical Research Foundation Grant
UT system Rising STARs grant

Title: SRPX2 protects synapses from excess complement-mediated elimination during development

Authors: Q. CONG, **B. SOTEROS**, *G.-M. SIA;
Pharmacol., UT Hlth. San Antonio, San Antonio, TX

Abstract: The complement system has emerged as an important mediator of synapse elimination during brain development and disease. However, whether there are endogenous mechanisms to inhibit complement activity remain unclear. Here, we show that sushi repeat protein X-linked 2

(SRPX2) is a neuronal complement regulator that protects synapses from excessive complement-mediated elimination during development. SRPX2 binds to C1q and inhibits initiation of the complement cascade, and mice lacking SRPX2 show increased C3b deposition and microglial activation. Absence of SRPX2 also causes a specific loss of thalamocortical synapses in the somatosensory cortex due to excessive pruning, which is reversed in the C1QA-SRPX2 and C3-SRPX2 double knockout mice. In addition, SRPX2 knockout mice show increased eye-specific segregation of retinal ganglion cell inputs in the visual thalamus, which is also reversed in both the C1QA-SRPX2 and C3-SRPX2 double knockout mice. These data reveal a new molecular mechanism that restricts complement activity to specific sets of synapses during development.

Disclosures: Q. Cong: None. **B. Soteros:** None. **G. Sia:** None.

Poster

732. Synaptogenesis and Activity-Dependent Development IV

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 732.05/A54

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: 2011CBA00404

Title: Layer-specific reconfiguration of cortical microcircuits by visual deprivation during the critical period

Authors: *L. YAO, M. MENG, X. GU, X. ZHANG;
State Key Lab. of Cognitive Neurosci. & Learning, Beijing Normal Univ., Beijing, China

Abstract: Abnormal sensory inputs or experience during a postnatal critical period markedly alters sensory cortical functions. However, experience-induced changes of local synaptic circuits across different cortical laminae, which underlie the sensory function alteration, are poorly understood. To address this question, we conducted extensively dual whole-cell recording in the layers 2/3 and 4 of primary visual cortex (V1) prepared from the mice that experienced monocular deprivation (MD) of visual inputs during the critical period. The results suggest that there exist distinct circuit wirings of excitatory pyramidal cells and inhibitory parvalbumin (PV)-, somatostatin (SOM)- or vasoactive intestinal peptide (VIP)-expressing interneurons within the layers 2/3 and 4. The MD experience selectively modifies the strength of certain excitatory or inhibitory synapses that targeted to distinct cell types in both two layers, but exhibiting apparent layer difference. The results also indicate that synapses of inhibitory SST and PV cells are primary targets for experience modification in the layer 2/3 and 4 local circuits, respectively. Our findings provide a systematic elucidation of layer-specific reconfiguration of visual cortical microcircuits by altered experience.

Disclosures: **L. Yao:** None. **M. Meng:** None. **X. Gu:** None. **X. Zhang:** None.

Poster

732. Synaptogenesis and Activity-Dependent Development IV

Location: Hall A

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Program #/Poster #: 732.06/A55

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: National Institute of Alcohol Abuse and Alcoholism of the National Institutes of Health under Award Number R28AA012725
National Health and Medical Research Council (NHMRC) of Australia Project Grant No. 568807

Title: Complement activation during early postnatal brain development suggests earlier onset of synaptic pruning in humans

Authors: *R. E. SAGER[1], A. K. WALKER[2], K. ROBINSON[2], M. J. WEBSTER[3], C. S. WEICKERT[2];
[1]Dept. of Neurosci., SUNY Upstate Med. Univ., Syracuse, NY; [2]Neurosci. Res. Australia, Sydney, Australia; [3]Stanley Med. Res. Inst., Rockville, MD

Abstract: Dysregulation of synaptic pruning has been theorized as a pathological cause for schizophrenia and autism. Over the past decade, synaptic pruning through the classical complement pathway has been increasingly recognized as a mechanism of regulating synapses in the developing brain. However, patterns of complement expression in the human brain are not well defined in the literature. Using the dorsolateral prefrontal cortex from post-mortem humans, we extracted RNA for targeted RT-PCR (n=48) of genes from the classical complement pathway. One of these genes, C4, is a risk factor for schizophrenia, with increased risk tied directly to increased C4 mRNA levels. Our cohort for this study (n=57) was divided into five categories representing different developmental periods: neonate, infant, toddler, school age, teenager, and young adult; ranging from age two months to 25 years. Group sizes were kept as consistent as possible, with seven to 13 cases per age group. Raw transcript levels were normalized to geomean values calculated from three housekeeper genes with no significant correlations between age, pH, post-mortem interval (PMI), or RNA integrity number (RIN). All data sets were tested for significant correlations with pH, PMI, and RIN and analyzed with ANOVA or ANCOVA accordingly. We found that the mRNA of many complement components changed significantly with age, with the typical pattern being low levels in neonates which increased and peaked in toddlers, before reducing or plateauing though school age and teenage years. Among these transcripts were the classical complement cascade initiator C1q, subunit b (C1qb mRNA, F=4.713, df=5, p=0.001), and C3, a key effector molecule that marks membranes for destruction (C3 mRNA, df=5, F=2.452, p=0.047). Subsequently, inhibition of the pathway

escalates, with inhibitors increasing significantly in toddlers (CD55 mRNA, F=7.598, df=5 p<0.001; CD59 mRNA, F=11.728, df=5, p<0.001) and reaching peak expression in schoolage (CD55 mRNA; CD46 mRNA, F=3.995, df=5, p=0.004). These data suggest an increased role for the classical complement cascade in toddlers, with no induction of complement in the teenage brain. Thus, our results suggest that complement-mediated synaptic pruning may increase during the age of onset for autism, but not that of schizophrenia.

Disclosures: R.E. Sager: None. **A.K. Walker:** None. **K. Robinson:** None. **M.J. Webster:** None. **C.S. Weickert:** None.

Poster

732. Synaptogenesis and Activity-Dependent Development IV

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 732.07/A56

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: Research Council of Norway BrainMatrix Grant NRF250259

Title: A new framework for modelling neural-ECM signaling

Authors: *N. IANNELLA[1], K. PRYDZ[1], A. MALTHE-SØRENSENN[2], G. T. EINEVOLL[3], M. FYHN[1];
[1]Dept. of Biosci., [2]Dept. of Physics, Univ. of Oslo, Oslo, Norway; [3]Norwegian Univ. Life Sci., Aas, Norway

Abstract: Electrical activity in cortical networks and their composite neurons provides the basis for understanding the information processing in single neurons and interconnected neural populations [1]. To this end, numerous studies have focused on how neurons and the networks they form, operate from an electrical perspective [2,3]. The underlying molecular activity of brain cells plays important roles where both neurons and glia are complex molecular machines, adapting their responses over short and long-time scales [4]. Recent experiments have implicated the Extracellular Matrix (ECM), including an ECM specialization called the Peri-Neuronal Network (PNN), and their molecular components in neural signaling and information processing, by virtue that it strategically occupies the synaptic cleft [5,6]. Recent studies show ECM/PNN involvement in Life-long learning and memory, synaptic remodeling and significantly, in the recall of fear memory [7,8]. Furthermore, other studies have illustrated that the expression of certain ECM/PNN molecules are directly involved in modulating the efficacy of neural transmission on multiple time scales [9]. Currently, a handful of computational studies have focused on understanding the role of how the ECM influences neural signaling [10]. How the interaction between ECM and neural activity impacts network behavior and information processing has yet to be explored from a computational perspective.

We present a new biologically inspired framework and an accompanying mathematical model that captures the nature of bidirectional neuron-ECM signaling. The framework considers the roles played by various ECM/PNN molecules through their activity-driven influence on neural transmission and impact on neural responses. Our model is computationally tractable and can be applied to study the bidirectional nature of neural-ECM signaling in different brain areas and their collective influence on both single neuron responses and network activity. Finally, we present preliminary results, using a classical spiking neural oscillator (recurrently connected excitatory and inhibitory pair of neurons), to illustrate how ECM-neural interactions impacts the behavior of a spiking neural oscillator.

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Poster

732. Synaptogenesis and Activity-Dependent Development IV

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 732.08/A57

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Title: Investigating the effects of chondroitin sulfate on dendritic spines of pyramidal neurons

Authors: *T. TANAKA[1], A. KEREVER[1], Y. SUZUKI[1], K. KATO[1], M. TOYODA[1], F. SAITOW[2], H. SUZUKI[2], H. HIOKI[3], E. HIRASAWA[1];
[1]Juntendo Univ., Tokyo, Japan; [2]Nippon Med. Sch., Tokyo 113-8602, Japan; [3]Dept. of Cell Biol. and Neurosci., Juntendo Univ. Grad. Sch. of Med., Tokyo, Japan

Abstract: [Introduction]: Research has shown that autism spectrum disorder (ASD) occurs as a result of an imbalance between excitation and inhibition of neurons in the cerebrum. However, the underlying mechanism inducing this imbalance remains unclear. One potential player in this mechanism could be the extracellular matrix (ECM), especially chondroitin sulfate (CS) which are known to repress the formation of dendritic spines. Furthermore, the expression pattern of CS dramatically changes during the critical period in the mammalian brain development, a period in which neural plasticity is known to be enhanced. From our past research, an immunostaining pattern ("CS patch") detected by an anti-CS antibody could be an indicator of an extracellular structure that orchestrates a normal neural environment. We previously found that BTBR mice, a model mouse for ASD, lack "CS patches" in the somatosensory cortex, suggesting the possible link between this observation and ASD. In this study, we first established a method to analyze dendritic spine density and morphology on pyramidal neurons of mouse cerebrum. We then investigated the effects of "CS patches" on spine density and morphology using C57BL/6 (B6) and BTBR mice. [Materials and Methods]: Pyramidal neuron from layer 2/3 of the somatosensory cortex were injected with biocytin on 300μm acute slices. Slices were cleared and immunostained with CS56 antibody to reveal the "CS patches" and streptavidin to reveal the pyramidal neuron. The image data were processed under IMARIS for rendering and analysis. During data processing, spines were classified as mushroom, thin, stubby, or filopodia depending upon the volume, length, and width. [Results]: Comparisons of dendrites inside and outside of the "CS patches" in B6 mice showed that dendrites inside had more mushroom spines. Additionally, the head volume of mushroom spines on the dendrites inside was significantly larger compared to that of dendrites outside the "CS patches". BTBR dendrites notably showed a lower spine density than B6 dendrites. [Conclusion]: Our analysis shows clear differences in density and morphology between spines inside and outside the "CS patches" for B6 mice. Additionally, those were different between B6 and BTBR mice. These results suggest an effect of specific CS recognized by CS56 antibody on pyramidal neuron spines.

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Poster

732. Synaptogenesis and Activity-Dependent Development IV

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 732.09/A58

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: The Women in World Neurosciences (WWN) Collaborative Research Network Program (CRNP) Award 2014, financed by IBRO/SfN
Universidad Icesi intramural research grant (2014-2019)

Title: Evaluation of neuroligin and FMR1 mRNA expression and memory and locomotion capacity in a sensory-deprivation rearing protocol in *Drosophila melanogaster*

Authors: *E. VIVEROS ARAQUE[1], Y. CARRERA SUAREZ[1], L. BECERRA HERNANDEZ[2], J. RENGIFO GOMEZ[1];
[1]Natural Sci., Univ. Icesi, Cali, Colombia; [2]Basic Hlth. Sci., Pontificia Univ. Javeriana, Cali, Colombia

Abstract: Consolidation and remodeling of synapses during the postnatal development stage strengthens the appropriate connections and eliminates wrong or unnecessary ones. These processes known as maturation and synaptic pruning, respectively, are highly dependent on sensory activity and responsible for neuronal plasticity. The development of the nervous system in Fragile X syndrome (FXS) presents abnormalities in these processes. This genetic disorder is the leading cause of hereditary mental disability, and the major genetic cause known in Autism Spectrum Disorders (ASDs). Both pathologies exhibit defective synapses that result in behavioral and learning disorders. The production of the FMRP (fragile X mental retardation protein) is eliminated in FXS. FMRP, a protein that binds and regulates the translation mRNA, plays an important role in the elimination of immature synapses. On the other hand, the Neuroligin protein, mutated in some ASDs, helps in the formation of the synaptic cleft and the maturation of neural connections. This project explores, through the molecular technique RT-PCR and behavioral assays Negative Geotaxis test and Aversive Phototaxic Suppression test, the comportment of Neuroligin and FMR1 mRNA expression as well as memory and locomotion capacity during the process of activity dependent synaptic pruning in a wildtype strain of *Drosophila melanogaster*, reared in a control protocol with normal levels of sensorial stimulation or in a sensory-deprivation rearing protocol with restriction of light, auditory, spatial and social stimuli. We found that, in the sensory-deprivation treatment, the Nlg*1* gene (present in excitatory synapses) is down-regulated and that Nlg2 (present in inhibitory synapses) and FMR1 genes are up-regulated. Also, the locomotor activity and learning capacity of the flies are reduced in this treatment, providing evidence of the importance of sensory input during nervous system development and also as an important player in the etiology of neuronal developmental disorders.

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Poster

732. Synaptogenesis and Activity-Dependent Development IV

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 732.10/A59

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: NIH T32GM007753
NIH T32MH020017
Stanley Center for Psychiatric Research
NIMH P50 MH112491
NINDS R01 NS092578
Howard Hughes Medical Institute

Title: The schizophrenia-associated gene CSMD1 encodes a brain-specific complement inhibitor

Authors: M. L. BAUM[1,2,4], ***M. B. JOHNSON**[4], R. FOX[4], E. NACU[5,4], W. CROTTY[4], D. WILTON[1], S. MCCARROLL[3,4], K. EGGAN[5,4], B. A. STEVENS[1,2,4,6];
[1]Boston Children's Hosp., Boston, MA; [3]Dept. of Genet., [2]Harvard Med. Sch., Boston, MA; [4]Stanley Ctr. for Psychiatric Res., Broad Inst. of MIT and Harvard, Cambridge, MA; [5]Harvard Univ., Cambridge, MA; [6]Howard Hughes Med. Inst., Boston, MA

Abstract: Four threads of biological observation have recently converged onto a theory in which over-exuberant synaptic pruning contributes to the pathogenesis of schizophrenia: 1) post mortem, there is a reduced number of dendritic spines in the frontal cortex of individuals with schizophrenia, 2) the disorder has a characteristic onset in late adolescence, a critical period for normal pruning and thinning of the frontal cortex, 3) clinical high risk young people who convert to psychosis have an accelerated rate of frontal cortex thinning coincident with psychosis onset, 4) human genetics strongly implicates hyper-function of synaptic pruning machinery in disease risk - specifically, disease risk increases with brain expression and genomic copy number of complement component 4 (C4), a member of a cascade of immune molecules repurposed in the brain to promote the sculpting of circuits. To further test a pruning hypothesis of schizophrenia, we investigated whether an inhibitor of this pruning machinery could also be functionally implicated in disease risk. Schizophrenia genetics, structural biology, *in vitro* biochemistry, and gene expression suggested that the large transmembrane protein encoded by the giant gene CSMD1 (CUB and Sushi Multiple Domains 1) could be such a disease associated complement inhibitor: a) a genome-wide significant association signal localizes to *CSMD1*, b) the gene encodes a protein composed almost entirely of domains conserved in regulators of the complement cascade, i.e., CUB (Complement, Urchin-EGF, BMP) and Sushi (aka CCP or Complement Control Proteins) domains, c) protein fragments of CSMD1 can directly and indirectly inhibit the activation of C4 and C3 *in vitro*, d) CSMD1 mRNA is brain-enriched.

Despite these intriguing observations, however, little was known about the about the normal functions of CSMD1 in neural tissues. Here, we show that CSMD1 protein is highly brain-enriched, particularly in cortex, present at synapses, and is expressed predominantly by neurons. Using a human stem cell line and a mouse each genetically lacking CSMD1, we present evidence that CSMD1 regulates complement activation on neural cells *in vitro* and *in vivo*, and that loss of Csmd1 abrogates the development of a complement-and-pruning-dependent neural circuit. Together, these data corroborate CSMD1 as a brain-specific complement inhibitor and further support a pruning hypothesis of neurodevelopmental etiology for schizophrenia.

Disclosures: M.L. Baum: None. **M.B. Johnson:** None. **R. Fox:** None. **E. Nacu:** None. **W. Crotty:** None. **D. Wilton:** None. **S. McCarroll:** None. **K. Eggan:** None. **B.A. Stevens:** F. Consulting Fees (e.g., advisory boards); Annexon Biosciences.

Poster

732. Synaptogenesis and Activity-Dependent Development IV

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 732.11/A60

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: Simons Foundation 429963
K99 MH120051
R37 NS028829
NIH Grant 2R01NS081297-06
NIH Grant 2P01NS074972-06A1

Title: Spontaneous retinal activity selectively influences the establishment of cortical inhibition prior to sensory experience

Authors: *T. J. BURBRIDGE[1,2], L. CHEADLE[3], M. E. ROBIE[2], M. E. GREENBERG[4], G. J. FISHELL[2];
[1]New York Univ., New York, NY; [2]Neurobio., [4]Dept. of Neurobio., [3]Harvard Med. Sch., Boston, MA

Abstract: Patterned, spontaneous brain activity propagates throughout sensory systems during stages of brain development that occur prior to the onset of environmentally-evoked sensory experience. While such activity is known to be important for neural development, the specific roles of these highly stereotyped, intrinsically generated patterns of activity in circuit assembly have not yet been fully characterized in large part due to a technical inability to manipulate these patterns without initiating compensatory activity *in vivo*. To interrogate the role of spontaneous activity in brain development, we focused on the visual system, in which patterned “waves” of activity driven by cholinergic signaling in the retina (retinal waves) propagate through retino-

recipient brain regions and extend to the visual cortex. To manipulate retinal waves without initiating compensatory activity, we employed a transgenic mouse in which the Beta-2 subunit of the nicotinic acetylcholine receptor is conditionally removed from roughly two-thirds of the retina, leaving retinal waves in the remaining third of the retina intact. By performing *in vivo* calcium imaging, we found that retinal wave disruption in these mice persists throughout the visual system to the primary visual cortex. Microdissection and single-cell RNA-sequencing of wave-positive and wave-negative cortical regions identified through calcium imaging revealed that two inhibitory neuron subtypes, Parvalbumin (PV) and Somatostatin (SST) neurons, are particularly sensitive to patterned activity changes at the molecular level when compared to VIP interneurons and excitatory neurons. Ontological analysis of misregulated genes in PV and SST neurons suggest possible effects on inhibitory synapse formation and neurotransmission. Consistently, we found that loss of retinal waves leads to a decrease in the density of SST synapses onto pyramidal cells. These experiments reveal cell-type-specific roles for early patterned activity in cortical circuit assembly.

Disclosures: **T.J. Burbridge:** None. **L. Cheadle:** None. **M.E. Greenberg:** F. Consulting Fees (e.g., advisory boards); MEG is a member of the Board of Directors for Allergan and is on the advisory boards of Decibel and Amgen. **G.J. Fishell:** None. **M.E. Robie:** None.

Poster

732. Synaptogenesis and Activity-Dependent Development IV

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 732.12/A61

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: Stanley Center for Psychiatric Research
Dauten Family Foundation

Title: Integrative molecular analysis of synaptic pruning in a large psychiatric cohort of postmortem prefrontal cortex

Authors: *R. G. FOX[1], B. A. STEVENS[2,1,3,4], M. B. JOHNSON[1,2];
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Abstract: Synaptic pruning is a normal process of synapse removal and circuit refinement that occurs throughout the developing brain. This process is mediated in part by the classical complement pathway, which opsonizes or “tags” synapses and flags them for removal. Microglia, the immune phagocytes of the CNS, recognize this tag via complement receptors and engulf the unwanted synapses. In the prefrontal and other association areas of the cortex,

synaptic pruning peaks during adolescence and continues significantly later than in primary sensory cortical regions. Studies have found reduced synapse numbers in prefrontal and association cortex of patients with schizophrenia, as well as exaggerated thinning of prefrontal grey matter, suggesting that excessive synaptic pruning may contribute to the emergence of this severe mental illness. Notably, the adolescent peak of prefrontal synaptic pruning coincides with a developmental window of vulnerability for psychiatric disorders including schizophrenia. Additionally, genome-wide association studies have identified genetic risk factors for schizophrenia that implicate the complement pathway, including complement component C4A. However, studies utilizing human postmortem brain tissue have been limited by sample availability and the low-throughput of methods for synapse analysis and quantification in brain tissue sections. We have applied higher-throughput techniques for synapse counting and analysis in human prefrontal cortex tissue sections from a large cohort of psychiatric cases and controls (n=50 Schizophrenia, n=50 Bipolar Disorder, n=50 Control). In addition to a large sample size, this cohort has the advantages of extensive prior characterization, including haplotype copy number and brain RNA expression levels of complement component 4 (C4A), as well as matching DNA, RNA, and protein lysate samples for correlative measures. Applying a variety of methods to these samples, we aim to calculate the densities of molecularly defined synaptic subtypes, quantify complement protein expression and pathway activation, characterize microglia cellular phenotypes, and correlate these new data with psychiatric diagnoses, genetic risk, and other existing measurements from this cohort.

Disclosures: R.G. Fox: None. **B.A. Stevens:** F. Consulting Fees (e.g., advisory boards); Annexon Biosciences. **M.B. Johnson:** None.

Poster

732. Synaptogenesis and Activity-Dependent Development IV

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 732.13/A62

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: CB-254887

Title: Postnatal developmental functional changes between the retinohypothalamic tract and the suprachiasmatic nucleus of the rat

Authors: *M. E. REYES-MENDEZ[1], R. A. NAVARRO-POLANCO[2], E. G. MORENO-GALINDO[2], J. F. ALAMILLA[2];
[1]Ctr. Universitario de Investigaciones Biomedicas, Univ. of Colima, Colima, Mexico; [2]Ctr. Universitario de Investigaciones Biomedicas, Univ. de Colima, Colima, Mexico

Abstract: The suprachiasmatic nucleus (SCN) is the main circadian pacemaker in mammals that synchronizes several physiological processes to the environment light through the retinohypothalamic tract (RHT). Glutamate is released by RHT terminals towards SCN neurons to activate NMDA and AMPA-kainate receptors, which induces phase shifts. Previous behavioral and functional evidence indicates that rat pups are able to synchronize to the light at postnatal day (P) 6 - P8. In this work, we aimed to study the pre- and postsynaptic changes between the unmyelinated RHT-SCN connexions during the postnatal development. We carried out electrophysiological recordings in acute coronal hypothalamic slices of rat pups from three groups of age: P3-5, P7-9 and P13-18. Miniature NMDA and AMPA-kainate excitatory postsynaptic currents (EPSCs) exhibited an increase in their amplitude along postnatal development, indicating an increment of the presynaptic quantum. Also, in both NMDA and AMPA-kainate events there were a greater frequency at P13-18, suggesting presynaptic changes in the neurotransmitter release machinery. In addition, electrically evoked AMPA-kainate and NMDA components increased with age, although the rise was larger for the former. With paired-pulse stimulation, we found modifications in the short-term synaptic plasticity from *synaptic depression* to *synaptic facilitation* during postnatal development, and also changes in the readily releasable vesicle pool and in the probability of initial release. Taken together, our results showed developmental modifications in the unmyelinated RHT-SCN synapses, implying that synchronization to light at adult ages requires functional changes similar to those of myelinated fast communication systems.

Disclosures: M.E. Reyes-Mendez: None. **R.A. Navarro-Polanco:** None. **E.G. Moreno-Galindo:** None. **J.F. Alamilla:** None.

Poster

732. Synaptogenesis and Activity-Dependent Development IV

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 732.14/A63

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: Start-up grant from Truman State University

Title: Retrograde control of presynaptic development by postsynaptic calcineurin at the *drosophila* neuromuscular junction

Authors: L. LE[1], H. S. KESHISHIAN[3], ***B. A. BERKE**[2];
[2]Dept. of Biol., [1]Truman State Univ., Kirksville, MO; [3]MCDB Dept., Yale Univ., New Haven, CT

Abstract: Postsynaptic Ca can influence synaptic plasticity by activating downstream kinases and phosphatases. The activation of the Ca^{2+}/Calmodulin-dependent protein kinase II (CaMKII)

or the Ca^{2+}/Calmodulin-dependent phosphatase Calcineurin (Cn) lead to distinct effects on postsynaptic physiology. However, the retrograde transsynaptic effects of postsynaptic Ca signaling on the presynaptic terminal are less well understood. We examined this phenomenon at the glutamatergic *Drosophila* neuromuscular junction (NMJ). The postsynaptic bodywall muscles *Drosophila* larvae can be experimentally manipulated for gain or loss-of-function studies using a variety of mutations and transgenes. Moreover, the subsequent effects on the presynaptic NMJ can be readily visualized and quantified. Previous work has implicated CaMKII in the retrograde control of synaptic homeostasis, but a role for postsynaptic Cn and its complex interactions with CaMKII remain to be evaluated. Our data indicate that of the three isoforms of the Cn catalytic subunit in *Drosophila*, only Pp2B-14D (14D) influences presynaptic motoneuron growth in a retrograde fashion. Expression of RNAi transgenes against 14D increased the number of presynaptic boutons, while a constitutively-active transgene decreased bouton number. This bidirectional modulation of synaptic size was not accompanied by a change to postsynaptic glutamate receptors or retrograde BMP signaling, mechanisms known to influence presynaptic growth through retrograde, transsynaptic effects. In addition, the retrograde control of growth by 14D acted at a branch-specific level. We examined the ventral Common Exciter (vCE) motoneuron that innervates multiple ventral muscles, and transgenes affecting 14D were driven in distinct subsets of the vCE's postsynaptic targets. NMJ size was affected specifically at those branches opposite the affected muscle fibers, as compared to vCE's synapses on neighboring, non-manipulated muscles. We propose that an imbalance between postsynaptic, Ca-dependent phosphorylation (by CaMKII) and dephosophorylation (by Cn) may be a trigger for local, retrograde signaling. To directly test this, we expressed multiple transgenes in postsynaptic muscle fibers to increase CaMKII activity while simultaneously increasing the activity of Cn, and visa versa. These manipulations restored NMJ size to that of controls, suggesting that this pair of enzymes function as a toggle switch in postsynaptic muscles to influence motoneuron development at the fly NMJ.

Disclosures: L. Le: None. **H.S. Keshishian:** None. **B.A. Berke:** None.

Poster

732. Synaptogenesis and Activity-Dependent Development IV

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 732.15/A64

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: NIH Grant 5R01NS031651
NIH Grant 1R21NS053807

Title: Target-dependent signaling mediates synaptic plasticity at the *drosophila* neuromuscular junction

Authors: B. A. BERKE[1], L. LE[1], ***H. S. KESHISHIAN**[2];
[1]Biol. Sci., Truman State Univ., Kirksville, MO; [2]MCDB, Yale Univ., New Haven, CT

Abstract: Neurons typically innervate multiple targets, establishing synapses with varied strengths and expressions of synaptic plasticity. We examined the molecular-genetic mechanisms that allow a single motoneuron, the ventral Common Exciter (vCE) of *Drosophila*, to establish connections with distinct morphology and synaptic strength. By driving transgenes in a subset of vCE's muscle targets, we tested whether a postsynaptic cell could independently control presynaptic neuromuscular junction (NMJ) growth and physiology at its own vCE branch. In this system, postsynaptic glutamate receptor activity stimulates the release of a BMP4/5/6 homologue, Glass bottom boat (Gbb). As larvae mature and motoneuron terminals grow, Gbb facilitates presynaptic development by activating distinct pools of an R-Smad transcription factor (pMad): one in the motoneuron nucleus and another in presynaptic boutons. pMad regulates transcription within the nucleus, but its function in boutons is not fully understood. We find that postsynaptic manipulations of glutamate receptors or Gbb within subsets of target muscles leads to local effects that are mostly specific to the manipulated muscles and correlate with the presence/absence of presynaptic pMad. Specifically, RNAi knockdown of the dGluRC or dGluRIIA glutamate receptor subunits reduced quantal release at that contact and blocked the activity-dependent addition of boutons to that vCE branch. Adjacent vCE branches on unaltered muscles showed normal synaptic function and plasticity. The RNAi knockdown also resulted in the loss of presynaptic pMAD accumulation. To directly address a role for Gbb release in local synaptic plasticity, wild-type Gbb was expressed in a subset of vCE targets within a gbb mutant, which rescued synaptic function and plasticity only within local branches. Conversely, growth and plasticity were locally suppressed by an RNAi knockdown of Gbb, with vCE branches onto unaltered muscles remaining unaffected. pMAD therefore accumulates in presynaptic boutons due to Gbb release from the corresponding postsynaptic cell. Our results suggest that presynaptic pMad directs local growth and plasticity as part of a "synaptic tagging" mechanism, while nuclear pMad stimulates presynaptic development in a more global fashion.

Disclosures: B.A. Berke: None. **L. Le:** None. **H.S. Keshishian:** None.

Poster

733. Rett Syndrome: Molecular and Cellular Mechanisms

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 733.01/A65

Topic: A.07. Developmental Disorders

Support: Brain Mapping by Integrated Neurotechnologies for Disease Studies (Brain/MINDS) JP18dm0207002
NPO Rett Syndrome Supporting Organization

Title: Generation and analysis of MECP2 mutant marmosets

Authors: *N. KISHI[1,2], K. SATO[3], J. HATA[1,4], M. OKUNO[1], T. ITOU[1], J. OKAHARA[1,3], H. J. OKANO[1,4], E. SASAKI[1,3], H. OKANO[1,2];
[1]RIKEN CBS, Wako, Japan; [2]Keio Univ. Sch. of Med., Tokyo, Japan; [3]CIEA, Kawasaki, Japan; [4]Jikei Univ. Sch. of Med., Tokyo, Japan

Abstract: Our human brains are composed of structures conserved through evolution and those unique to primates. Recently-evolved brain structures involve the enlargement of the cerebral neocortex and provide essential substrates for acquisition of novel brain functions unique to primates, and eventually humans. Because of the unique structure and function of the primate brain, it is impossible to gain a full, accurate understanding of either normal human brain function or mental illness (neurological and psychiatric disorders) through rodent-based studies. Traditionally-used rats and mice only possess fundamental neuronal circuits conserved across mammalian species. Particularly, the primate prefrontal cortex is responsible for higher cognitive processes, and it contains vulnerable domains involved in some psychiatric disorders. The prefrontal cortex has no clear structural or functional homolog in rodents, which suggests advantages of using non-human primates to model human neurological and psychiatric diseases. The pathophysiology of human neurological and psychiatric diseases is not always recapitulated in genetically modified (GM) rodent models, possibly due to the differences in genome information, life span, and brain structure and functions between humans and rodents.
To overcome these issues, we are developing a technique for creating knockout marmosets using zinc finger nuclease (ZFN) and CRISPR/Cas9 technology. We created and are analyzing MECP2 mutant marmosets suitable for research on Rett syndrome. MRI imaging shows that the brain size of MECP2 +/- marmoset was smaller than wild-type ones by approximately 15% at 24 months of age, and less active than wild-type ones in the daytime. Furthermore, we also obtained MECP2-null marmosets, which have smaller brains and are less active even at early developmental stages. Those results indicate that those MECP2 mutant marmosets recapitulate symptoms of Rett syndrome.

Disclosures: N. Kishi: None. **K. Sato:** None. **J. Hata:** None. **M. Okuno:** None. **T. Itou:** None. **J. Okahara:** None. **H.J. Okano:** None. **E. Sasaki:** None. **H. Okano:** None.

Poster

733. Rett Syndrome: Molecular and Cellular Mechanisms

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 733.02/A66

Topic: A.07. Developmental Disorders

Title: FoxG1 controlled transcription in the mouse hippocampus

Authors: *T. VOGEL, D. O'HAILIN, C. HACKER, R. VEZZALI, S. HEIDRICH;
Albert-Ludwigs-University Freiburg, Freiburg, Germany

Abstract: FoxG1 syndrome is a severe neurodevelopmental disorder characterised by microcephaly and typically associated with intellectual impairment and autistic traits. Underlying this condition are mutations in the Forkhead box G1 (FOXG1) gene. A member of the forkhead box family of transcription factors, FOXG1 is involved in forebrain and telencephalon development, but both its mechanism of transcriptional control and its role in the adult hippocampus are yet to be elucidated. Our present study first employed ChIP-seq to map the distribution of FoxG1 on the chromatin landscape in an adult FOXG1-heterozygote mouse hippocampus model and discovered both shared and field-specific enrichment in the dentate gyrus (DG) and cornu ammonis (CA) regions. Peak enrichment frequently identified putative binding sites in promoter, intronic, and intergenic regions, suggesting multiple functions for FOXG1 in transcriptional control. RNA-seq and subsequent qRT-PCR validation in our FOXG1-heterzygous mouse model revealed a panel of differentially regulated neurodevelopment-associated transcripts which had been predicted on the chromatin level. As expected, the nature of FoxG1-mediated transcriptional regulation was region-dependent in a selection of identified genes. We found using a luciferase reporter assay for overexpressed FoxG1 and a truncated form bereft of the forkhead binding domain that FoxG1 might bind directly to the chromatin at some target genes, but might also act in complex with other transcription factors. Analysis of peak sequences in our ChIP-seq dataset reveals significant enrichment for other forkhead box family members as well as basic helix-loop-helix transcription factors, suggesting a synergistic and/or antagonistic function of FoxG1 within the transcriptional machinery. Manipulating these candidate co-factors by lentiviral knockdown will yield a greater understanding of the mechanism behind FoxG1's versatility in different regions of the hippocampus. Considering the memory deficits associated with hippocampal dysfunction in FoxG1 syndrome, unravelling novel molecular mechanisms for FoxG1 could highlight promising avenues of investigation for the benefit of patients and their treatment.

Disclosures: T. Vogel: None. **D. O'hAilin:** None. **C. hacker:** None. **R. Vezzali:** None. **S. Heidrich:** None.

Poster

733. Rett Syndrome: Molecular and Cellular Mechanisms

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 733.03/A67

Topic: A.07. Developmental Disorders

Support: NIH (5R01NS057819 to HYZ),
NIH 5U54 HD083092

Howard Hughes Medical Institute (HYZ)
the Rett Syndrome Research Trust
The 401 project

Title: Antisense oligonucleotide therapy in a humanized mouse model of MECP2 duplication syndrome

Authors: *Y. SHAO[1], Y. SZTAINBERG[1], P. JAFAR-NEJAD[2], F. RIGO[3], H. ZOGHBI[1]; [1]Howard Hughes Med. Inst. - Baylor Col. O, Houston, TX; [2]Neurosci. Drug Discovery, [3]Ionis Pharmaceuticals, Carlsbad, CA

Abstract: Many intellectual disability disorders are due to copy number variations, and to date there have been no treatment options tested for this class of diseases. *MECP2* duplication syndrome (MDS) is one of the most common genomic rearrangements in males and results from duplications spanning the methyl-CpG binding protein 2 (*MECP2*) gene locus. Previously, we have shown that antisense oligonucleotide (ASO) therapy can successfully reduce MeCP2 levels in an MDS mouse model and reverse the disease-like phenotypes. However, our previous MDS mouse model carried one transgenic human allele and one mouse allele, with the latter being protected from human specific *MECP2*-ASO targeting. In humans, the two *MECP2* alleles are identical and because MeCP2 is a dosage-sensitive protein, one must ensure that the ASO is titrated to target the human allele such that MeCP2 levels are reduced from 2X to 1X. Therefore, in preparation for clinically relevant studies, we characterized the effects of a human-specific *MECP2*-ASO in a new "humanized" mouse model of MDS, that carries two human *MECP2* alleles, and no mouse endogenous allele. We found that after intracerebroventricular injection in the cerebrospinal fluid, the *MECP2*-ASO efficiently downregulates MeCP2 expression throughout the brain. Moreover, *MECP2*-ASO can dose-dependently ameliorate several behavioral deficits without any dose-limiting toxic effect or safety concern. We also characterized the pharmacodynamic effect of the *MECP2*-ASO on MeCP2 and selected MeCP2-regulated genes during the duration of the treatment. Taken together, our results demonstrate that central nervous system administration of *MECP2*-ASO is well tolerated, has beneficial effects, and support a feasible translatable approach for the treatment of MDS.

Disclosures: Y. Shao: None. **Y. Sztainberg:** None. **P. Jafar-Nejad:** None. **F. Rigo:** None. **H. Zoghbi:** None.

Poster

733. Rett Syndrome: Molecular and Cellular Mechanisms

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 733.04/A68

Topic: A.07. Developmental Disorders

Support: NIH R01MH116582
NIH R01NS105200
NIH R01MH078972
NIH R56MH113146
NIH R21NS095632
NIH U54HD090256
International Rett Syndrome Foundation

Title: Loss of MeCP2 in immature neurons leads to impaired network integration

Authors: Y. SUN, Y. GAO, J. TIDEI, J. T. HOANG, D. P. WAGNER, ***X. ZHAO**;
Univ. of Wisconsin-Madison, Madison, WI

Abstract: Rett syndrome (RTT) is a neurodevelopmental disorder caused by mutations or deletions in Methyl-CpG-binding Protein 2 (MeCP2), a brain-enriched transcriptional regulator. MeCP2 is highly expressed during neuronal maturation and its deficiency results in impaired dendritic morphogenesis and reduced dendritic spine numbers in developing neurons. However, whether MeCP2 deficiency impacts the integration of new neurons has not been directly assessed. In this study, we developed a modified rabies virus-mediated monosynaptic retrograde tracing method to interrogate presynaptic integration of MeCP2-deficent new neurons born in the adult hippocampus, a region with lifelong neurogenesis and plasticity. We found that selective deletion of MeCP2 in adult-born new neurons impaired their long-range connectivity to the cortex, whereas their connectivity within the local hippocampal circuits or with subcortical regions was not significantly affected. We further showed that knockdown of MeCP2 in primary hippocampal neurons also resulted in reduced network integration. Interestingly, (1-3) IGF-1, a small peptide under clinical trial testing for RTT, rescued neuronal integration deficits of MeCP2-deficient neurons *in vitro* but not in *vivo*. In addition, (1-3) IGF treatment corrected aberrant excitability and network synchrony of MeCP2-deficient hippocampal neurons. Our results indicate that MeCP2 is essential for immature neurons to establish appropriate network connectivity.

Disclosures: Y. Sun: None. **Y. Gao:** None. **J. Tidei:** None. **J.T. Hoang:** None. **D.P. Wagner:** None. **X. Zhao:** None.

Poster

733. Rett Syndrome: Molecular and Cellular Mechanisms

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 733.05/A69

Topic: A.07. Developmental Disorders

Support: MDBR-18-106-CDKL5

IFCR-Giustetto2019

Title: CDKL5 deficiency disorder: A neuropathological study of postmortem human brains

Authors: S. GNAVI, R. PIZZO, A. GURGONE, *M. GIUSTETTO;
Dept. of Neurosci., Univ. of Torino, Turin, Italy

Abstract: The CDKL5 gene provides instructions for making a protein, a serine/threonine kinase, that is essential for normal brain development by regulating both the structural organization of dendritic spines and excitatory synapse function. CDKL5 deficiency disorder (CDD) is a rare X-linked genetic disorder that results in early-onset, difficult to control, seizures, severe intellectual disability, stereotypies, limited or absent speech, autism and sensory impairments. Clinical studies indicated that CDD patients show both visual and somatosensory deficits, as well as atypical electroencephalographic waveforms deriving from epileptic activity of the cerebral cortex. However, no anatomical, cellular or molecular evidences underlying these functional alterations are available from postmortem human brains. This lack of information severely hampers the development of effective therapeutic interventions, considering that, so far, no animal model of CDD has been able to model the epileptic seizures produced by CDKL5 mutations. It is thus imperative to explore the brain of CDD individuals to obtain any possible information about the causes of such severe epileptic activity with a level of resolution that surpasses available in-vivo examination approaches in patients. We will present both anatomical and molecular datasets from the cerebral cortex, hippocampus and cerebellum of two female CDD individuals (5 and 30 years), and age/sex-matched controls, made available by the Harvard Brain Tissue Resource Center and NIH NeuroBioBank, respectively. The analyses will assess the consequences of CDKL5 mutation on both the cyto-architecture and the structural and molecular organization of synapses in the human brain. Brain blocks from the indicated brain areas are currently processed with methods for best detection of both excitatory and inhibitory synaptic molecules and for their quantitative assessment. Immunofluorescence followed by confocal microscopy as well as western blotting analysis of synaptosomes preparation are being used to reveal both the localization and expression of synaptic molecules. Moreover, we will present data on the organization and maturation of perineuronal nets (PNNs) in CDD human cortices. PNNs are critical regulators of parvalbumin interneurons network activity that is crucially involved in seizures control. Our multilevel analysis, with inherent translational potential, will provide a high quality assessment of both CDKL5 function in the human brain and disease pathophysiology to expedite therapeutic development.

Disclosures: **S. Gnavi:** None. **R. Pizzo:** None. **A. Gurgone:** None. **M. Giustetto:** None.

Poster

733. Rett Syndrome: Molecular and Cellular Mechanisms

Location: Hall A

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Program #/Poster #: 733.06/DP01/A70

ControlExtraData.DynamicPosterDisplay:
Dynamic Poster
Topic: A.07. Developmental Disorders

Support: SFARI

Title: Developmental population-level differences of stem cell derived excitatory networks from SHANK2 ASD patients

Authors: *K. PRADEEPAN[1], J. MARTINEZ-TRUJILLO[1], J. ELLIS[2], R. MOK[3], F. MCCREADY[3];
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Abstract: Autism spectrum disorders (ASDs) are heterogenous group of neurodevelopmental disorders that have a strong genetic contribution to the etiology of the disease. Human genome wide association studies (GWAS) have identified numerous genetic variants across hundreds of loci that contribute to this complex genetic architecture. MECP2 and SHANK2 are two genes that have been associated with ASD in functional gene clusters that encode proteins critical to synapse homeostasis. Despite SHANK2 ASD resulting from SHANK2 haploinsufficiency in human cases, animal models have been inconsistent in displaying ASD phenotypes. Due to this inconsistency and to account for genetic background, human induced pluripotent stem cells (hIPSCs) have become employed as an alternative system to investigate complex neurodevelopmental disorders. Previous research from collaborators has shown that glutamatergic cortical neurons from hIPSCs derived from neurotypical and ASD-affected donors exhibited increases in dendritic length and complexity, synapse number, and frequency of spontaneous excitatory postsynaptic currents. Their results provide evidence for structural and functional hyperconnectivity in SHANK2 neurons of ASD patients. To explore whether these single neuron differences emerge to a differentiable population difference, multielectrode array (MEA; Axion Biosystems) technology was used. By culturing glutamatergic cortical neurons on a 12-well MEA plate across approximately 8 weeks of development, we observed how the fine spatial-temporal mapping of electrical activity around each of the electrodes in the 8-by-8 grid developed spontaneous networks and differentially developed between SHANK2 mutants and wildtype populations. To characterize this development, we used a population-level analysis to show that the network burst frequency of SHANK2 mutants exhibited a peak shift towards higher frequency along development whereas wildtype was maintained within lower frequencies.

A spike time tiling correlation was calculated between electrodes to investigate functional network connectivity, reflecting both structural and functional hyperconnectivity. Individual electrode burst characterization also analyzed to reveal how the dynamics within bursts differ between the different populations. With the rise of high-throughout recording techniques, neural activity data has grown exponentially. This population analysis has been used to take advantage of this when trying to understand how circuits between neural ensembles dynamically change in response to development due to various mutations. Additional neural data being analyzed.

Disclosures: K. Pradeepan: None. **J. Martinez-Trujillo:** None. **J. Ellis:** None. **R. Mok:** None. **F. McCready:** None.

Poster

733. Rett Syndrome: Molecular and Cellular Mechanisms

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 733.07/A71

Topic: A.07. Developmental Disorders

Support: DuPont Scholarship

Title: Characterizing mitochondria markers and activity in models of neurodevelopmental disorders

Authors: *L. A. NEAL[1], J. LARIMORE[2];
[2]Biol. Dept., [1]Agnes Scott Col., Atlanta, GA

Abstract: Mitochondria are eukaryotic organelles that execute a diverse range of functions including ATP synthesis through cellular respiration, regulation of cell metabolism, calcium buffering and regulation of programmed cell death or apoptosis. Studies have implicated mitochondrial dysfunction in neurodevelopmental disorders such as Rett Syndrome and Schizophrenia. Analysis of lymphomonocytes isolated from patients with Rett Syndrome indicate genes related to mitochondrial function are upregulated due to an increased bioenergetic need. Brains from patients with schizophrenia also demonstrate a decrease in mitochondrial activity, which may contribute to the cellular abnormalities in synaptic activity, vesicle trafficking, and neurite outgrowth. This study characterized mitochondrial markers in models of both RTT and SZ to provide novel insight into mitochondrial activity in both of these neurodevelopmental disorders.

Disclosures: L.A. Neal: None. **J. Larimore:** None.

Poster

733. Rett Syndrome: Molecular and Cellular Mechanisms

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 733.08/A72

Topic: A.07. Developmental Disorders

Support: NIH Grant 5T32GM007067
NIH Grant F31NS108574
Klingenstein-Simons Fellowship Fund Grant
G. Harold and Leila Y. Mathers Foundation Grant
Brain and Behavior Research Foundation Grant

Title: MeCP2 represses enhancers through chromosome topology-associated DNA methylation

Authors: A. W. CLEMENS, ***D. Y. WU**, G. ZHAO, H. W. GABEL;
Washington Univ. In St. Louis, St. Louis, MO

Abstract: The genomes of mammalian neurons contain uniquely high levels of non-CG DNA methylation that can be bound by the Rett syndrome protein, MeCP2, to regulate gene expression. How patterns of non-CG methylation are established in neurons and the mechanism by which this methylation works with MeCP2 to control gene expression is unclear. Here we find that genes repressed by MeCP2 are often located within megabase-scale regions of high non-CG methylation that correspond with topologically-associating domains of chromatin folding. MeCP2 represses enhancers that are found in these domains and are enriched for non-CG and CG methylation, with the strongest repression occurring for enhancers located within MeCP2-repressed genes. These alterations in enhancer activity provide a mechanism for how MeCP2 disruption in disease can lead to widespread changes in gene expression. Hence, we have found that DNA topology can shape non-CG DNA methylation across the genome to dictate MeCP2-mediated enhancer regulation in the brain. Current work in the lab is focused on experimental manipulations of mCA, DNMT3a, and enhancers, in order to test this model.

Disclosures: A.W. Clemens: None. **D.Y. Wu:** None. **G. Zhao:** None. **H.W. Gabel:** None.

Poster

733. Rett Syndrome: Molecular and Cellular Mechanisms

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 733.09/A73

Topic: A.07. Developmental Disorders

Support: MRC Grant MR/P006590/1

Title: Impaired hippocampal sharp-wave ripples in MeCP2 knock out mice

Authors: *N. W. JOHNSON, D. GOFFIN;
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Abstract: Methyl-CpG-binding protein 2 (MeCP2) binds to methylated cytosines where it regulates gene transcription. Mutations in the gene encoding MeCP2 are the leading cause of Rett syndrome, the second most common form of intellectual disability in females. Mice lacking MeCP2 exhibit deficits in learning and memory, synaptic connectivity and synaptic plasticity. Sharp-wave ripples (SPW-Rs) in the CA1 region of the hippocampus are important in memory formation and consolidation. We performed *in vivo* recordings using chronically implanted silicon probes to investigate whether of SPW-Rs were affected in hippocampus of MeCP2 knockout mice. We found that the loss of MeCP2 decreased the frequency and incidence of hippocampal SPW-Rs during non-REM sleep. The amplitude of SPW-Rs, however, were not affected. These changes were associated with a decrease in the firing probability of putative excitatory, but not inhibitory, neurons. These results suggest that MeCP2 is required for the proper generation of SPW-Rs. These findings may play an important role in the pathogenesis of learning and memory deficits observed in MeCP2-related neurodevelopmental disorders.

Disclosures: N.W. Johnson: None. **D. Goffin:** None.

Poster

733. Rett Syndrome: Molecular and Cellular Mechanisms

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 733.10/A74

Topic: A.07. Developmental Disorders

Support: IFCR-Giustetto2019
CRT-2018.0889
ASFR-Giustetto2017
Albero di Greta-Giustetto2018

Title: Early signs of CDKL5 deficiency disorder: Atypical barrel cortex connectivity precedes autistic features in mutant mice

Authors: A. RASPANTI[1], R. PIZZO[1], ***A. GURGONE**[1], C. PERNACI[3,4], A. MARCANTONI[2], M. GIUSTETTO[1];
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Neurol., [4]Dept. for BioMedical Res. (DBMR), Inselspital Univ. Hospital, Univ. of Bern, Bern, Switzerland

Abstract: Mutations of CDKL5 gene, coding for a serine/threonine kinase located on the X chromosome, are responsible for the onset of CDKL5 deficiency disorder (CDD), a rare neurodevelopmental disease with no cure. Clinical features of this pathology appear shortly after birth and include severe drug-resistant epilepsy, intellectual disability, strong sensory impairment (both in visual and somatosensory perception) characterized by a prominent hyposensitivity, in addition to autistic-like tendencies. Mounting evidence indicate that CDKL5 is a kinase involved in the formation and maturation of neurons, as well as in the organization of excitatory post-synapse. Less is known on the role of CDKL5 in the wiring and function of specific brain areas. This lack of information hampers both our understanding of CDKL5 function in the brain and the development of effective therapeutic interventions. To fill this gap, by using a multidisciplinary approach we investigate whether defects in thalamocortical (TC) connectivity, reaching the barrel cortex (BC), match the onset of sensorimotor impairments and autistic features in CDKL5 mutant mice. First, we revealed that the expression of c-Fos, a marker of neuronal activation, is robustly reduced in the BC of juvenile CDKL5 null mice at post-natal day (P) 15, indicating that an hypoactivation of the BC occurs right after the end of the critical period. The reduction of c-Fos^{+} cells is associated with atypical TC connectivity in mutant mice, as revealed by the strong decrease of vGluT2^{+} thalamic afferents conveying whiskers-mediated tactile information in layer IV of the BC. Remarkably, analysis of spontaneous firing of BC derived primary neuronal network, performed at three different in-vitro developmental stages (DIV7, DIV12 and DIV16), reveal a failure of network maturation in CDKL5 null cultures. Moreover, a battery of behavioral tests, strongly relying on whiskers function, show an atypical development of innate sensory-motor reflexes in CDKL5 null mice, including a strong impairment in the cliff avoidance test starting from P3 and detectable up to P15. Finally, when tested in the juvenile play and three-chamber sociability tests, P21 CDKL5 null mice show significative early-onset alterations of social responses. Our data disclose a novel role of CDKL5 in the early establishment and function of TC connectivity in the BC. These circuit alterations that are linked to the somatosensory and motor deficits shown by CDKL5 null mice that are likely to play a crucial role in the emergence of the autistic features associated with CDD.

Disclosures: A. Raspanti: None. **R. Pizzo:** None. **A. Gurgone:** None. **C. Pernaci:** None. **A. Marcantoni:** None. **M. Giustetto:** None.

Poster

733. Rett Syndrome: Molecular and Cellular Mechanisms

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 733.11/A75

Topic: A.07. Developmental Disorders

Support: NIH Grant MH085802

Title: Early molecular and cellular deficits in 3D cerebral organoid models of Rett syndrome

Authors: *V. A. PHAM[1], C. DELEPINE[1], H. W. S. TSANG[1], N. MORSHED[2], F. WHITE[2], M. SUR[1];
[1]Brain and Cognitive Sci., Picower Inst. for Learning and Memory, Massachusetts Inst. of Technol., Cambridge, MA; [2]Biol. Engin., David H. Koch Inst. for Integrative Cancer Research, Massachusetts Inst. of Technol., Cambridge, MA

Abstract: Rett Syndrome (RTT, OMIM 312750) is a pervasive, X-linked neurodevelopmental disorder that predominantly affects girls. With an incidence of 1:10 000-15 000, it is the second most common cause of severe intellectual disability in females after Down Syndrome. The vast majority of typical RTT cases is triggered by a sporadic mutation in the gene encoding methyl CpG-binding protein 2 (MeCP2). RTT is a progressive disorder, characterized by deficits that are prominently manifested by early childhood. Although most research has focused on symptomatic mice and humans, recent studies have shown that MeCP2 deficiency triggers molecular and cellular defects at very early stage of embryonic brain development. We used isogenic RTT patient-derived induced pluripotent stem cells to generate 3D human cerebral organoids to recapitulate these early developmental events and to better understand the molecular and cellular complexity that underlies RTT pathology. Previously, we showed that MeCP2 deficiency was associated with an increase in neural progenitor proliferation and concomitant decrease in neurogenesis and neuronal migration and maturation (Mellios et al., Molecular Psychiatry 2018). These data suggested that dysregulation of the AKT/ERK pathway due to MeCP2 deficiency were causal for the observed phenotype. In the current study, we have further investigated the molecular underpinnings of the deficits in neuronal migration observed in RTT organoids. Using transcriptomic, proteomic and phospho-proteomic techniques, we have interrogated the consequences of RTT MeCP2 mutations on molecular signaling pathways and found an associated increase in GSK3β-β-catenin signaling, downstream of AKT. Using fluorescent markers and immunostaining, combined with multi-photon microscopy and confocal microscopy, we find that, although the morphology and polarity of radial glial cells are mostly preserved, adhesion molecules are dysregulated and neuronal migration patterns are disturbed in RTT MeCP2 mutant organoids compared to isogenic controls. These findings confirm and further clarify the role and mechanisms of early deficits during cortical development in RTT.

Disclosures: V.A. Pham: None. **C. Delepine:** None. **H.W.S. Tsang:** None. **N. Morshed:** None. **F. White:** None. **M. Sur:** None.

Poster

733. Rett Syndrome: Molecular and Cellular Mechanisms

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 733.12/A76

Topic: A.07. Developmental Disorders

Support: Orphan Disease Center & Loulou Foundation
Caley J Brown Foundation
Rettsyndrome.org

Title: Targeted CRISPR/dCas9-mediated escape of CDKL5 from X-chromosome inactivation

Authors: *J. A. HALMAI[1], P. DENG[3], C. GONZALEZ[1], D. CAMERON[1], J. CARTER[1], J. WALDO[1], S. DEL CAMPO[1], F. BUCHANAN[1], D. SEGAL[3], J. NOLTA[2], K. FINK[1]; [1]Dept. of Neurol. and Stem Cell Program, [2]Stem Cell Program, UC Davis Med. Ctr., Sacramento, CA; [3]Genome Ctr., UC Davis, Davis, CA

Abstract: In the wake of genome engineering, rewriting of the epigenome has risen as a promising approach for precision medicine. This approach is even more relevant in tissues that traditionally have been more difficult to edit at the genomic level, such as neurons. Neurological diseases are a heterogeneous group of disorders caused by alterations in nervous system function and many of these disorders can be attributed to genetic factors such as chromosomal aberrations or gene mutations. The neurodevelopmental disorder *CDKL5* deficiency is caused by *de novo* mutations in the *CDKL5* gene on the X-chromosome. Due to random X-chromosome inactivation, females affected by the disorder form a mosaic of cells expressing mutant and wild type alleles. Our research is focused on methods to reactivate the healthy *CDKL5* allele on the silenced X-chromosome in human neuronal-like cell lines using CRISPR/dCas9 fused to epigenetic effector domains. Our group has been the first to identify proximal *cis* regulatory elements in the *CDKL5* core promoter for CRISPR/dCas9-mediated programmable transcription in the female neuronal-like cell line SH-SY5Y. Allele-specific qPCR and targeted RNA sequencing shows a significant increase in gene expression in stable SH-SY5Y cells treated with a VP64 trans-activator is predominantly due to superactivation of the active allele in combination with limited reactivation of the silenced allele. Epigenetic editing of the *CDKL5* core promoter using a dCas9-Tet1 fusion protein for targeted DNA demethylation results in a significant increase in reactivation of the inactive allele likely due to a significant reduction in methylated CpG diresidues as demonstrated by bisulfite sequencing. This approach can be further potentiated by a combinatorial approach of targeting VP64 and Tet1 synergistically to the same locus. In addition, our approach shows we can reduce the abundance of repressive histone marks that are normally associated with the inactive X chromatin in a manner that is confined exclusively to the reactivated escape allele. We then evaluated the level of specificity via RNA-

and ChIP-sequencing. In addition, we explored global changes in methylation status using EPIC-Chip. Further elucidating and understanding the epigenetics underlying X chromosome inactivation holds great potential for children suffering from *CDKL5* deficiency and other disorders with an X-linked dominant pattern of inheritance.

Disclosures: **J.A. Halmai:** None. **P. Deng:** None. **C. Gonzalez:** None. **D. Cameron:** None. **J. Carter:** None. **J. Waldo:** None. **S. Del Campo:** None. **F. Buchanan:** None. **D. Segal:** None. **J. Nolta:** None. **K. Fink:** None.

Poster

733. Rett Syndrome: Molecular and Cellular Mechanisms

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 733.13/A77

Topic: A.07. Developmental Disorders

Support: Rettsyndrome.org Grant #3211

Title: IGF1 signaling pathway defect in Rett syndrome models

Authors: *C. BILAGODY[1], A. SOGGE[2], L. LLACI[3], R. PANDEY[5], V. NARAYANAN[6], S. RANGASAMY[4];
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Abstract: Mutation in Methyl-CpG-Binding Protein 2 (MECP2, OMIM 300005) cause classical Rett syndrome (RTT) in females. MECP2 mutations have also been linked to severe encephalopathy in male infants, X-linked mental retardation, and other disorders such as autism spectrum disorder (ASD) and learning disabilities. RTT is characterized by neuropathological changes such as small neurons (reduced soma size), increased cell packing density, and decreased dendritic arborization. However, the mechanisms by which MECP2 mutation leads to these cellular and neurological phenotypes remain unknown. Emerging evidence also indicates that the mTOR pathway is dysfunctional in *Mecp2*-deficient mice and human embryonic stem cell-derived models of RTT. Currently IGF1, a tropical growth factor, is the only FDA approved therapy in Phase III trial for RTT. However, we do not know how IGF1 works in the Rett syndrome patients. The IGF1/PI3K pathway has been identified to regulate neuronal growth and activity through the Akt/mTOR pathway. Using murine *Mecp2* knockout (Mecp2tm1.1Bird mice) (KO) and *MeCP2 A140V* "knock-in" mutant (Mut) model we aimed to understand the connection between the IGF1 and the Akt/mTOR signaling pathway. Brain lysates from KO, Mut and wild type (WT) of six-week-old male mice were compared through RNA expression

and western blot analysis. Proteins of interest were chosen based on the IGF/Akt/mTOR network interaction. Analysis in *MeCP2 A140V* mutation identified moderate gene expression changes linked to IGF-1 pathway. Western analysis from A140V mice revealed alterations in mTOR phosphorylation including SGK1 defect compared to control mice. In *Mecp2* knock out mice, there was a significant downregulation of pS6, correlating to the reduced neuronal size seen in RTT. Interestingly, we found rescued phosphorylation of MAPK protein at both 42 and 44kDa, however without any alteration in the activation of IGFIRβ. These data suggest an intricate alteration of mTOR pathway in *Mecp2* models linked to the IGF1 pathway and in-depth understanding of this pathway in RTT may improve our ability to design better therapeutics.

Disclosures: C. Bilagody: None. **A. Sogge:** None. **L. Llaci:** None. **R. Pandey:** None. **V. Narayanan:** None. **S. Rangasamy:** None.

Poster

733. Rett Syndrome: Molecular and Cellular Mechanisms

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 733.14/A78

Topic: A.07. Developmental Disorders

Support: JSPS KAKENHI Grant 16J03827
JSPS KAKENHI Grant 16K18391
JSPS KAKENHI Grant 17H01390

Title: MeCP2-mediated miR-199a processing regulates fate specification of neural stem cells

Authors: *H. NAKASHIMA[1], K. TSUJIMURA[2], K. IRIE[3], T. IMAMURA[1], K. NAKASHIMA[1];
[1]Kyushu Univ., Fukuoka, Japan; [2]Nagoya Univ., Aichi, Japan; [3]Waseda Univ., Tokyo, Japan

Abstract: Rett syndrome (RTT) is a severe progressive neurodevelopmental disorder in females, mainly caused by mutations in the X-linked gene encoding methyl-CpG binding protein 2 (MeCP2). Although initial observations had suggested that RTT patients appear relatively normal at birth and during very early stages of development, increasing evidence suggests early developmental delays in RTT patients. Previously, we have found that MeCP2 regulates processing of specific microRNAs as a component of Drosha complex and identified miR-199a as a MeCP2 target. To understanding the role of MeCP2 in developing brain, we performed single-cell analysis of MeCP2 and miR-199a deficient hippocampus. We found that neuronal population was decreased and astrocytic population was increased in MeCP2 and miR-199a deficient hippocampus. According to these results, we hypothesized that abnormal neural stem cells (NSCs) differentiation was occurred in MeCP2 and miR-199a deficient NSCs.We examined whether MeCP2 and miR-199a is indeed implicated in the process of NSCs fate determination.

We first found that neuronal differentiation was suppressed and astrocytic differentiation was enhanced in MeCP2 and miR-199a deficient NSCs. We also observed that overexpression of miR-199a rescued abnormal differentiation of MeCP2 deficient NSCs, indicating that miR-199a acts downstream of MeCP2. Taken together, our findings suggest that MeCP2 plays an important role in fate determination of NSCs by post-transcriptionally processing of miR-199a.

Disclosures: H. Nakashima: None. **K. Tsujimura:** None. **K. Irie:** None. **T. Imamura:** None. **K. Nakashima:** None.

Poster

733. Rett Syndrome: Molecular and Cellular Mechanisms

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 733.15/A79

Topic: A.07. Developmental Disorders

Support: NIDCD R21 DC012447
The Rett syndrome Research Trust
the Sheryl and Daniel R. Tishman Charitable Foundation

Title: Atypical basic auditory processing in females with Rett syndrome could implicate effective speech comprehension

Authors: *T. BRIMA[1], S. MOLHOLM[2], E. NICHOLAS[1], A. DJUKIC[3], E. G. FREEDMAN[1], J. J. FOXE[1];
[1]Dept. of Neurosci. and The Del Monte Inst. for Neurosci., Univ. of Rochester Sch. of Med. and Dent., Rochester, NY; [2]Dept. of Pediatrics, The Cognitive Neurophysiol. Laboratory, Albert Einstein Col. of Med. & Montefiore Med. Ctr., Bronx, NY; [3]Rett Syndrome Ctr. Dept. of Neurol. Montefiore Med. Ctr. & Albert Einstein Col. of Med., Bronx, NY

Abstract: Rett Syndrome (RTT) is a non-inherited X-linked neurodevelopmental disorder accompanied by progressive loss of previously acquired intellectual, language and motor abilities. This decline renders behavioral assessment of cognitive function difficult, at best. As such, very little is known about cognitive processing, including perceptual capabilities and speech comprehension across the progressive clinical stages of RTT. High-density electrophysiological recordings allow for objective examination of sensory-perceptual and cognitive processing leading to more sensitive outcome measures against which to assess the effectiveness of disease-modifying therapeutic approaches currently in development. Here we characterize basic auditory responses in RTT using auditory evoked potentials (AEPs) in response to unpredictable changes in stimulus duration. AEPs were recorded in an auditory oddball task from 18 RTT and 27 age-matched typically developing (TD) controls (Ages: 6-22 years). This task consisted of regularly occurring standard tones (1 kHz; 100ms duration)

occasionally interrupted by deviant tones (1 kHz; 180ms). Intervals between stimuli were varied in blocks and were either 450ms, 900ms or 1800ms. This task allowed us to record large numbers of trials making it possible for detailed time frequency analysis on a trial to trial level for individual participants. Classical AEPs that changed as a function of stimulus duration were present for all presentation rates in TDs. In RTT, AEPs were strikingly atypical in morphology with reduced amplitude, pointing to impaired auditory processing. However, these AEPs changed as a function of stimulus duration suggesting preserved ability of basic auditory function to track with changes in stimulus duration. Outcomes from this study show that although participants with RTT produced AEPs to basic standard auditory stimuli that track with changes in stimulus duration, these responses reveal deficits that might impact effective speech comprehension.

Disclosures: **T. Brima:** None. **S. Molholm:** None. **E. Nicholas:** None. **A. Djukic:** None. **E.G. Freedman:** None. **J.J. Foxe:** None.

Poster

734. Neurodevelopmental Disorders: Molecular and Cellular Mechanisms

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 734.01/A80

Topic: A.07. Developmental Disorders

Support: R21GM8944
R01DK93501

Title: A novel role for the Na-K-2Cl cotransporter in metabolism

Authors: *S. OMER[1], R. KOUMANGOYE[1], E. DELPIRE[2];
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Abstract: The Na-K-Cl cotransporter-1, NKCC1, plays an important role in cell volume regulation. In the developing brain, studies have shown that during the perinatal period, NKCC1 facilitates the development of seizures due to its role in maintaining elevated $[Cl^-]_i$ and promoting excitatory γ-aminobutyric acid (GABA) responses. Recently we reported the first known human mutation in SLC12A2 the gene encoding NKCC1.The 17-year old patient has a complex syndrome which includes complete gastrointestinal and bladder failure; thyroid, parathyroid, and pancreatic insufficiencies; orthostatic intolerance. The patient carries a *de novo* mutation in SLC12A2. The 11 bp deletion resulted in a *non-functional* transporter. Laboratory tests conducted on the patient's muscle biopsy showed an abnormal increase in mitochondrial DNA copy number and increased glycogen levels, indicating the possibility that the transporter may play a role cell metabolism. In addition to observing an increase in mitochondrial density,

analyzed by fluorescent activated cell sorting (FACS), the patient fibroblasts also demonstrated significantly higher mitochondrial respiration, compared to control when analyzed by mitochondrial respiration stress tests. In addition, MDCK cells transfected with EGFP-tagged mutant NKCC1 also demonstrated higher mitochondrial respiration compared to cells expressing EGFP-tagged wild-type NKCC1. To further assess the role of NKCC1 in mitochondrial respiration, control MDCK cells were subjected to 20 uM bumetanide which led to increased mitochondrial respiration, compared to DMSO vehicle. Fibroblasts extracted from $NKCC1^{DFX/+}$ and $NKCC1^{DFX/DFX}$ mice also demonstrated a significant elevation in mitochondrial respiration, compared to fibroblasts isolated from wild-type littermates. Finally, mutant fibroblasts elicited an increase in mRNA transcript levels for protein involved in the unfolded protein response (UPR) pathway. These data reveal a novel role for NKCC1 in mitochondrial respiration and ER stress.Our data demonstrate that expression of a truncated Na-K-2Cl cotransporter causes increased oxygen consumption and up-regulated expression of genes involved in UPR. These data establish for the first time that NKCC1 plays a role in mitochondrial respiration and ER stress.

Disclosures: S. Omer: None. **R. Koumangoye:** None. **E. Delpire:** None.

Poster

734. Neurodevelopmental Disorders: Molecular and Cellular Mechanisms

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 734.02/A81

Topic: A.07. Developmental Disorders

Support: NRF-2014R1A2A1A11053289
2017R1D1A3B03033533
2016M3A9B6904244

Title: Propionic acid affects gene expression for mitochondria biogenesis and neuron differentiation in SH-SY5Y cell line

Authors: *S. A. KIM;
Eulji Univ., Daejeon, Korea, Republic of

Abstract: Propionic acid (PPA) shows neurotoxicity and behavioral abnormalities in several animal models. In this study, it was observed the reduction of mitochondrial potential with dose-dependent manner after PPA treatment in SH-SY5Y cells. In the electron microscopic analysis, the size of mitochondria was significantly reduced by the PPA treatment. A dose-dependent increase in mitochondrial DNA copy number and mitochondrial biogenesis related gene PGC1-α, TFAM, SIRT3 and mitochondrial COX4 were significantly increased at 5mM PPA treatment in SH-SY5Y. Transcriptome analysis were performed and the genes which were revealed more

than 2-fold difference in mRNA expression level were selected. Most of all, notch signaling related genes such as ASCL1 and LFNG were selected.

Disclosures: S.A. Kim: None.

Poster

734. Neurodevelopmental Disorders: Molecular and Cellular Mechanisms

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 734.03/A82

Topic: A.07. Developmental Disorders

Support: JSPS KAKENHI Grant Number 17K16292

Title: SON haploinsufficiency, a cause of human intellectual disabilities, affects the neuronal migrations and dendritic spine formations in the developing mouse brain

Authors: *M. UEDA, T. MATSUKI, S. EDA, A. NAKAYAMA;
Cell. Pathology, Aichi Developmental Disability Ctr. Inst. for Developmental Res., Kasugai, Japan

Abstract: SON, an RNA splicing co-factor protein, is involved in several cellular processes including transcription and cell-cycle regulations. However, the function of SON in the central nervous system is largely unknown. Previous studies revealed that 28 individuals with intellectual disability and developmental delay had *de novo* heterozygous loss-of-function (LoF) mutations in SON gene (*SON*). Neuroimaging examinations revealed most of affected individuals had brain malformations including polymicrogyria. SON expression is reduced in some tissues derived from patients, indicating that *de novo* LoF mutations of *SON* result in a haploinsufficiency. These results suggest that appropriate SON expression is important for normal brain development. This study has been carried out in order to clarify a role of SON in the brain formation during development. To examine the effects of SON-knockdown on mammalian brain development, we prepared shRNA constructs for the knockdown of mouse SON. We electroporated the shRNA constructs into the lateral ventricles of mouse brain at embryonic day 14 (E14), to address a role of SON in neuronal migration during brain development. Interestingly, neural progenitor cells in a SON-knockdown state did not effectively migrate to upper cortical plate at E18. The impairments of neuronal migrations were rescued by overexpression of human full-length SON, which is composed of 2,455 amino acids, but not with a disease-related truncation mutant (N-terminal 704 amino acids), lacking most functional domains. To investigate whether SON plays a role in dendritogenesis, we focused on analysis of dendritic spines in the postnatal cerebral cortex. At postnatal day 60, the numbers of the dendritic spines of layer II-III neurons in a SON-knockdown state were reduced compared with those in normal state. The impaired dendritic spine formation was rescued by overexpression of human

full-length SON. These data suggest that sufficient SON protein is critical to cortical neuronal migration and dendritic spine formations during development in mouse brain.

Disclosures: M. Ueda: None. **T. Matsuki:** None. **S. Eda:** None. **A. Nakayama:** None.

Poster

734. Neurodevelopmental Disorders: Molecular and Cellular Mechanisms

Location: Hall A

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Program #/Poster #: 734.04/A83

Topic: A.07. Developmental Disorders

Support: NIH Grant 5F30HD093285
NIH Grant 5R01NS099178

Title: Developmental iron deficiency alters TET methylcytosine dioxygenase activity and decreases global DNA hydroxymethylation in the rat cerebellum

Authors: *A. BARKS[1], P. V. TRAN[2], M. K. GEORGIEFF[2];
[1]Neurosci., [2]Pediatrics, Univ. of Minnesota, Minneapolis, MN

Abstract: Background: Iron deficiency (ID) during neurodevelopment is associated with lasting cognitive deficits and increased risk for neuropsychiatric dysfunction in humans and rodents. In rodent models, the deficits are associated with long-term gene dysregulation in the central nervous system that lasts into adulthood. The iron-dependent mechanisms that establish and maintain this gene dysregulation are incompletely understood. 5-hydroxymethylcytosine (5hmC), or DNA hydroxymethylation, is an epigenetic modification generated by TET methylcytosine dioxygenases. TETs require iron as a cofactor for their enzymatic activity. 5hmC is uniquely abundant in the brain, and is enriched in genes critical for neurodevelopment and neuronal function.
Objective: Determine the effect of a clinically relevant level ID on TET activity, *Tet* expression and DNA hydroxymethylation in the developing rat cerebellum.
Methods: Timed pregnant Sprague-Dawley rats were fed iron deficient diet (ID; 4 mg/kg Fe) starting at gestational day (G)2 to generate iron deficient anemic (IDA) offspring. Control dams were fed iron sufficient diet (IS; 200 mg/kg Fe). At postnatal day (P)7, a subset of ID-fed litters were randomized to IS diet, generating treated IDA (TIDA) offspring. All rats were euthanized at P15 and cerebellum was collected and flash frozen. Nuclear proteins were isolated from one-half cerebellum, and TET enzymatic activity was quantified by ELISA (n=5-10/group). RNA and DNA were isolated from one-quarter cerebellum. Expression of Tet1, Tet2, and Tet3 was quantified by qPCR (n=6-8/group). Global %5hmC was quantified by ELISA (n=6-10/group).
Results: Untreated P15 IDA cerebellum had decreased TET activity compared to IS controls ($p=0.03$), accompanied by decreased global %5hmC ($p<0.001$). *Tet* expression was not reduced

in the IDA cerebellum, suggesting that the decrease in %5hmC was likely due to a decrease in iron-dependent TET enzymatic activity. Treatment with iron at P7 corrected both the TET activity and the %5hmC deficits in TIDA cerebellum by P15, suggesting a mutable iron-dependent epigenetic mechanism.
Conclusions: Our results indicate that epigenetic dysregulation during neurodevelopment, through altered TET enzymatic activity, may play a role in the lasting CNS dysfunction associated with developmental ID. While the effect of IDA on global %5hmC appears to be reversible with iron repletion within this relatively short developmental time frame, it will be important to determine whether changes in 5hmC persist at the gene-specific level, and when the critical period for reversibility with iron treatment closes.

Disclosures: A. Barks: None. **P.V. Tran:** None. **M.K. Georgieff:** None.

Poster

734. Neurodevelopmental Disorders: Molecular and Cellular Mechanisms

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 734.05/A84

Topic: A.07. Developmental Disorders

Support: Medical Research Scotland
Aquila Biomedical

Title: Abnormal circadian rhythms in the hypothalamus in a mouse model of early life stress

Authors: *E. FITZGERALD, M. C. HOLMES, J. P. BOARDMAN, A. J. DRAKE;
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Abstract: Preterm birth is a leading cause of intellectual disability and is a major risk factor for neurodevelopmental disorders such as schizophrenia and autism spectrum disorders, but the underlying mechanisms are not fully understood. Abnormal circadian rhythms are a core feature of many neurodevelopmental disorders. Circadian rhythms are established in early postnatal life, a time which is associated with a high burden of environmental and physiological stress for infants born preterm (e.g. handling, pain, noise, sub-optimal nutrition and co-morbidities of preterm birth). We hypothesized that exposure to early life stress alters circadian rhythms in the hypothalamus during the neonatal period. We developed a novel model of early life stress in mice with relevance to preterm infants by modifying the traditional maternal separation paradigm to include manual gentle agitation. This was carried out for 2 hours per day for 3 consecutive days (postnatal day 5-7) in C57/Bl6 mice. Control littermates were left in the home cage, which was adjacent to the area of stress induction. Pups were weighed daily and were killed by decapitation at P7. Brains were dissected and divided at the midline, with half fixed for paraffin embedding and subsequent immunohistological evaluation. The other half was dissected

and snap frozen for transcriptome profiling using 3' mRNA sequencing and qPCR validation. Stressed pups gained weight at the same rate as control pups ($p=0.347$) and there was no difference in Iba1+($p=0.211$), GFAP+ ($p=0.867$) or Olig2+ ($p=0.855$) staining in the hypothalamus. The expression of several core circadian rhythm genes was altered in the hypothalamus of stressed pups, including Per1, Cry1 and NR1D1 (all $p<0.01$). Analysis of transcription factor binding enrichment implicated abnormal NFkB signalling (Fischer score=23.255), and genes involved in NFkB signalling were also differentially expressed (e.g. MyD88 and Nsfl1c: both $p<0.05$) in the hypothalamus of stressed pups. We also found altered expression of the DNA methyltransferase DNMT1 ($P<0.05$). In conclusion, early life stress leads to alterations in the expression of core circadian regulators in the hypothalamus. The altered expression of a key enzyme involved in the maintenance of DNA methylation suggests that epigenetic dysregulation could be one mechanism underpinning the disruption of circadian genes seen in this novel model of neonatal stress associated with preterm birth.

Disclosures: E. Fitzgerald: None. **M.C. Holmes:** None. **J.P. Boardman:** None. **A.J. Drake:** None.

Poster

734. Neurodevelopmental Disorders: Molecular and Cellular Mechanisms

Location: Hall A

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Title: Impact of cardiopulmonary bypass on postnatal SVZ neurogenesis and cortical maturation

Authors: *C. LEONETTI[1], Z. DHARI[1], L. KOROTCOVA[1], S. LIN[3], A. V. KOROTCOV[1], J. HOWICK[1], J. LI[1], P. C. WANG[3], R. A. JONAS[2], N. ISHIBASHI[1];
[1]Ctr. for Neurosci. Res. and Children's Natl. Heart Inst., [2]Children's Natl. Heart Inst., Children's Natl. Hlth. Syst., Washington, DC; [3]Dept. of Radiology, Howard Univ., Washington, DC

Abstract: Introduction: Many children with congenital heart disease (CHD) manifest various levels of neurodevelopmental impairments following cardiac surgery with cardiopulmonary bypass (CPB). The subventricular zone (SVZ) in the postnatal/adult brain is the region where

most neural stem/progenitor cells (NSPC) originate. Recent studies suggest that the SVZ plays an important role in neocortical growth of the gyrencephalic frontal lobe (FL) during postnatal life. However the effect of CPB-induced insults on postnatal SVZ neurogenesis is poorly understood. **Methods:** 3 week-old piglets were randomly assigned to control, mild-CPB (34°C full-flow, reproduces systemic inflammation) and severe-CPB insult groups (25°C circulatory-arrest, reproduces systemic inflammation with ischemia/reperfusion injury). Brains were fixed at day 3 or week 4 postoperatively. In the SVZ, we used GFAP and Sox2 to identify NSPCs, and DCX for neuroblasts. The SVZ was subdivided into three tiers, as previously described in humans, and into ventral and dorsolateral regions. In the FL, immunohistochemistry was performed in the upper and lower layers. NeuN and Tbr1 were used for mature and maturing neurons respectively, and PV, SST and CalR for subpopulations of interneurons. MRI images were analyzed to measure gyrification index (GI), fractional anisotropy (FA), total brain and cortical grey matter volumes. **Results:** Following CPB, there was a significant reduction in NSPC proliferation, $GFAP^+$ processes length, neuroblast density, and number and occupancy of neuroblast clusters. These results suggest reduced neurogenic activity in the SVZ and disruption of neuroblast migration and their contributions to FL maturation after CPB. These changes were observed 3 days and 4 weeks after surgery in both CPB groups, indicating prolonged impairment of postnatal SVZ neurogenesis. FL analysis by MRI revealed a decrease in GI and an increase in FA along with reduced cortical grey matter and total brain volumes 4 weeks after surgery. Histological analysis revealed a significant decrease of PV and SST interneuron density only in the severe group, and $Tbr1^+$ neurons in both groups. These results suggest prolonged FL dysmaturation induced by CPB. **Conclusion**: The frontal cortex is the region responsible for many higher-order cognitive functions; our results therefore provide novel insights into cellular mechanisms underlying complex neurological impairment in the CHD population. Designing new treatment aimed at restoration of SVZ neurogenic potential is required for improving cortical growth in children with CHD.

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Poster

734. Neurodevelopmental Disorders: Molecular and Cellular Mechanisms

Location: Hall A

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Program #/Poster #: 734.07/A86

Topic: A.07. Developmental Disorders

Support: Non-linear Neuro-oscillology Grant 15H05872

Title: Gad1 heterozygotes subjected to prenatal stress undergo epigenetic dysregulation of genes perturbing neurodevelopment and behavioral phenotypes

Authors: T. WANG[1], A. S. SINHA[1], H. MUTOH[1], T. AKITA[1], Y. YANAGAWA[2], T. KAWAI[3], K. HATA[3], *A. FUKUDA[1];
[1]Hamamatsu Univ. Sch. Med., Hamamatsu, Japan; [2]Gunma Univ. Grad. Sch. of Med., Maebashi, Japan; [3]Natl. Res. Inst. Child Hlth. Dev., Tokyo, Japan

Abstract: Exposure to prenatal stress (PS) and mutations in *Gad1*, which encodes the GABA synthesizing enzyme glutamate decarboxylase (GAD) 67, are both risk factors for psychiatric disorders. Using GAD67-GFP knock-in heterozygous (HT) mice subjected to PS from embryonic day 15.0 to 17.5, we previously reported disruption of GABAergic neurogenesis in the MGE. Postnatally, the density of parvalbumin (PV)-positive GABAergic interneurons was significantly decreased in the mPFC of HT-PS mice, which is a common trait shared by different psychiatric diseases. These results suggested that these two key genetic and environmental susceptibility factors could specifically disturb the proliferation of PV-positive neurons. By contrast, these findings were not observed in wild type offspring. In this study using a genetic risk factor (*Gad1* heterozygosity) with prenatal stress, an environmental risk factor, we evaluated effect on epigenetic programming and subsequent behavioral deficits. Our results indicated multiple genes functionally associated with neurogenesis and behavior were hyper- or hypo-methylated in HT-PS mice. Some differentially expressed genes detected by high-throughput microarray expression were strongly correlated to their altered epigenetic status as validated by real-time PCR. In addition, we examined the behavioral phenotypes and found that HT-PS mice demonstrated significant deficits in sensorimotor gating, cognitive processes, social engagement, without change in anxiety and exploratory behaviors. When assessing the function of interneurons in the mPFC of HT-PS, we found that inhibitory postsynaptic currents were altered and tonic inhibition was significantly enhanced. Finally, electrocorticogram recording showed reduction in power spectrum density at gamma-frequency range in mPFC of HT-PS mice, indicating GABAergic dysfunction could underlie the behavioral deficit. These findings may provide new insights into mechanisms of the pathogenesis of psychiatric disorders.

Disclosures: T. Wang: None. **A.S. Sinha:** None. **H. Mutoh:** None. **T. Akita:** None. **Y. Yanagawa:** None. **T. Kawai:** None. **K. Hata:** None. **A. Fukuda:** None.

Poster

734. Neurodevelopmental Disorders: Molecular and Cellular Mechanisms

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 734.08/B1

Topic: A.07. Developmental Disorders

Support: RF1AG057884

R56AG053491

Title: Sex differences in corticotropin releasing factor receptor 1 expression in the brain across the lifespan

Authors: *A. LOCCI, *Y. YAN, G. RODRIGUEZ, H. DONG;
Psychiatry and Behavioral Sci., Northwestern Univ. Feinberg Sch. of Med., Chicago, IL

Abstract: Corticotropin releasing factor (CRF)-mediated signal transduction represents a central neuroendocrine pathway in stress response. Emerging studies indicate that during the development, signaling through CRF1 exerts long lasting effects on the brain structure and function both in physiological conditions and following stress. However, studies on the distribution of CRF1 in the mouse brain are limited, and more comprehensive investigation of CRF1 brain distribution will enhance our understanding of the basis of stress-related neural circuitries. In humans, specific CRF1 polymorphisms have been linked to the onset of adult depression following early-life adversity. Moreover, deletion of CRFR1 results in differential effects on anxiety-like behavior in male and female mice. Overall, sex differences in expression and function of CRF and CRF1 and in response to stress may potentially contribute to the etiology of stress-related psychiatric disorders such as anxiety and depression both of which are more prevalent in women than men. Therefore, the aim of this study is to characterize CRF1 expression in the brain of C57BL/6J mice at different life stages, including postnatal day 7, 1, 6, 12 and 18 months of age, both males and females in normal condition as well as after 2-hour-restraint stress. We used western blot quantification to compare CRF1 expression in the brain sub-regions including cortex, hippocampus, amygdala and hypothalamus. Our preliminary results demonstrate that at postnatal day 7 females showed higher CRF1 expression than males in the amygdala and hypothalamus ($P<0.01$), but not in the cortex and hippocampus. Moreover, we observed a higher hippocampal and hypothalamic CRF1 expression in females compared to males at 6 months of age ($P<0.05$); in addition, CRF1 expression also showed a trend of increasing in the amygdala of females compared to males at 6 months without reaching a statistically significant effect. Finally, we found that CRF1 is more abundant in the hypothalamus and cortex of females than males at 18 months of age ($P<0.05$). We are continuing this work to confirm our preliminary findings and to determine how these differences impact on both males and females in response to acute and chronic stress. Taken together, our findings suggest that CRF1 expression in the brain sub-regions changes dynamically across the lifespan, with sex- and age-dependent manner. Sex differences in the CRF1 expression and functioning may contribute to the etiology of stress-related neuropsychiatric disorders such as depression and Alzheimer's disease which are characterized by specific gender prevalence.

Disclosures: **A. Locci:** None. **Y. Yan:** None. **G. Rodriguez:** None. **H. Dong:** None.

Poster

734. Neurodevelopmental Disorders: Molecular and Cellular Mechanisms

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 734.09/B2

Topic: A.07. Developmental Disorders

Support: NIH Grant DK095908
NIH Grant MH096050

Title: Dio3 deficiency alters the daily profile of serum glucocorticoids and circadian gene expression patterns in a sexually dimorphic fashion

Authors: *Z. WU, A. HERNANDEZ;
MMCRI, Scarborough, ME

Abstract: *Dio3* is an imprinted gene that inactivates thyroid hormones. Previous studies have shown that cerebro-cortical and adrenal *Dio3* is expressed in a diurnal pattern, and that DIO3 deficiency in mice lengthened the periods of daily physical activity. We aimed to examine the role of *Dio3* in the regulation of circadian rhythms. We used 3-month old Dio3KO mice and wild type (WT) littermates to determine daily variations in: (i) Physical activity in metabolic cages with or without running wheels; (ii) Serum levels of glucocorticoids; (iii) Tissue expression levels of circadian genes. Metabolic cages data from Dio3KO males showed prolonged night-time activity with running wheels, but no changes in day/night walking time and walking distances. Female Dio3KO mice showed decreases in both wheel running and pedal walking distances compared to WT controls. The normal rise in serum corticosterone at the start of the dark cycle was absent in Dio3KO females, but was not altered in Dio3KO males. DIO3 deficiency also resulted in sexually-dimorphic changes in the hypothalamic expression of circadian genes. Expression of *Clock, Per1, per2, Dbp, Rora, and Cry2* at 18:00 h was significantly decreased in male KO mice, while expression of *Per2, Dbp and Rora* at 6:00 was increased in female KO mice. *Dio2*, which increases local thyroid hormone action, showed a circadian profile in WT males but not females, with elevated expression during the dark cycle. DIO3 deficiency resulted in significantly decreased *Dio2* expression in males at 18:00 h only, and a significant increased in females at 6:00 h. In WT females, *Dio3* expression showed a 12-fold elevation at 18:00, but this was not observed in WT males, who exhibited a significant trough in *Dio3* expression at 00:00 h. DIO3 deficiency resulted in *Dio3* expression being elevated at 6:00 h in females and at 00:00 h in males. The expression of *Hairless* (*Hr*), a gene highly sensitive to thyroid hormone, was elevated in Dio3KO females at 00:00 and 6:00 h, while in males it was reduced at 18:00 h and slightly increased at 6:00 h. These results suggest that the changes in circadian activity associated with DIO3 deficiency may be mediated through thyroid hormone-dependent regulation of circadian genes and/or abnormalities in the circadian variations

of circulating glucocorticoids. Overall, our study indicates that *Dio3* and local control of thyroid hormone action contribute to the normal circadian physical activity, the regulation of the adrenal axis and the hypothalamic expression of clock genes in a sexually dimorphic manner.

Disclosures: Z. Wu: None. **A. Hernandez:** None.

Poster

734. Neurodevelopmental Disorders: Molecular and Cellular Mechanisms

Location: Hall A

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Topic: A.07. Developmental Disorders

Support: Intramural Research Program of the National Institutes of Health, NICHD
DFG LI 2044/4-1
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NS034007
NS047384
HD08201

Title: hIPSC-derived neurons from MEHMO syndrome patients exhibit altered dendritic morphology that is rescued by the small molecule ISRIB

Authors: *M. K. ELDER[1], S. K. YOUNG-BAIRD[2], T. E. DEVER[2], E. KLANN[1];
[1]Ctr. for Neural Sci., New York Univ., New York City, NY; [2]NICHD, NIH, Bethesda, MD

Abstract: Dysregulation of protein synthesis results in catastrophic consequences for the functioning of cells, and as such, has been linked to a wide range of human diseases. Recent studies of the rare X-linked intellectual disability disorder MEHMO syndrome has revealed underlying mutations in *EIF2S3*, which encodes the γ subunit of the heterotrimeric translation initiation factor eIF2. This subunit plays a crucial role in the translation initiation pathway, and while previous studies have determined that MEHMO-linked mutations affect the formation of the ternary initiation complex in yeast, the effect of these mutations on neuronal morphology has not been investigated.
Human induced pluripotent stem cells (hIPSCs) expressing either the MEHMO mutation eIF2γ-I465Sfs*4 C-terminal frameshift or wild-type eIF2γ were differentiated to cortical neurons using regulated neurogenin-2 expression. The complexity of the dendritic arbor was evaluated using immunofluorescent detection of MAP2, and branching complexity was measured using Sholl analysis. Although the mutation had no effect on somatic size, the number of dendrites and level of branching was significantly impaired. Intriguingly, differentiation and culturing of these cells in the presence of ISRIB, which has previously been shown to suppress phenotypes associated with *EIF2B* mutations in Vanishing White Matter disease, rescued the phenotype and restored

branching complexity to WT levels.
These findings show for the first time that the eIF2γ-I465Sfs*4 C-terminal frameshift mutation found in MEHMO syndrome results in severely impaired dendritic branching. The rescue of such striking neuronal phenotypes with ISRIB suggest that it, or a related compound, could be of benefit for treatment of individuals with MEHMO syndrome in the future.

Disclosures: M.K. Elder: None. **S.K. Young-Baird:** None. **T.E. Dever:** None. **E. Klann:** None.

Poster

734. Neurodevelopmental Disorders: Molecular and Cellular Mechanisms

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 734.11/B4

Topic: A.07. Developmental Disorders

Support: Shriners Hospital for Children 85220-NCA-14
Shriners Hospital for Children 84306-NCAL
NSF 1754340
NIH R01NS073055

Title: Folate receptor 1 regulates neural plate cell apical constriction during neural tube formation via interacting with CD2-associated protein

Authors: O. A. BALASHOVA, *L. N. BORODINSKY;
Shriners Hosp. for Children, Univ. of California Davis, Sacramento, CA

Abstract: Neural tube defects (NTDs) are one of the most common serious birth defects diagnosed with an incidence of ~1/1,000. Clinical studies have established that folate is a prominent environmental factor needed for appropriate neural tube closure. Our study focuses on identifying the cellular and molecular mechanisms of folate action during neural tube formation. Previously we found that knockdown of folate receptor 1 (FOLR1) impairs neural tube formation and leads to NTDs. FOLR1-deficient neural plate cells fail to apically constrict and are defective in endocytosis-mediated cadherin trafficking from apical adherens junctions. Further investigation of C-cadherin endocytosis implies that this process is ubiquitination-dependent and involves proteolytical cleavage of C-cadherin.
We carried out proteomics studies through Mass Spectrometry analysis to identify the molecular partners of FOLR1 in the prospective folate-triggered signaling pathway regulating neural plate cell apical constriction during neurulation. Proteins interacting with FOLR1 include signaling molecules, regulators of actin and microtubule dynamics and ubiquitination-related proteins. We screened among FOLR1-interacting candidates for proteins with apical localization in superficial neural plate cells and found that CD2-associated protein (CD2AP) is localized to the

apical pole of neural plate cells during apical constriction. CD2AP is a scaffolding protein that regulates cytoskeletal rearrangements and protein trafficking. In non-neural tissues CD2AP mediates ubiquitination-dependent endocytosis of transmembrane proteins through its association with the ubiquitin E3 ligase c-Cbl. Knockdown of CD2AP protein by morpholinos results in NTDs. Moreover, similarly to FOLR1 downregulation, knockdown of CD2AP perturbs neural tube formation via disruption of neural plate cell apical constriction. In addition, we found that protein ligase c-Cbl localizes along with FOLR1 and CD2AP to the apical membrane of superficial neural plate cells.
Altogether these data suggest that FOLR1 and CD2AP are involved in the same molecular pathway necessary for neural tube morphogenesis.

Disclosures: O.A. Balashova: None. **L.N. Borodinsky:** None.

Poster

734. Neurodevelopmental Disorders: Molecular and Cellular Mechanisms

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 734.12/B5

Topic: A.07. Developmental Disorders

Title: Overexpression of neuroinflammatory gene sets in postmortem autism but not MDD cortex

Authors: *K. A. YOUNG[1], A.-V. V. NGUYEN[2], H. K. YOUNG[2], P. J. TANSEY[2], M. M. MARZIALE[2], J. A. BOURGEOIS[3];
[1]Psychiatry, CTVHCS, TAMUHSC and BSWH, Temple, TX; [3]Psychiatry, [2]BSWH and TAMUHSC, Temple, TX

Abstract: Neuroinflammatory mechanisms have been proposed to mediate behavioral deficits in neurodevelopmental disorders such as autism and in mood disorders such as major depression (MDD). We interrogated differentially expressed microarray gene (DEG) sets from the cortex to compare and contrast processes that may be impacted in MDD and autism using the gene set enrichment analysis (GSEA) platform. Autism (N=50) and MDD (N=87) cases were compared to separate groups of age and gender matched controls (Gandal et al., 2018, PMID:29439242). Both interneuron and pyramidal neuron-specific gene sets were underexpressed in autism, but only interneurons were down-regulated in MDD. Astrocyte-specific genes were highly up-regulated in autism (FDR q< 0.0001) but were not differentially expressed in MDD (NS). Gene transcripts up-regulated in rodent models of middle coronary artery occlusion and LPS-induced astrogliosis (N=199; Zamanian et al., 2012 PMID:22553043) were selectively up-regulated in autism (FDR q<0.0001) compared to MDD (NS). We noted that GFAP was among the most robustly up-regulated gliosis transcripts in autism (#3/199); this transcript was not differentially regulated in MDD cortex. Microglial transcripts were similarly overexpressed in autism, but this

gene set was significantly *down*-regulated in MDD (FDR q<0.02). Toll-like receptors, which detect pathogen and host inflammatory signals in the CNS, were overexpressed in autism (FDR q<0.005) but were not differentially regulated in MDD (NS). Although neuroinflammation has been previously implicated in autism, microglial pathology has been emphasized. The present analysis suggests that additional studies of classical reactive astrocyte responses to neuroinflammation may be warranted to better characterize apparently robust neuroinflammatory proceses in autism. In contrast, while neuroinflammation has also been proposed to play a role MDD cortical pathophysiology, the present study suggests that reactive astrogliosis, microglial proliferation and inflammatory signalling by toll-like receptors may not be prominent participants in MDD cortical pathology.

Disclosures: K.A. Young: None. **A.V. Nguyen:** None. **H.K. Young:** None. **P.J. Tansey:** None. **M.M. Marziale:** None. **J.A. Bourgeois:** None.

Poster

734. Neurodevelopmental Disorders: Molecular and Cellular Mechanisms

Location: Hall A

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Program #/Poster #: 734.13/B6

Topic: A.07. Developmental Disorders

Support: NRF-2018M3C7A1024152
NRF-2017R1D1A1B03029997
10Z20130012243

Title: Investigating mitochondrial dynamic change caused by domain-specific missense mutations in DNM1L associated with a varying degree of neurological phenotypes in patients

Authors: *K. SO[1], S. BAEK[2];
[1]Div. of Integrative Biosci. and Biotech., [2]Div. of Integrative Biosci. and Biotechnology, Dept. of Life Sci., POSTECH, Pohang, Korea, Republic of

Abstract: Mitochondrial dynamics, including mitochondrial fission and fusion, plays an essential role in neurodevelopment. *DNM1L* encodes a dynamin-related GTPase which functions in mitochondrial and peroxisomal fission. Pathogenic mutations affecting different domains of *DNM1L* are associated with a wide range of neurological phenotypes from relatively mild optic atrophy to neonatal lethality. However, the underlying molecular mechanisms of genotype-phenotype correlation is not well studied. Using induced pluripotency stem cell (iPSC)-derived neural progenitor cell (NPC), we aim to investigate the neurodevelopmental function of *DNM1L* variants. We will knock out the endogenous *DNM1L* gene via CRISPR/Cas9, overexpress the *DNM1L* variants by lentiviral delivery and observe mitochondrial dynamics change in

differentiated NPCs. Our work may help to expand the comprehension of *DNM1L*-related diseases thus to develop targeted therapy.

Disclosures: K. So: None. **S. Baek:** None.

Poster

734. Neurodevelopmental Disorders: Molecular and Cellular Mechanisms

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Topic: A.07. Developmental Disorders

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Nellie Ball Trust
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Elizabeth Ring Mather & William Gwinn Mather Fund
S. Livingston Samuel Mather Trust
University of Iowa Graduate College Post-Comprehensive Research Fellowship

Title: Protective efficacy of P7C3 compounds in a mouse model for the study of perinatal depression

Authors: *R. SCHROEDER[1], L. NGUYEN[2], A. A. PIEPER[3], H. E. STEVENS[1];
[1]Univ. of Iowa, Iowa City, IA; [2]Grinnell Col., Grinnell, IA; [3]Psychiatry, Univ. Hosp., Cleveland, OH

Abstract: Depression during pregnancy is difficult to treat, as both depression and its currently available pharmacologic treatments may impair offspring embryonic neurodevelopment. Therefore, new, safe, and effective treatments for antenatal depression are needed. P7C3 compounds rescue depressive-like phenotypes in multiple animal models. Additionally, when administered to dams during gestation and nursing, no apparent negative impacts on embryonic or early postnatal development are observed. We hypothesize that P7C3 compounds will rescue maternal depressive-like behavior in an animal model for the study of stress-induced depression, while maintaining normal offspring neurodevelopment and preventing maternal neurobiological deficits. To test this, pregnant CD1 dams underwent restraint stress in 45-minute sessions 3x daily. Concurrently, P7C3 compounds or vehicle was administered via oral gavage twice daily. Outcomes were assessed after non-stressed or stress conditions either with or without P7C3 compound administration in two protocols: prolonged (starting on embryonic day (E) 5), and brief (starting on E12). In two independent cohorts, we assessed anxiety- and depressive-like behaviors in dams during pregnancy (E17) and postpartum day 7. Open field, elevated plus maze, tail suspension, and forced swim tests were used to measure chronic stress-induced behavior changes and investigate a potential rescue by P7C3 compounds. In E14 offspring

embryonic brain, we examined a known prenatal-stress induced deficit, GABAergic progenitor migration delay measuring GAD67GFP+ cell distribution in developing cortical plate. We also tested adult offspring on a battery of behavioral assays, including open field, elevated plus maze, tail suspension test, forced swim test, pre-pulse inhibition, rotarod, and context-dependent fear conditioning. We then assessed their brains for GAD67GFP+ cell distribution. Our preliminary data show that chronic stress caused behavioral changes in pregnant and postpartum dams. and Rescue experiments demonstrated that P7C3 compound administration corrected the embryonic GABAergic migration deficit induced by prenatal stress. These results support the feasibility of P7C3 compounds as a treatment for maternal antenatal depression that protects offspring neurodevelopment.

Disclosures: R. Schroeder: None. **L. Nguyen:** None. **A.A. Pieper:** None. **H.E. Stevens:** None.

Poster

734. Neurodevelopmental Disorders: Molecular and Cellular Mechanisms

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Program #/Poster #: 734.15/B8

Topic: A.07. Developmental Disorders

Support: NIH 5R01GM110373

Title: SEC24D is required for collagen processing and neural development

Authors: M. POPPENS[1], ***J. T. CAIN**[1], R. LAUFMANN[1], S. DAVIS[1], C.-L. LU[2], J. KIM[2], J. WEIMER[1];
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Abstract: Cranio-lenticulo-sutural-dysplasia (CLSD) is a disorder that manifests with craniofacial and skeletal defects as well as neural deficits. CLSD is caused by perturbations in collagen transport and secretion resulting from loss of SEC23A. SEC23A is required for COPII vesicle assembly, and more specifically assembly of COPII megavesicles for the transportation and secretion of collagen. Procollagen forms 300nm-long rigid rods, which cannot be packaged is standard 60nm COPII vesicles and require specialized COPII vesicles for packaging. Loss of SEC23A disrupts COPII-collagen megavesicle formation resulting in decreased collagen secretion and increased cellular accumulation of collagen. Recently, a patient was diagnosed with CLSD linked to a mutation in the SEC24D gene. Here we show that *Sec24d* is also necessary for the packaging, transport, and secretion of collagen in *COPII* megavesicles. Loss of *Sec24d* function results in craniofacial defects and embryonic lethality in mice. Loss of *Sec24d* in fibroblasts results in altered procollagen processing, decreased secretion of collagen, and increased accumulation of collagen in the cell.

Disclosures: **M. Poppens:** None. **J.T. Cain:** None. **R. Laufmann:** None. **S. Davis:** None. **C. Lu:** None. **J. Kim:** None. **J. Weimer:** None.

Poster

734. Neurodevelopmental Disorders: Molecular and Cellular Mechanisms

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 734.16/B9

Topic: A.07. Developmental Disorders

Support: NIH Grant T32HL007627

Title: A role for mitochondrial trafficking and localization in cortical interneuron migration

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Abstract: Normal cerebral cortical development requires the orderly migration of excitatory neurons (ENs) and inhibitory neurons (INs) into defined laminae. Perturbations in EN or IN migration and final cortical positioning underlies some defects in cerebral cortex circuit formation and some forms of epilepsy. Our lab has discovered that defects to oxidative phosphorylation, a mitochondrial ATP producing pathway, disrupts early IN migration but not EN migration. Additionally, our previously published data suggest INs localize mitochondria more dynamically than ENs which could make them sensitive to defects in mitochondrial trafficking. Mitochondrial transport is mediated by the trafficking proteins Miro and Trak, with Miro recruiting Trak (Milton) proteins to link mitochondria to molecular motors, thus allowing for microtubule- and actin-dependent movement. Interestingly, mutations in MIRO1 or TRAK1 proteins are associated with epilepsy. In this study, we assessed the necessity of Miro1 in neuronal migration. Using *ex vivo* electroporation to label mitochondria in excitatory or inhibitory neuron progenitors of embryonic day (E) 14.5 mouse brains, we expressed knockdown plasmids for Miro1 to disrupt mitochondrial trafficking and assessed the impact on EN and IN migration. Our data indicate that ENs and INs have similar but distinct patterns of mitochondrial localization. Mitochondria in ENs predominately localize anterior to the cell body. In contrast, mitochondria are highly dynamic as INs migrate, moving from the rear of the cell to the leading process and back. Further, our data suggests that knockdown of Miro1 disrupts mitochondrial trafficking and specifically perturbs inhibitory neuron migration, branching dynamics, and mitochondrial localization. Currently, the connection between mitochondria localization and neuronal migration is poorly studied. Our data indicate that impaired mitochondrial localization may impact embryonic brain development, specifically neuronal migration. By elucidating the mechanisms necessary for proper mitochondrial trafficking during IN migration and the

consequences of its dysfunction, we expect to define new pathways that may lead to treatment or prevention of mitochondria-related epileptic disorders.

Disclosures: A.K. Myers: None. **G. Cho:** None. **J.A. Golden:** None.

Poster

734. Neurodevelopmental Disorders: Molecular and Cellular Mechanisms

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Topic: A.07. Developmental Disorders

Support: NIH Grant MH113352
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Jordan's Guardian Angels
Roy J. Carver Charitable Trust

Title: Novel *de novo* mutations in the PP2A regulatory subunit PPP2R2B causing neurodevelopmental disorders

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Abstract: Serine/threonine protein phosphatase 2A (PP2A), is a heterotrimeric protein comprised of a conserved scaffold A subunit, catalytic C subunit, and a variable regulatory B subunit. The regulatory subunit determines PP2A substrate specificity and subcellular localization. Mutations in PPP2R2B, one of twelve regulatory subunit genes is mammals, causes spinocerebellar ataxia 12 (SCA12), a rare neurodegenerative disorder. PPP2R2B encodes neuron specific and alternatively spliced cytosolic Bβ1 and mitochondria-targeted Bβ2 splice variants. The N-terminal mitochondrial targeting sequence of Bβ2 recruits it to the outer mitochondrial membrane (OMM) and induces mitochondria fragmentation and increases susceptibility to neuronal insults. Furthermore, a mouse knockout (KO) of Bβ2 shows elongated mitochondria and neuroprotection. Recently, Hamdan et al. performed whole exome sequencing on severe to moderate intellectually disabled patients and identified a possibly damaging de novo missense mutation, Arg138Pro, in the PPP2R2B gene in one patient. The patient suffered from intellectual disability (ID), intractable seizures and autistic features. A different, as yet unpublished *de novo* missense mutation was identified in a patient from New Zealand, who presents with microcephaly, cerebellar atrophy and spastic diplegia. We generated and expressed these mutations by itself and in complex with A subunit in mammalian HEK cells and initial co-immunoprecipitation experiments indicate that these mutations do not affect holoenzyme assembly. We have previously shown that under cellular stress, Bβ2 rapidly translocates to

mitochondria to promote apoptosis. In order to understand the effect of these mutations, we studied the co-localization of these mutants in Hela cells and do not see any significant difference in mitochondrial localization between these mutants and the wildtype Bβ2. We are further investigating the effect of these mutations on mitochondrial shape and localization by expressing them in hippocampal neurons. We are also generating stable mammalian cell lines to identify cellular substrates by phospho-proteomics.

Disclosures: P. Sandal: None. **Y. Kong:** None. **L. Bicknell:** None. **S. Strack:** None.

Poster

734. Neurodevelopmental Disorders: Molecular and Cellular Mechanisms

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 734.18/B11

Topic: A.07. Developmental Disorders

Support: NIH Grant NS097537

Title: Cortical GABAergic interneurons require ERK/MAPK for postnatal maturation and function

Authors: *M. HOLTER[1], N. R. FRY[2], G. R. BJORKLUND[3], J. S. MARTINEZ[1], K. NISHIMURA[5], J. NICHOLS[6], T. R. ANDERSON[7], J. NEWBERN[4];
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Abstract: The canonical RAS/RAF/MEK/ERK (ERK/MAPK) pathway is a highly conserved signaling cascade, the components of which have differential expression in numerous cell types. ERK/MAPK signaling is dynamic throughout neurodevelopment and present at varying levels in neuron subtypes. Consequently, dysregulated ERK/MAPK is involved in numerous neurodevelopmental syndromes, including the RASopathies and some genetic forms of Autism Spectrum Disorder (ASD). Both gain- and loss-of-function signaling through ERK/MAPK have been observed in the RASopathies and ASD. How reduced ERK/MAPK signaling affects the development and basic function of cortical neuronal subtypes such as GABAergic interneurons has not been determined. Here, we generated quadruple transgenic mutant mice to specifically delete the principal ERK/MAPK components *Mapk3/Erk1* (*Erk1*$^{-/-}$) and *Mapk1/Erk2* (*Erk2*$^{fl/fl}$) using Slc32A1:Cre or Nkx2.1:Cre from GABAergic interneurons endogenously labeled with the Cre-dependent Ai9 reporter. We determined that ERK/MAPK is not required to establish cortical GABAergic interneuron number, but is necessary for the expression of SST, a key genetic marker of approximately 30% of all cortical interneurons. Preliminary evidence suggests altered

excitatory drive onto GABAergic interneurons in *Erk1*$^{-/-}$ *Erk2*$^{fl/fl}$ Nkx2.1:Cre mutants during the second postnatal week. To determine if these physiological abnormalities were due to altered interneuron morphology, we injected a Cre-dependent AAV2/9-CAG-GFP into the neonatal somatosensory cortex to examine interneuron dendritic complexity. Due to well established roles of ERK/MAPK in activity-dependent development, we asked whether chemogenetic stimulation of GABAergic circuitry in adulthood was sufficient to rescue interneuron phenotypes in *Erk1*$^{-/-}$ *Erk2*$^{fl/fl}$ Nkx2.1:Cre mice. Models of several genetically-defined neurodevelopmental syndromes have frequently observed changes in perineuronal net (PNN) accumulation. How normal ERK/MAPK signaling is involved in this critical process of cortical maturation is still unclear. Utilizing GABAergic-specific RIP-Seq, we have identified differentially expressed genes in *Erk1*$^{-/-}$ *Erk2*$^{fl/fl}$ Slc32A1:Cre and caMEK1 Slc32A1:Cre cortices during the first week of postnatal development. Overall, our data highlight the important roles of ERK/MAPK in the development and maturation of cortical GABAergic circuitry.

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Poster

734. Neurodevelopmental Disorders: Molecular and Cellular Mechanisms

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 734.19/B12

Topic: A.07. Developmental Disorders

Support: Anatomical Society PhD Studentship
CHARGE syndrome foundation pilot grant

Title: Cortical growth and patterning anomalies in a mouse model for CHARGE syndrome

Authors: *A. P. A. DONOVAN[1], C. MOHAN[1], J. ELLEGOOD[2], J. P. LERCH[3], A. BASSON[1]; [1]King's Col. London, London, United Kingdom; [2]Mouse Imaging Ctr., Hosp. For Sick Children, Toronto, ON, Canada; [3]Hosp. for Sick Children, Toronto, ON, Canada

Abstract: Dominant mutations in the gene encoding the ATP dependent chromatin remodeling factor CHD7 cause CHARGE syndrome (**C**oloboma, **H**eart defects, **A**tresia of the choanae, **R**etardation of growth, **G**enital anomalies and **E**ar defects). Individuals with CHARGE syndrome often have intellectual disability and have been reported to have deficits in executive functioning. The neurodevelopmental and neuroanatomical underpinnings of these defects are not yet known, but cortical abnormalities are linked to both intellectual disability and executive dysfunction.
To identify structural changes in the brain associated with *Chd7* haploinsufficiency in the mouse, we performed MRI studies in *Chd7*$^{+/-}$ mice. These studies identified pronounced and widespread

abnormalities in the cortex and associated structures, including within the prefrontal, visual, auditory, motor, somatosensory and cingulate cortices. To investigate the underlying mechanisms, neural progenitor proliferation and apoptosis was quantified in the developing neocortex.
A genome-wide comparison of gene expression in *Chd7*$^{+/-}$ and *Chd7*$^{+/+}$ embryonic neocortices was carried out at E12.5. Gene expression changes suggestive of abnormal anterior-posterior (A-P) cortical patterning were identified and validated using *in situ* hybridization and qPCR. Restrictions in the size of frontal/motor and expansion of visual cortical modules were also identified by *in situ* hybridisation. Additionally, at E9.5, a specific reduction in the expression of *Fgf8* in the anterior neural ridge, an important A-P cortical patterning centre, was identified by *in situ* hybridisation and validated via qPCR. Together, these studies provide insights into developmental alterations in cortical patterning and subsequent A-P cortical organisation, that could underlie abnormalities in the mature cortex and aspects of neuropsychiatric dysfunction in CHARGE syndrome patients.

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Poster

734. Neurodevelopmental Disorders: Molecular and Cellular Mechanisms

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 734.20/B13

Topic: A.07. Developmental Disorders

Support: R01MH112763
Howard Hughes Medical Institute

Title: Disruption of DNA methylation by conditional knockout of Dnmt3a leads to compensation by Polycomb-mediated repression in cortical pyramidal neurons

Authors: *J. LI[1], M. ZANDER[3,5], A. PINTO-DUARTE[4], C. LUO[3,5], J. R. NERY[3], R. CASTANON[3], J. LUCERO[4], C.-Y. LAI[4], J. OSTEEN[4], K. UM[4], T. J. SEJNOWSKI[4,5], S. B. POWELL[2], J. R. ECKER[3,5], E. A. MUKAMEL[1], M. BEHRENS[4];
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Abstract: Epigenetic modifications of the genome, including DNA methylation and covalent modifications of histone proteins, are critical regulators of brain cell differentiation, maturation and synaptic plasticity. However, the causal relationships among these epigenetic modifications and their impact on neuronal function are unknown. Here, we studied the interaction between

DNA methylation and histone modifications in a conditional knockout (cKO) mouse in which Dnmt3a ablation was initiated during late gestation (around embryonic day 15). We have previously shown that Dnmt3a cKO mice lack a neuron-specific epigenetic mark, namely DNA methylation at non-CG dinucleotides (mCH). This epigenetic alteration is accompanied by differential expression of ~2000 genes. Computational analysis using Binding Analysis for Regulation of Transcription (BART) suggested that a significant number of these genes may be regulated by transcription factors and chromatin regulators associated with the Polycomb repressive complex (PRC). In addition to the loss of mCH, we found ~140,000 differentially methylated regions (DMRs) with lower mCG in the cKO. These DMRs mainly mark regions that gain methylation during normal brain development, but fail to do so in the absence of Dnmt3a. To link DNA methylation with a broader context of epigenetic regulation, we profiled histone modifications in pyramidal cells by sequencing DNA fragments extracted by chromatin immunoprecipitation (ChIP-Seq). We found that a significant fraction of DMRs gained trimethylation at lysine 27 of histone 3 (H3K27me3) in cKO animals. This chromatin modification is associated with PRC-mediated repression of gene expression. By contrast, two chromatin modifications which mark active regions, acetylation of lysine 27 (H3K27ac) and trimethylation of lysine 4 (H3K4me3), were largely unaffected by Dnmt3a ablation. These results suggest that PRC-mediated repression may compensate for the loss of mCG and/or mCH, acting as an alternative repressive mechanism when DNA methylation is disrupted. Overall, our results support a link between two epigenetic mechanisms for suppressing gene expression, which may confer robustness on this critical regulatory program.

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Poster

734. Neurodevelopmental Disorders: Molecular and Cellular Mechanisms

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 734.21/B14

Topic: A.07. Developmental Disorders

Title: Inhibition of inflammasome activation as a potential treatment for francisella tularensis infection

Authors: *A. TENA[1], C. SPENCER[2];
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Abstract: *Francisella tularensis* is a gram-negative coccobacillus bacterium that causes the zoonotic disease tularemia in humans. *Ft* is transmitted through direct contact with infected

animals, consumption of contaminated food or water, inhalation or arthropod bites. Given its possible use as a bioterror agent, *Ft* is classified as a Tier 1 select agent by the CDC. Infection by *Ft* triggers an overactive inflammatory response known as a cytokine storm that results in major tissue damage leading to death of the host before onset of adaptive immunity. This inflammation is mediated intracellularly by the activation of the multi-protein cytosolic inflammasome complexes. The inflammasomes regulate the activation of caspase-1 to produce proinflammatory cytokines interleukin-1β (IL-1β) -and IL-18. Nod-like receptor (NLR) proteins, especially NLR-family pyrin domain containing 3 (NLRP3) sense the presence of *Ft* in the cytosol and activates the inflammasomes. Previous studies report that *Ft* live vaccine strain (LVS) is sensed by NLRP3 in human macrophages and by a non-NLR protein, absent in melanoma 2 (AIM2) in mouse macrophages. NLRP3 and AIM2 form a caspase-1-activating inflammasome by engaging the caspase-1-activating adaptor protein apoptosis-associated speck-like protein containing CARD (ASC) adapter protein. ASC is crucial for production of IL-1β and plays an important role in innate immune signaling by linking the communication between pathogen recognition receptors and caspase 1 in inflammasome complexes. The purpose of this project is to prevent the formation and activation of inflammasomes. We hypothesize that disrupting the formation of the inflammasome would prevent generation of the cytokine storm and its associated tissue damage and death. Bone-marrow derived macrophages were be infected with *Ft* and treated with novel inflammasome inhibitors at varying concentrations. Treated macrophages were then be stained with α-cryopyrin (NLRP3), α-ASC, and α-AIM2 and visualized via fluorescent microscopy. Activation of the inflammasomes leads to overlapping localization of the sensor and ASC. Inflammasome disrupting compounds would prevent this overlapped localization.

Disclosures: A. Tena: None. **C. Spencer:** None.

Poster

734. Neurodevelopmental Disorders: Molecular and Cellular Mechanisms

Location: Hall A

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Topic: A.07. Developmental Disorders

Support: NINDS RO1NS081281
M-cubed grant by the University of Michigan
the Dr. Miriam and Sheldon G. Adelson Medical Research Foundation

Title: Conditional knockout of Plxna2 in forebrain impairs the development of the dentate gyrus and leads to schizophrenia-like behaviors

Authors: *X.-F. ZHAO[1], R. PARENT[2], R. KOHEN[3], G. G. MURPHY[4], R. J. GIGER[5];
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Abstract: Overwhelming evidence suggests that Schizophrenia (SCZ) is a neurodevelopmental disorder with a strong genetic underpinning. Genome-wide association studies identified numerous SCZ risk genes, including rare variants of members of the *SEMAPHORIN (SEMA)* family of axon guidance molecules and their receptors the *PLEXINs (PLXNs)*. Human variants of *PLXNA2* have been identified that lead to reduced *PLXNA2* gene expression in the forebrain and increased SCZ susceptibility. The underlying biology and neural circuitry perturbed by *SEMA/PLXNA2* mutations that can cause SCZ symptoms in patients remain unknown. We previously showed that in mice global *Plxna2* deficiency (*Plxna2*$^{-/-}$) disrupts migration and proliferation of early-born dentate granule cells (GCs) as they travel from the primary neuroepithelium to the dentate gyrus (DG) primordium. In mature *Plxna2-/-* mice, the stem cell niche in the subgranular zone produces fewer neurons and DG-CA3 laminar connectivity is impaired. Behavioral studies with *Plxna2* wildtype, heterozygous and null male and female mice revealed gene-dosage and sex-specific defects. Contextual fear conditioning, but cued fear conditioning, is defective in *Plxna2-/-* mice. *Plxna2*$^{-/-}$ females show reduced sociability in the 3-chamber-approach test. *Plxna2-/-* and *Plxna2+/-* males and *Plxna2-/-* females show a striking reduction in PPI (Pre-Pulse Inhibition) of the acoustic startle response. To assess the anatomical substrate associated with *Plxna2* behavioral defects, we conditionally deleted *Plxna2* in the embryonic forebrain. Conditional mutants (cKO) show defects in DG development similar to global knock-outs. Behavioral studies with *Plxna2* cKO mice revealed defects in contextual fear conditioning, and PPI. Thus, forebrain specific depletion of *Plxna2* recapitulates anatomical and behavioral defects observed in *Plnxa2*$^{-/-}$ mice. Ongoing experiments, including neural cell type specific deletion of *Plxna2*, is expected to provide insights into the neural circuits affected by *PLXNA2* mutations. Characterization of the biochemical pathways regulated by PlxnA2 signaling may be exploited therapeutically in psychiatric disorders.

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Poster

734. Neurodevelopmental Disorders: Molecular and Cellular Mechanisms

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Topic: A.07. Developmental Disorders

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Jordan's Guardian Angels

Roy J. Carver Charitable Trust

Title: Exploring the phospho-proteome of Jordan's Syndrome, an autosomal dominant neurodevelopmental disorders caused by *de novo* mutations in a protein phosphatase 2A regulatory subunit

Authors: *C. JONG, R. A. MERRILL, Y. KONG, S. STRACK;
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Abstract: Jordan's Syndrome (JS) or autosomal-dominant mental retardation 35 (MRD35) is caused by *de novo* germline mutations in the protein Ser/Thr phosphatase 2A (PP2A) regulatory subunit B'δ (PPP2R5D). Relatively common among monogenic causes of neurodevelopmental disorders, JS typically presents with intellectual disability (ID) and autism. Most JS mutations switch a negatively to a positively charged residue (glutamate to lysine) in the highly conserved acidic loop that extends from B'δ towards the active site of the PP2A catalytic subunit. We hypothesize that JS-associated mutations change PP2A substrate specificity (e.g. from positively to negatively charged phospho-peptides), which would enhance cellular signaling cascades that promote growth and proliferation. To identify cellular and biochemical phenotypes of JS causing ID, we generated stable HEK293 cell lines inducibly expressing either wild-type (WT) or mutant B'δ using a PP2A reduction model. We characterized the most common B'δ mutation in JS, E198K. The PP2A reduction cell lines were induced with doxycycline or vehicle for at least three days followed by assessment of PP2A subunit expression, cellular growth, and substrate dephosphorylation by unbiased phosphoproteomics. In our reduction model, WT and mutant B'δ were overexpressed by 3-fold, concomitant with a 3-fold loss of endogenous PP2A regulatory subunits. Quantitative global phosphoproteomic analyses of reduction and overexpression models shows that the reduction model, but not the overexpression model, defines consensus dephosphorylation motifs for B'δ-containing PP2A holoenzymes. In the reduction model, WT B'δ expression caused growth arrest within 4 days, while the E198K mutation attenuated the growth inhibitory effect of B'δ, effects that are likely associated with a change in substrates specificity. Indeed, our global phosphoproteomic analyses suggest that WT B'δ preferentially dephosphorylates substrates containing positively charged residues, while E198K-mutant B'δ dephosphorylates negatively charged residues adjacent to the phosphorylation site. Our data also suggest that the E198K mutation confers high basal activity to the PP2A holoenzyme, while WT PP2A/B'δ requires phosphorylation by PKA for full activity. In conclusion, using the PP2A reduction model, we provide preliminary evidence that *de novo* mutations in PPP2R5D blunt the growth inhibitory effect of B'δ likely by a change in PP2A substrates specificity. We speculate that altered PP2A activity in JS deregulates signaling pathways mediating cell proliferation, differentiation, and morphogenesis, which in turn leads to abnormal brain development.

Disclosures: C. Jong: None. **R.A. Merrill:** None. **Y. Kong:** None. **S. Strack:** None.

Poster

734. Neurodevelopmental Disorders: Molecular and Cellular Mechanisms

Location: Hall A

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Program #/Poster #: 734.24/B17

Topic: A.07. Developmental Disorders

Support: NINDS F99NS105208
NIMH R21MH108867
NIMH R21117434
NIH R56MH111459

Title: Quetiapine changes our genes, but does it change our minds?

Authors: K. E. SCHOONOVER[1], L. J. MCMEEKIN[2], C. B. FARMER[2], N. VARGHESE[2], S. L. QUEERN[2], S. E. LAPI[2], R. M. COWELL[3], *R. C. ROBERTS[4];
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Abstract: *DTNBP1* variations and decreased dysbindin-1 protein are associated with schizophrenia. Downregulated dysbindin-1 decreases copper transporters ATP7A and CTR1, required for blood brain barrier crossing of copper. To further study this relationship, the role of antipsychotic treatment, and to assess if such alterations would impact cognitive function, the current study measured behavioral indices of cognitive function in dysbindin-1 knockout (sdy) mice and their wild-type (WT) littermates with or without quetiapine treatment. Peripheral blood and exsanguinated brain copper levels were assessed, plus relevant markers of mRNA expression in cortex and hippocampus.
qRT-PCR revealed that after treatment, WTs exhibited elevated cortical transthyretin (TTR), a female-driven effect. Quetiapine-mediated cortical myelin basic protein (MBP) elevation in sdys was a female-driven effect. Hippocampal CTR1, TTR, and MBP mRNA were decreased by quetiapine regardless of genotype, but a genotype/treatment interaction was observed in WT hippocampal CTR1. Male sdys exhibited excess peripheral copper that was rescued with quetiapine treatment. Untreated male sdys expressed more hippocampal MBP than other male groups. Both hindlimb clasping severity and ledge instability were exacerbated in untreated sdy vs WT mice. Interestingly, these tasks were rescued with quetiapine in a genotype and sex-specific manner.
Cerebellar ataxia is sensitive to genotype, sex, and quetiapine interactions, as is regional genetic expression. While cerebellar ataxia was responsive to treatment, quetiapine did not alter other cognitive indices indicating that quetiapine-induced alterations are not sufficient for treatment-resistant cognitive impairments. Thus, expansion for proteomic assessment and other mechanisms underlying cognitive deficiencies are needed to develop better treatments.

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Poster

734. Neurodevelopmental Disorders: Molecular and Cellular Mechanisms

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Topic: A.07. Developmental Disorders

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Fundacion FULTRA

Title: Toxoplasma seropositivity interacts with haplotypes of risk in schizophrenia to distinguish affected individuals from unaffected siblings

Authors: J. SEVILLANO-ORTIZ[1], C. GALLO[1], G. POLETTI-FERRARA[1], J. ARNEDO[2], I. ZWIR[2,3], M. CALVO[4], E. PADILLA[4], G. GONZALEZ ALEMAN[4], N. V. FLORENZANO[4], D. KAMIS[5], J. MOLINA[6], J. TORANZO[4,7], M. USCAMAYTA AYVAR[4,7], O. MALDONADO[7], *G. A. DE ERAUSQUIN[4];
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Abstract: Chronic, non affective psychotic illness is a highly heritable neurodevelopmental disorder, which nonetheless probably requires environmental injuries to interact with predisposing genes. In a sample of individuals with well-established, chronic, neuroleptic-naive non affective psychosis, their unaffected siblings, and matched healthy controls, we used a machine learning algorithm to unbiasedly uncover candidate genes associated with risk of parkinsonism and psychosis, and identified three genes containing multiple significant SNPs (KLRG1, MYO16 and RIT2). We then inputed extended haplotypes for each and evaluated the interaction between the presence of risk haplotypes and antibody titers to known infections contributing to risk of psychosis (toxoplasma, herpes virus 1) or not related to such risk (herpes virus 2). Logistic regressions of the disease status (healthy control, unaffected sibling, proband) using as predictors the risk haplotypes of the candidate genes and the antibody titers to each of the infections were run to test the interaction. Significant GXE interactions predictive of disease

status (proband) were found for the three candidate genes and toxoplasma seropositivity, such that the latter distinguished probands from unaffected siblings when both carried haplotypes of risk. Interactions for herpes virus were less consistent. This is, to the best of our knowledge, the first demonstration of a putatively causative GXE interaction between infections known to contribute to risk and extended haplotypes of risk.

Disclosures: **J. Sevillano-Ortiz:** None. **C. Gallo:** None. **G. Poletti-Ferrara:** None. **J. Arnedo:** None. **I. Zwir:** None. **M. Calvo:** None. **E. Padilla:** None. **G. Gonzalez Aleman:** None. **N.V. Florenzano:** None. **D. Kamis:** None. **J. Molina:** None. **J. Toranzo:** None. **M. Uscamayta Ayvar:** None. **O. Maldonado:** None. **G.A. de Erausquin:** None.

Poster

734. Neurodevelopmental Disorders: Molecular and Cellular Mechanisms

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 734.26/B19

Topic: A.07. Developmental Disorders

Support: NIH Grant NS110687

Title: Unique blockage of host RNAi machinery by the zika virus capsid in fetal NSCs and mouse model

Authors: ***J. ZENG**[1], Z. ZHAO[1], Q. LIANG[2];
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Abstract: Zika virus (ZIKV) is a single-stranded RNA virus of the Flaviviridae family. It rapidly spread worldwide during 2015-2016 and is causally associated with fetal microcephaly, intrauterine growth retardation, and other congenital malformations. ZIKV is reported to infect placenta and fetal brain during pregnancy, particularly targeting human neural stem and progenitor cells (NSCs). Among the flavivirus family, only ZIKV is linked to microcephaly, suggesting uniqueness of ZIKV infection compared to other members, which calls for a better understanding of the molecular drivers of ZIKV immune evasion and pathogenesis in fetal brain. In addition, host molecular targets of ZIKV proteins remain elusive, which not only limits our understanding of ZIKV infection and pathogenesis, but also impedes anti-ZIKV drug development. Since the ZIKV outbreak in 2015, we have focused on understanding the complexity of ZIKV infection and pathogenesis of microcephaly. To fully understand the roles of viral proteins during ZIKV life cycle, we established the ZIKV-host interactome in human iPSC-derived NSCs. By analyzing this ZIKV-host interactome, we found that the key microRNA processing protein DICER was the top target of ZIKV capsid protein, and DICER deficiency facilitated ZIKV infection in mouse embryonic NSCs. Dysregulation of microRNAs has been

associated with many human disease diseases, including developmental neurological disorders such as microcephaly. More importantly, DICER-dependent microRNA production is commonly used by plants, fungi and invertebrates, and remains active in mammalian stem cells to produce antiviral small RNAs from the viral genomes, which inhibits viral replication via RISC-mediated RNA interference. Mechanistically, we further identified that ZIKV capsid directly interacts with DICER and blocks its ribonuclease activity, dampening the production of both viral interfering RNAs and host microRNAs that are essential for neurogenesis. Taken together, we have constructed the first interactome based on protein-protein interaction between ZIKV viral proteins and host targets in NSCs, providing unique insights into the ZIKV-specific immune evasion mechanisms. Our findings are consistent with the notion that ZIKV infection alters host mRNA and miRNA profile in NSCs or astrocytes and provided the potential molecular mechanism to the question “Why only ZIKV is link to microcephaly in clinic among flaviviruses”.

Disclosures: **J. Zeng:** None. **Z. Zhao:** None. **Q. Liang:** None.

Poster

734. Neurodevelopmental Disorders: Molecular and Cellular Mechanisms

Location: Hall A

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Topic: A.07. Developmental Disorders

Support: NIH grant R01NS107428
EU FP7 grant 241995
DFG grant AB 3939 / 2-2
NRPU Projects from Higher Education commission of Pakistan

Title: Biallelic variants in METTL5 cause autosomal recessive intellectual disability and microcephaly

Authors: *E. M. RICHARD[1], D. L. POLLA[3,4], M. Z. ASSIR[5,6,7], M. CONTRERAS[2], M. SHAHZAD[5,7], A. A. KHAN[8], A. RAZZAQ[3,8], J. AKRAM[5,7], M. N. TARA[7], T. A. BLANPIED[2], Z. M. AHMED[1], R. ABOU JAMRA[9,10], D. WIECZOREK[11,12], H. VANBOKHOVEN[3], S. RIAZUDDIN[5,7,8], S. RIAZUDDIN[1];
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Abstract: Intellectual disability (ID) is a genetically and clinically heterogeneous disorder, characterized by limited cognitive abilities and impaired adaptive behaviors. In recent years, exome sequencing (ES) has been instrumental in deciphering the genetic etiology of ID. Here, through ES of a large cohort of individuals with ID, we identified two bi-allelic frameshift variants in *METTL5*: c.344_345delGA (p.(Arg115Asnfs*19)) and c.571_572delAA (p.(Lys191Valfs*10)), in families of Pakistani and Yemenite origin. Both of these variants were segregating with severe ID, microcephaly and various facial dysmorphisms, in an autosomal recessive fashion. METTL5 is a member of the methyltransferase-like protein family, which encompasses proteins with a seven-beta-strand methyltransferase domain. We found *METTL5* expression in various substructures of rodent and human brains and METTL5 protein to be enriched in the nucleus and synapses of the hippocampal neurons. Functional studies of these truncating variants in transiently transfected orthologous cells and cultured hippocampal rat neurons revealed no effect on the localization of METTL5 but alter its level of expression. Our in-silico analysis and 3D modeling simulation predict disruption of METTL5 function by both variants. Finally, *mettl5* knockdown in zebrafish resulted in microcephaly, recapitulating the human phenotype. This study provides evidence that biallelic variants in *METTL5* cause ID and microcephaly in humans and highlights the essential role of METTL5 in brain development and neuronal function.

Disclosures: E.M. Richard: None. **D.L. Polla:** None. **M.Z. Assir:** None. **M. Contreras:** None. **M. Shahzad:** None. **A.A. Khan:** None. **A. Razzaq:** None. **J. Akram:** None. **M.N. Tara:** None. **T.A. Blanpied:** None. **Z.M. Ahmed:** None. **R. Abou Jamra:** None. **D. Wieczorek:** None. **H. vanBokhoven:** None. **S. Riazuddin:** None. **S. Riazuddin:** None.

Poster

734. Neurodevelopmental Disorders: Molecular and Cellular Mechanisms

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 734.28/B21

Topic: A.07. Developmental Disorders

Support: NIH Grant R01 NS107428

Title: Cellular and neurodevelopmental defects of a DCTN2 missense variant causing severe intellectual disability

Authors: *B. ALTAS[1], E. M. RICHARD[2], M. CONTRERAS[3], A. ROMANOWSKI[1], R. R. RICHARDSON[1], S. KHIM[1], U. L. JEAN-BAPTISTE[1], S. R. METZBOWER[3], S. A. RIAZUDDIN[4], Z. AHMED[2], T. A. BLANPIED[3], A. POULOPOULOS[1], S. RIAZUDDIN[2]; [1]Pharmacol., [2]Otorhinolaryngology Head & Neck Surgery, [3]Physiol., Univ. of Maryland Sch. of Med., Baltimore, MD; [4]Allama Iqbal Med. Col., Lahore, Pakistan

Abstract: Wiring of cortical circuits is carried out by coordinated developmental mechanisms of neuronal migration, dendritic arborization, axon projection, and synaptogenesis. It is estimated that mutations in over 2500 genes can underlie cortical miswiring that leads to intellectual disability, a complex group of neurodevelopmental disorders characterized by significant impairment in cognition and adaptive behaviors. Up to 50% of intellectual disability cases have genetic etiologies. Identification of the specific gene variants underlying cortical wiring pathology has provided critical insights to the molecular processes behind physiological and pathological cortical circuit development.In this study, using whole exome sequencing in a large cohort of consanguineous families, we identified a missense variant of *DCTN2* that segregates with severe intellectual disability and epilepsy in an autosomal recessive fashion. DCTN2 is one of the 23 subunits of dynactin, a regulator of the dynein motor complex. It has been studied with respect to endocytosis in non-neural cells, and has been associated with motor neuron degeneration. We investigate DCTN2 in the developing brain and find it to be broadly expressed, including in neocortex and hippocampus. Using subcellular proteomics and immunolabeling, we find DCTN2 heavily enriched in growth cones of developing cortical axons. Using *in* vivo CRISPR knockout in callosal projection neurons, we identify pervasive dysmorphic axon growth cones resulting from *Dctn2* deletion both in the developing and adult cerebral cortex. These findings indicate that disruption of *Dctn2* function results in specific abnormalities in the development of cortico-cortical circuitry, potentially underlying intellectual disability and epilepsy seen in patients.

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Poster

734. Neurodevelopmental Disorders: Molecular and Cellular Mechanisms

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 734.29/B22

Topic: A.07. Developmental Disorders

Support: AutDB is licensed as SFARI Gene to the Simons Foundation

Title: Insight from modeling of non-genetic risk factors for autism in rodents

Authors: *M. A. ESTEVEZ, A. A. SARKAR, S. BANERJEE-BASU;
Mindspec, Inc., McLean, VA

Abstract: There is a growing consensus that autism spectrum disorder (ASD) has a complex etiology, encompassing both genetic and non-genetic factors. Here we analyze animal models derived from non-genetic factors curated in AutDB, a comprehensive resource for autism research. Our dataset from March 2019 catalogues 327 rodent models derived from 92 non-genetic factors (inducers) related to ASD. We classify the inducers as evidence-based when these recapitulate etiological mechanisms with human clinical or epidemiological evidence. The etiological models take into consideration developmental time points (pre-conception, prenatal or early-life) as well as their biological role. Using a large dataset of rodent models derived from 58 evidence-based environmental factors associated with ASD, we identify several research trends: (1) the bulk of the induced models originate from etiological categories in the prenatal period reflecting the importance of maternal factors; (2) the most commonly modeled inducer in rat is the prenatal exposure of valproic acid categorized under the etiological model "Maternal intake: anticonvulsant drug", while the most commonly modeled inducer in mouse is polyinosinic:polycytidylic acid categorized under the etiological model of "Maternal immune activation"; (3) while the majority of the inducers are species-specific, a total of 11 inducers (19%) have been modeled in both mouse and rat; (4) a number of induced models based on environmental factors with uncertain links to ASD are also part of this dataset; finally (5) assessment of developmental time points of induction of environmental models of ASD indicate that there is a correlation between the emergence of ASD-specific phenotypes and the neurodevelopmental trajectory. Together, our unique and comprehensive collection of non-genetic rodent models and meta-analytical approaches provide important insights into the research trends and biological underpinnings of environmental risk factors of ASD.

Disclosures: M.A. Estevez: None. **A.A. Sarkar:** None. **S. Banerjee-Basu:** None.

Poster

735. Synaptic Transmission, Integration, and Signal Propagation

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 735.01/B23

Topic: B.06. Synaptic Transmission

Title: Effects of bacterial endotoxin LPS on the neuronal regulation of the heart, a sensory-CNS-motor nerve circuit as well as at neuromuscular junctions: Crustacean model

Authors: *M. C. MCNABB[1], C. M. SAELINGER[1], R. MCNAIR[2], S. M. BIERBOWER[2], R. L. COOPER[1];
[1]Dept. of Biol., Univ. of Kentucky, Lexington, KY; [2]Dept. of Biol., William Paterson Univ., Wayne, NJ

Abstract: Eatable crustaceans are susceptible to bacterial septicemia from injury or compromised defense by bacterial strains which can possibly have detrimental effects in mammals. Since many crustaceans (i.e., crabs, lobsters, crayfish) are used for animal food and human consumption, it is of interest to understand the effects potential bacterial infections can have on their and our health. The Red Swamp crayfish (Procambarus clarkii) was used as a model crustacean to investigate the effect of direct exposure to endotoxin lipopolysaccharide (LPS) and associated peptidoglycans from gram-negative bacteria (Serratia marcescens). S. marcescens is a common strain identified to cause septicemia in mammals (500 µg/ml) and is prevalently found in nature. LPS injection into the hemolymph of crayfish revealed acute changes in heart rate and effects on survival. Direct LPS exposure on an in situ sensory-CNS-motor circuit produces a decrease in function at 500 µg/ml but has no significant effect at 100 µg/ml. At the isolated neuromuscular junction, the direct action of the LPS endotoxin (500 µg/ml) enhances evoked synaptic transmission and alters facilitation, while no effect on the occurrence of spontaneous vesicle fusion events. These direct actions on tissues appear to be independent of innate immune responses and suggests the LPS receptors on these tissues have a role in excitability of neuronal function. In addition, we embarked on examining reproducibility in the data analysis with different participants.

Disclosures: M.C. McNabb: None. **C.M. Saelinger:** None. **R. McNair:** None. **S.M. Bierbower:** None. **R.L. Cooper:** None.

Poster

735. Synaptic Transmission, Integration, and Signal Propagation

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 735.02/B24

Topic: B.06. Synaptic Transmission

Support: Hussman Foundation Grant HIAS18001

Title: Regulation of E/I balance by active conductances

Authors: S. SHIN, M. BRIDI, S. PARK, ***S. HUANG**;
Hussman Inst. for Autism, Baltimore, MD

Abstract: Excitation and inhibition (E/I) appear concomitantly during neural activity in vivo. Balanced excitation and inhibition is required for normal brain function while imbalanced excitation and inhibition has been linked to autism and other neurodevelopmental disorders. Restoring E/I balance could potentially be a useful strategy for the development of therapeutics in these disorders. Thus, identification of factors that regulate E/I balance in neurons is important for translational research. Here we investigated the integration of excitatory and inhibitory inputs at the induction of action potentials in realistic biophysical neuronal models, and revealed that

the relationship of excitation and inhibition is a linear function with a y-intercept. This function was further validated in actual neurons with artificial synaptic inputs and in neurons with inhibitory synaptic inputs activated by optogenetic stimulation. Moreover, we showed that voltage-dependent ion channels, which control the threshold of action potentials, can regulate the function of E/I integration. These findings provide insights into potential therapeutic targets for correcting E/I imbalance in neurodevelopment and psychiatric conditions.

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Poster

735. Synaptic Transmission, Integration, and Signal Propagation

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 735.03/B25

Topic: B.06. Synaptic Transmission

Support: MOST 107-2321-B-001-011
MOST 105-2311-B-001-061-MY3
AS-IA-106-L04

Title: Interhemispheric amygdalar connectivity potentiates basolateral amygdalae activity

Authors: *T.-T. HSU[1], T.-N. HUANG[1], M.-H. LIN[1], H.-C. CHUANG[1], H.-T. HU[1], C.-P. SUN[2], M.-H. TAO[2], J. LIN[3], Y.-P. HSUEH[1];
[1]Inst. of Mol. Biology, Academia Sinica, Taipei, Taiwan; [2]Inst. of Biomed. Sciences, Academia Sinica, Taipei, Taiwan; [3]Sch. of Medicine, Univ. of Tasmania, Tasmania, Australia

Abstract: Our study suggests that interhemispheric connectivity between basolateral amygdalae (BLA) is critical for BLA activity and function. However, the exact circuit mechanism remains unclear. Here we combined optogenetics and *ex vivo* slice electrophysiology to investigate the role of contralateral BLA afferents on BLA principle neuron (PN) activities. We found that no matter there were weak or strong circuit-driven inhibitions, activation of contralateral BLA afferents potentiated PN activities and had synergistic effect when paired with cortical or thalamic input stimulation. Moreover, when using theta-burst frequency stimulation (TBS) to repetitively activate contralateral BLA afferents, the inter-BLA synaptic dynamic exhibited multiple-pulse facilitation and potentiated the cortical - BLA or thalamic - BLA synaptic potentials more in the late stimulus train. Although the relationship between plasticity changes and functional significances of different cell types remains to be investigated, our study evidences that interamygdalar connectivity potentiates the BLA PN activities and plays a critical role in regulation of amygdalar activity and function.

Disclosures: T. Hsu: None. **Y. Hsueh:** None.

Poster

735. Synaptic Transmission, Integration, and Signal Propagation

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 735.04/B26

Topic: B.06. Synaptic Transmission

Support: MOST 105-2320-B-002-055-MY3 (Taiwan)

Title: Somatic and synaptic modulation by muscarinic cholinergic receptors at synaptic connection of inhibitory interneuron onto noradrenergic neuron in locus coeruleus

Authors: *C.-C. KUO[1], M.-Y. MIN[1], H.-W. YANG[2];
[1]Dept. Life Sci., Natl. Taiwan Univ., Taipei, Taiwan; [2]Dept. Biomed. Sci., Chung-Shan Med. Univ., Taichung, Taiwan

Abstract: Activation of muscarinic acetylcholine receptors (mAChRs) is well known to increase the excitability of noradrenergic neurons in the locus coeruleus (LC) and to result in change of electroencephalography activity in anesthetized animals. Here we test, in addition to directly targeting on NAergic neurons (LC neurons), whether activation mAChRs modulated the activity of local inhibitory interneurons (IN) and the transmission at synapses of the IN onto LC neurons. To this end, we used optogenetic method to selectively activate the IN and recorded inhibitory postsynaptic currents (IPSCs) from LC neurons. Stereotaxic Injection of adeno- associative virus (AAV) carrying double a double-floxed inverted open reading frame of enhanced yellow florescent protein and channelrhodopsin2 was made into the LC in of Vgat-cre mice, in which the promoter of vesicular GABA transporter drives expression of cre recombinase. The animals were killed 3-8 weeks after the surgery for brainstem slice preparation and whole-cell patch recording was made from LC neurons. Illuminating the slices with a single blue-light pulse (2 ms) evoked IPSCs in LC neurons. Bath application of 25 μM carbamoylcholine (CCh), a potent agonist of mAChRs, attenuated the IPSCs, which was associated with an increase in the paired-pulse ratio, showing that the effect of CCh was presynaptic. In addition, bath application of CCh also dramatically increased the firing rate of both LC neurons and the IN. The presynaptic effect of CCh on inhibiting the transmission at synapses of the IN onto LC neurons was blocked by mAChR 2 (M2R) and mAChR 4 (M4R) but not by mAChR 1 (M1R) and mAChR 3 (M3R) antagonists; in contrast, the increase in firing rate of LC neurons and the IN by CCh were abolished by M1R/M3R but not by M2R /M4R antagonists. Together, the above results show the inhibitory transmission from the local IN onto LC neuron was modulated by presynaptic M2R/M4R but not M1R/M3R. Furthermore, the activation of M1R/M3R, but not M2R/M4R increased the excitability of LC neurons and the local IN. (Grant support: MOST, Taiwan).

Disclosures: C. Kuo: None. **M. Min:** None. **H. Yang:** None.

Poster

735. Synaptic Transmission, Integration, and Signal Propagation

Location: Hall A

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Topic: B.06. Synaptic Transmission

Support: National Natural Science Foundation of China Projects 31430038
National Natural Science Foundation of China Projects 31630029
National Natural Science Foundation of China Projects 31661143037

Title: A circuit function of asynchronous glutamate release in neocortex

Authors: *S. DENG[1], J. LI[1], J. ZHU[2], Q. HE[1], L. LI[1], Y. SHU[1];
[1]Beijing Normal Univ., Beijing, China; [2]Yale Univ., New Haven, CT

Abstract: Cortical inhibition is crucial for dynamic excitation-inhibition balance and information processing in the neocortex. The temporal control of cortical inhibition determined by distinct microcircuit motifs has been extensively studied. The underlying mechanism, however, remains unclear. In this study, we performed dual whole-cell recordings from pyramidal cells (PCs) and nearby inhibitory interneurons in layer 5 of rodent neocortical slices (Sprague Dawley rats and mice, postnatal 15-20 days). We found that PC output synapses onto Martinotti cells (MCs) have two release modes: synchronous and asynchronous release. The delayed and long-lasting asynchronous release (AR) of glutamate prolongs and desynchronizes the firing in MCs, causing prolonged and imprecise inhibition in neighboring PCs. AR is much stronger at PC-MC synapses as compared with those onto fast-spiking cells and other PCs. In addition, AR is also dependent on PC subtypes, with crossed-corticostriatal PCs producing the strongest AR as compared to corticopontine and commissural PCs. Further experiments revealed that knocking out the slow calcium sensor synaptotagmin-7 reduced both the AR event number and the AR-induced basal currents, leading to a reduction of recurrent inhibition between PCs. In conclusion, our results highlight the effect of a cell-type specific glutamate AR on the operation of microcircuits mediating the slow recurrent inhibition, an important mechanism for controlling the timing and size of cortical inhibition.

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Poster

735. Synaptic Transmission, Integration, and Signal Propagation

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Topic: B.06. Synaptic Transmission

Support: NIDDK 1R01DK119811 to INK
NSF CAREER 1553067 to INK

Title: Circadian rhythms of viscerosensory to brainstem signaling

Authors: *F. J. SHAFFER, B. PETERSON, J. H. PETERS, I. N. KARATSOREOS; Integrative Physiol. and Neurosci., Washington State Univ., Pullman, WA

Abstract: Circadian rhythms synchronize physiological and behavioral responses to environmental light/dark cycles, including the maintenance of autonomic tone and reflex pathways. The nucleus of the solitary tract (NTS) receives glutamatergic afferent inputs from the viscera through the vagus nerve and is directly responsive to circulating factors and hormones. It also has dense reciprocal connections to the paraventricular nucleus (PVN) of the hypothalamus, positioning it as a key integrator of circadian rhythms and visceral status. However, rhythmicity of neural communication has never been explored in the NTS. The purpose of this study was to investigate this region of the brainstem as a key candidate for the extra-SCN rhythmic control of the autonomic nervous system. To begin, we investigated the basic components of the molecular circadian clock using quantitative PCR and *in vitro* luciferase activity as reporters of clock gene expression. We extended these results using patch-clamp electrophysiology and demonstrated the additional presence of rhythmic glutamatergic neurotransmission onto NTS neurons. Spontaneous EPSC frequency, but not amplitude or tau, oscillated throughout the day with a peak at ZT8. Current-voltage relationship analysis also revealed diurnal rhythmicity of resting ionic conductances intrinsic to NTS neurons, suggesting daily changes in excitability. These findings provide a basis for future experiments exploring how the molecular clock mechanism translates to rhythmic changes in fast neurotransmission and neural activity. This provides a framework for how disruption of circadian rhythms may lead to autonomic disorders.

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Poster

735. Synaptic Transmission, Integration, and Signal Propagation

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 735.07/B29

Topic: B.06. Synaptic Transmission

Title: Stronger and more reliable synaptic transmission between identified pyramidal neurons in human temporal association cortex relative to mouse

Authors: *S. HUNT[1], E. MERTENS[1], L. KANARI[2], F. SCHÜRMANN[2], H. D. MANSVELDER[1], C. P. J. DE KOCK[1];
[1]Ctr. for Neurogenomics and Cognitive Res., Vrije Univ., Amsterdam, Netherlands; [2]Blue Brain Project, École Polytechnique Fédérale de Lausanne, Geneva, Switzerland

Abstract: Detailed knowledge of how neurons are wired together is essential for our understanding of the human brain. What we currently know about the function of neuronal microcircuits, however, is based predominantly on rodent research. At the single-cell level, pyramidal neurons are fundamentally different between human and rodent brains: human pyramidal neurons are three times larger with a distinct dendritic structure, both in terms of complexity and distribution, contain a much higher total spine count and have larger presynaptic active zones and postsynaptic densities compared to rodent. We therefore wanted to address the question what is the impact of these human-specific properties on information processing between connected pyramidal neurons? To study synaptic communication we used non-pathological human medial temporal gyrus tissue obtained through resection surgery and compared results to mouse temporal association cortex. We performed whole-cell patch-clamp recordings from up to four pyramidal neurons simultaneously, in layers 2 and 3 of human and mouse temporal cortices. We subsequently stained recorded neurons for digital morphological reconstruction and cell-type classification. Pyramidal-to-pyramidal connections were found in both species and overall connectivity rates in human and mouse layers 2 and 3 were statistically comparable. Human pyramidal connections were, however, stronger and more reliable than in mouse; excitatory postsynaptic potential amplitude was higher, while response failure rate and coefficient of variation were lower in human compared to mouse connections. Our findings uncover the functional outcome of known human-specific structural properties of human pyramidal neurons and could underlie more efficient information transfer between human neurons.

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Poster

735. Synaptic Transmission, Integration, and Signal Propagation

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Topic: B.06. Synaptic Transmission

Support: National Natural Science Foundation of China Projects 31430038
National Natural Science Foundation of China Projects 31630029
National Natural Science Foundation of China Projects 31661143037

Title: Selective formation of autapses in hippocampal subiculum pyramidal cells

Authors: W. KE, *Y. SHU;
State Key Lab. of Cognitive Neurosci. and Learning, Beijing Normal Univ., Beijing, China

Abstract: Autapses are special synapses formed in a single neuron, from the axon onto its own soma and dendrites. Previous studies reveal massive autaptic self-innervation in cortical GABAergic neurons. Autaptic transmission produces immediate inhibition after an action potential (AP) and increases the precision of APs in a burst. We demonstrate recently that functional autapses form in neocortical pyramidal cells (PCs), particularly those in layer V projecting to subcortical brain regions. These glutamatergic autapses generate giant postsynaptic currents that are exclusively mediated by AMPA receptors. Importantly, these autapses promote burst firing and coincidence detection. Considering that hippocampus PCs share common morphological features with neocortical PCs, we sought to examine whether hippocampal PCs also form functional autapses. In this study, we performed whole-cell recording from PCs in different regions of rodent hippocampal slices. With a bath solution containing 8 mM Sr^{2+} that could desynchronize and prolong the synaptic transmission, we detected autaptic events only in subiculum PCs, but not CA1 or CA3 PCs. These autaptic events could be blocked by the ionotropic glutamate receptor blocker, kynurenic acid. To examine whether autapses selectively form in subgroups of subiculum PCs, we injected retrograde beads to nucleus accumbens and amygdala and found that subiculum PCs projecting to the nucleus accumbens show a relatively higher probability of autaptic connections than those targeting the amygdala. PCs in the subiculum can be also subdivided into two separate groups by their firing patterns: bursting and regular spiking. We found that the bursting PCs are more likely to form autapses as compared with the regular spiking PCs. Together, our results indicate that in the hippocampus excitatory autapses selectively form in distinct subpopulations of subiculum PCs. The selective formation of autapses in bursting PCs suggest an important role of autapses in the generation of AP bursts, which may enhance functional connectivity between the subiculum and downstream brain regions.

Disclosures: W. Ke: None. **Y. Shu:** None.

Poster

735. Synaptic Transmission, Integration, and Signal Propagation

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 735.09/B31

Topic: B.06. Synaptic Transmission

Support: MSIP 2012R1A5A2A44671346

Title: Cerebellar microcircuit regulates long-term fear memory by the STAT3-mediated excitatory-inhibitory balance

Authors: *J.-K. HAN[1], S. KIM[2];
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Abstract: It has been overlooked that emotional memory processing is associated with bodily movement particularly in fear memory consolidation and retrieval. Here, we found a novel mechanism by which input-output control of Purkinje cells *via* signal transducer and activator of transcription 3 (STAT3) might modulate long-term fear memory. Transcriptome analyses showed that the expression of glutamate receptor subunits, GluA1/2, were significantly increased in the Purkinje cell-specific STAT3-deficient mice compared to controls. The results demonstrate the critical role of STAT3 as a transcriptional repressor that modulates the expression level of glutamate receptors within the dynamic range. In the sense of fear memory processing, we discovered that long-term potentiation (LTP) was reframed to long-term depression at parallel fiber to Purkinje cell synapse in the STAT3 knockout mice. On the other hand, fear-conditioned Purkinje cells induced LTP at molecular layer interneuron to Purkinje cell synapse without being affected by STAT3. Unlike the synaptic changes, cerebellar STAT3 is independent on intrinsic excitability of Purkinje cells. Interestingly, STAT3-deficient mice had an aberrant long-term memory of fear, while no motor-related behavioral phenomenon was observed. All things considered, our data strongly suggest that the disruption of excitatory-inhibitory synaptic balance mediated by STAT3 in cerebellar microcircuits causes the aberrant fear memory formation, and might lead to develop the novel therapeutics for psychiatric disorders, such as posttraumatic stress disorders.

Disclosures: **J. Han:** None. **S. Kim:** None.

Poster

735. Synaptic Transmission, Integration, and Signal Propagation

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

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Topic: B.06. Synaptic Transmission

Support: FAPESP
CNPq

Title: Short-term sustained hypoxia increases the evoked excitatory transmission in NTS neurons of mice

Authors: *D. ACCORSI-MENDONCA[1], B. H. MACHADO[2];
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Abstract: In this study we evaluated the effect of short-term sustained hypoxia [(SH) 24 hours, FiO_2 0.10] on the synaptic activity in the NTS neurons from mice (C57Bl/6 mice). Brainstem slices and whole-cell patch clamp were used to study the electrophysiological properties of NTS neurons from control (CON) and SH mice. We observed that passive properties of NTS neurons of mice were not affected by SH [input resistance, CON: 0.69 ± 0.1 MΩ (n=9) vs SH: 0.74 ± 0.19 MΩ (n=8)][RMP, CON: -57.4 ± 3.3 mV (n=10) vs SH: -61 ± 3.5 mV (n=7)]. SH also produced no changes in the spontaneous excitatory transmission [sEPSC frequency, CON: 1.13 ± 0.4 Hz (n=5) vs SH: 1.88 ± 0.7 Hz (n=6); amplitude, CON: 29 ± 9 pA (n=5) vs SH: 22 ± 9 pA (n=6); half-width, CON: 2.3 ± 0.5 ms (n=5) vs SH: 2.4 ± 0.3 ms (n=6)]. In contrast, SH increased the excitatory transmission in response to afferent fibers stimulation in NTS neurons of mice; the amplitude of evoked excitatory currents was larger in NTS neurons from SH mice compared to NTS neurons from control mice [CON: -62 ± 17 pA (n=8) vs SH: -153 ± 30 pA (n=9)] with no changes in the kinetic of evoked current. We conclude that SH exposure increases the evoked glutamatergic synaptic transmission in the NTS neurons of mice.
Financial support: FAPESP and CNPq

Disclosures: D. Accorsi-Mendonca: None. **B.H. Machado:** None.

Poster

735. Synaptic Transmission, Integration, and Signal Propagation

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Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 735.11/B33

Topic: B.06. Synaptic Transmission

Support: NIMH R01MH104638

Title: Acetylcholine promotes theta oscillations and drives increased network synchrony in parvalbumin-positive interneurons in the basolateral amygdala

Authors: *J. X. BRATSCH-PRINCE, G. C. JONES, J. W. WARREN, III, A. J. MCDONALD, D. D. MOTT;
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Abstract: The neurotransmitter acetylcholine (ACh) plays a central role in generating and pacing theta oscillations in the hippocampus and cortex during memory encoding and consolidation. Cholinergic activation of local inhibitory interneurons is critically important in driving these oscillations, but how ACh modulates specific inhibitory networks to promote oscillogenesis in large neuronal ensembles remains unclear. The basolateral amygdala (BLa) receives dense cholinergic innervation and is involved in emotional memories. Understanding ACh modulation of rhythmic oscillations in the BLa has important implications in emotional learning and memory consolidation. This study used brain slice electrophysiology and optogenetics to explore modulation of BLa rhythmicity by ACh. We found that endogenously released ACh caused prolonged local field potential oscillations at theta frequency in the BLa. Recordings from single pyramidal neurons revealed theta oscillations that were driven by GABAergic inhibition. Between pairs of pyramidal neurons, this ACh-induced inhibition was synchronized, pointing to involvement of an inhibitory network. Selective inhibition of parvalbumin-containing (PV) interneurons disrupted ACh-induced oscillations, suggesting these cells play a role. In agreement, we found that ACh induced and enhanced synchrony in PV interneurons. In response to focal ACh application, PV interneurons were depolarized via M3 muscarinic receptors and fired spikes at theta frequency. These spikes were synchronized between pairs of PV interneurons. Below spike threshold, activation of muscarinic receptors on PV interneurons induced theta frequency membrane potential oscillations, which were synchronous across PV cell pairs. PV interneurons in the BLa are electrically coupled. We found that muscarinic receptor activation significantly increased the strength of this electrical coupling between PV cells, suggesting a mechanism through which ACh could entrain synchronous PV network activity. Collectively, this study suggests ACh can promote rhythmicity in neuronal ensembles in the BLa by activating and enhancing synchrony in the PV interneuron network.
Supported by the NIMH (R01MH104638 to DDM and AJM).

Disclosures: J.X. Bratsch-Prince: None. **G.C. Jones:** None. **J.W. Warren:** None. **A.J. McDonald:** None. **D.D. Mott:** None.

Poster

735. Synaptic Transmission, Integration, and Signal Propagation

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Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 735.12/B34

Topic: B.06. Synaptic Transmission

Support: NS094499
Harold and Leila Y. Mathers Charitable Foundation

Title: Myelination of mouse neocortical parvalbumin interneurons: Physiology and anatomy

Authors: M. KIRALY[1], K. D. MICHEVA[2], M. M. PEREZ[3], *D. V. MADISON[4];
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Abstract: Parvalbumin (PV+) basket interneurons participate in regulating excitatory/inhibitory balance in neural circuits, neuronal synchronization, cortical rhythm generation, and in synaptic plasticity. We have characterized the electrophysiology of synaptic connections between individual presynaptic PV+ interneurons and postsynaptic pyramidal cells in simultaneous dual whole cell recordings, with subsequent anatomical reconstructed using array tomography. Arrays were immunostained for myelin basic protein to reveal the location and extent of myelin on the axons of the previously recorded PV+ interneurons. **Results**: we have recorded numerous PV+ interneuron/pyramidal neuron pairs in acute neocortical brain slices taken from animals ranging in age from P14 days to 8 months. We measured multiple parameters of the interneuron axon including path length (between PV cell and postsynaptic pyramidal neuron), length of myelin segments, % length myelinated, number and length of nodes and internodes, axon thickness, myelin thickness, branching and the number/position of synaptic contacts onto the recorded pyramidal neuron. These anatomical measurements were correlated with the physiological measurements made during the electrophysiological recordings, namely IPSC amplitude and latency. This allowed us to make an accurate estimation of action potential conduction velocity, and to correlate the number of synapses with the amplitude of the IPSC. **Conclusion:** PV+ Interneurons from young mice are very sparsely myelinated and the axonal branching is relatively simple. Synapses are few, and the IPSC relatively small. Conduction velocity is very slow, on the order of 0.05 m/s. As the animals reach adulthood, myelination increases dramatically, axon branching becomes more complicated, and the number of synapses onto the recorded target cell increases. Conduction velocity roughly doubles. There is also a trend that the IPSC grows larger on average with age. We have also shown that we can reliably induce synaptic plasticity (“iLTD”) in these unitary PV+ to pyramidal cell synaptic connections. The combination of electrophysiology and array tomography has allowed for an unprecedented

correlation between the electrical properties of single interneurons and their detailed anatomy, including the properties of and physiological significance of their myelination.
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Disclosures: M. Kiraly: None. **K.D. Micheva:** None. **M.M. Perez:** None. **D.V. Madison:** None.

Poster

735. Synaptic Transmission, Integration, and Signal Propagation

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Program #/Poster #: 735.13/B35

Topic: B.06. Synaptic Transmission

Support: U01MH114812
RF1MH114126

Title: Characterization of intrinsic and synaptic properties of genetically-targeted human neocortical neurons using an *ex vivo* brain slice culture and viral labeling paradigm

Authors: C. RADAELLI[1], *M. KIM[1], B. LEE[3], L. NG[3], E. THOMSEN[3], L. CAMPAGNOLA[3], J. LEE[3], A. L. KO[5], J. G. OJEMANN[6], C. COBBS[7], R. P. GWINN[7], C. D. KEENE[5], D. L. SILBERGELD[5], R. ELLENBOGEN[5], B. P. LEVI[1], J. L. CLOSE[2], R. NICOVICH[1], K. SMITH[3], S. A. SORENSEN[3], J. BERG[1], T. JARSKY[3], G. J. MURPHY[1], H. ZENG[4], C. KOCH[3], J. TING[1], E. LEIN[1];
[2]Human Cell Types, [1]Allen Inst. For Brain Sci., Seattle, WA; [4]Structured Sci., [3]Allen Inst. for Brain Sci., Seattle, WA; [6]Dept Neurosurg., [5]Univ. of Washington, Seattle, WA; [7]Swedish Neurosci. Inst., Seattle, WA

Abstract: Although electrophysiological properties and synaptic connectivity of brain cell types have been extensively studied in the rodent brain slice preparation, the equivalent functional characterization of human brain cell types has received far less attention. The limited suite of available tools for genetic targeting and manipulation of human brain cell types has posed a formidable barrier to progress in characterizing the remarkable diversity of human neocortical cell types and their defining properties. Importantly, our recent work has demonstrated the feasibility of rapid viral genetic labeling of neurons in human *ex vivo* neocortical slice cultures derived from neurosurgical tissue specimens, thus opening up a wide range of new possibilities for human cellular neuroscience. Here we extend this work by further investigating the feasibility and potential broad applicability of viral genetic labeling in combination with cutting-edge approaches such as patch-seq and multi-patching to characterize intrinsic and synaptic properties of human neurons, respectively. We characterized the impact of short-term (<10 days *in vitro*) organotypic brain slice culture and Adeno-associated virus (AAV)-mediated viral transgene

expression on intrinsic properties and synaptic connectivity and dynamics of human neocortical neurons. Surgical tissue specimens were obtained with patient consent from both temporal and frontal neocortical brain regions, and the specimens were distal to the pathological focus and invariably not required for diagnostic purposes. We performed patch-seq analysis on >100 human neocortical interneurons labeled with a pan-GABAergic AAV vector to explore the morpho-electric-transcriptomic properties of the major interneuron classes (VIP, SST, PVALB), with comparison to acute slice interneuron patch-seq data. We also utilized multi-patch clamp recording to characterize local circuit synaptic connectivity and short-term plasticity of virus-labeled and unlabeled neurons. Both excitatory and inhibitory neurons were targeted for synaptic connectivity measurements by prospective marking with pan-glutamatergic or pan-GABAergic AAV vectors, respectively, and data were compared to the corresponding acute slice data. Our work demonstrates unprecedented novel applications of cell class-specific viral genetic labeling, together with *ex vivo* brain slice culture, to explore diverse functional properties of human brain cell types.

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Poster

735. Synaptic Transmission, Integration, and Signal Propagation

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VA Merit Review Grant I01-BX002949
DoD CDMRP W81XWH-18-1-0598

Title: Increased climbing fiber vesicle release and aberrant innervation in CACNA2D2 knockout mice

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Abstract: The alpha2delta family of proteins (CACNA2D1-4) are auxiliary subunits of voltage-dependent calcium channels, and also drive excitatory synapse formation and maturation. Unlike the majority of neurons in the central nervous system, Purkinje cells of the cerebellum exclusively express one isoform of this protein family, alpha2delta-2 (CACNA2D2), and provide a model system to understand the roles of these proteins in excitatory synaptic function. Using whole cell electrophysiologic recordings of acutely prepared cerebellar slices from wildtype and CACNA2D2 knockout mice, we found a dramatic change in the complex spiking of Purkinje cells induced by climbing fiber (CF) activation, which was coupled with increased amplitude and decay rate of underlying synaptic currents in cells from CACNA2D2 mutants. Detailed electrophysiologic analyses, in addition to immunofluorescence, electron microscopy, and computational modeling demonstrate that the larger currents in mutant mice are due to a combination of proximally shifted CF terminals and significantly increased multivesicular release, despite a reduced probability of release at these synapses. These apparently paradoxical findings are explained by the existence of a doubling in the number of vesicle release sites in CF terminals of mutant mice. In addition, enhanced glutamate transporter function compensates for increased vesicle release by accelerating glutamate clearance from the synaptic cleft, speeding decay kinetics of the synaptic currents and maintaining normal charge transfer during CF responses. Ultimately, the altered CF-induced spiking - an important signal responsible for prediction error and motor coordination - indicates that CACNA2D2 is required for normal cerebellar network activity. Thus, these studies demonstrate multiple unexpected, yet critical, roles of CACNA2D2 in synaptic structure and function.

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Poster

735. Synaptic Transmission, Integration, and Signal Propagation

Location: Hall A

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Program #/Poster #: 735.15/B37

Topic: B.09. Network interactions

Support: SFB 1134

Title: Noncanonical axon morphologies gate information flow in neuronal ensembles

Authors: A. HODAPP[1], M. E. KAISER[1], Y. YANOVSKY[1], M. KLUMPP[1], P. PFEIFFER[2], A. DRAGUHN[1], M. ENGELHARDT[3], C. THOME[1], ***M. BOTH**[1];
[1]Heidelberg Univ., Heidelberg, Germany; [2]Humboldt Univ. of Berlin, Berlin, Germany; [3]Inst. of Neuroanatomy, Med. Fac. Mannheim, Heidelberg Univ., Mannheim, Germany

Abstract: The hippocampus exhibits network oscillations during which selected groups of neurons are activated (ensembles), supporting spatial memory formation and consolidation.

During this process, they receive multiple synaptic inputs at their dendrites, which integrate within the somato-dendritic compartment and generate action potentials (AP) once voltage threshold is reached at the axon initial segment which is canonically believed to be located next to the soma in pyramidal cells. However, we have recently shown that in about 50% of CA1 hippocampal pyramidal cells the axon originates from a basal dendrite (axon-carrying dendrite cells, AcD cells) rather than from the soma. AcD cells are intrinsically more excitable and the axon-carrying dendrite might constitute a privileged input channel in this subset of cells. Additionally, previous work in vitro has shown that during sharp wave-ripple complexes (SPW-R) CA1 pyramidal cells are recruited in a peculiar way: their somatic action potential initiates abruptly from baseline resembling an ectopically generated spike. It is unknown how these neurons are selected to participate in the network pattern. Here we asked whether the anatomical feature of AcD cells underlies the selective activation of CA1 pyramidal cells during SPW-R. To test our hypothesis, we performed extra- and intracellular electrophysiological recordings as well as immunofluorescent staining in acute hippocampal mouse brain slices. Interestingly, excitatory input to axon-carrying dendrites remains efficient even during the strong perisomatic inhibition that accompanies SPW-Rs and prevents other pyramidal cells from firing. Thus, only AcD cells are able to fire APs during the events. In line with our previous data, AP waveforms resemble ectopically generated spikes. Multicompartment modelling of single cells confirms that in somatic recordings of AcD cells, APs initiate abruptly from resting membrane potential when excitatory and inhibitory inputs arrive with a certain spatio-temporal configuration. Intracellular administration of picrotoxin diminished perisomatic inhibition, recruited more cells into SPW-R and shifted ectopic AP waveforms towards classical APs.
In summary, AcD cells are selectively recruited during SPW-R activity while the firing probability of other neurons is controlled by perisomatic inhibition. As a result, reducing GABAergic input can modify ensemble composition within short time. Our findings suggest that perisomatic inhibition combined with different axon origins provide a mechanism to rapidly gate and route incoming information and thus enables fast modifications of ensemble compositions.

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Poster

735. Synaptic Transmission, Integration, and Signal Propagation

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Topic: B.09. Network interactions

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Shanghai Municipal Science and Technology Major Project 2018SHZDZX05

Key Research Program of Frontier Sciences of Chinese Academy of Sciences
QYZDY-SSW-SMC028

Title: Brain-wide varicosity activities of single locus coeruleus neurons

Authors: *W. CHEN[1,2], P. XIANG[1], J. DU[1,2];
[1]Inst. of Neuroscience, State Key Lab. of Neuroscience, CAS Ctr. for Excellence in Brain Sci. and Intelligence Technology, Chinese Acad. of Sci., Shanghai 200031, China; [2]Univ. of Chinese Acad. of Sci., Beijing 100049, China

Abstract: In the central nervous system, neurons are characterized by complex morphology, long-range projection and potentially heterogeneous presynaptic puncta. However, it is not clear how information is encoded by action potentials on the axonal arborization. We chose locus coerules (LC) neurons in zebrafish as an experimental model to address this question. By combining in vivo confocal imaging and electrophysiology recording, we found that calcium activities are reliably evoked in all axon arborizations in all brain regions during both low- and high-frequency neuronal activities. The presynaptic varicosities are heterogeneous in terms of their sizes, activity strength and frequency tuning. However, heterogeneous varicosities distribute homogeneously among the axon arborization in each brain regions, enabling equal modulation effects on all brain areas during different firing modes.

Disclosures: **W. Chen:** None. **P. Xiang:** None. **J. Du:** None.

Poster

735. Synaptic Transmission, Integration, and Signal Propagation

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 735.17/B39

Topic: B.09. Network interactions

Title: The influence of cortical layer 6 on neurophysiological evoked responses and spontaneous activity within a mouse barrel column

Authors: *V. MOCANU[1], A. R. ADAMANTIDIS[2], P. A. SEGUELA[3], A. SHMUEL[1];
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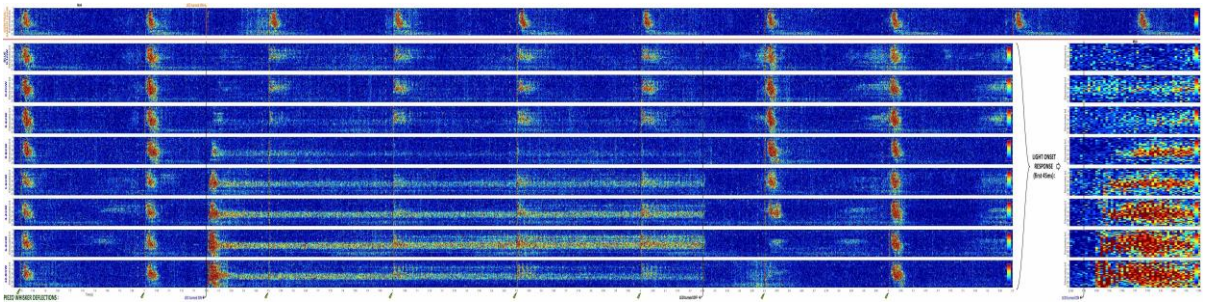
Abstract: The long term goal of our research is to decipher the role of cortical layer 6 and the way it interacts with other layers during evoked responses and spontaneous activity. Previous studies (Olsen et al., 2012; Bortone et al., 2014) excited or inhibited a subgroup of pyramidal neurons in cortical layer 6 (L6 Pyr) with high temporal, location and cell type precision, by using the GN220 transgenic mouse lineage and optogenetics. Whiskers are the main somatosensory modality of rodents. To test the effect of L6 Pyr on activity of the barrel cortex, we expressed

light-sensitive selective ion channels (opsins), introduced genetically via viral microinjections, in the L6 Pyr of the barrel cortex of 3-6 months old mice of indiscriminate gender. Then, by photostimulating at the appropriate wavelength and at power levels increasing from 0.1mW to 12.8mW, we modulated the activity of L6 Pyr during periods of either spontaneous neural activity or during a train of 2Hz piezoelectric-driven deflections of four major whiskers. We used optical imaging of intrinsic signals to guide the insertion of a laminar probe into a barrel, from which we recorded extracellular broadband electrophysiology. A layer-wise analysis of either current source density or action potentials time-courses showed that optogenetic activation of L6 Pyr suppressed stimulus-evoked responses (S-ER) in the upper cortical layers while increasing action potential activity in L6, all in a light power-dependent manner (see figure, left side). The onset and offset of the optogenetic photostimulating light engendered neurophysiological responses that became stronger and faster with increasing light power (see figure, right side). Conversely, inhibiting L6 Pyr using eArch3.0 increased the strength of incoming S-ER, to an extent where the hyperpolarization following the strongest S-ER trailed into the next stimulus cycle and diminished its S-ER. Our finding extend previous work on the inter-laminar interactions at the meso-scale to the domain of the barrel cortex.



Disclosures: **V. Mocanu:** None. **A.R. Adamantidis:** None. **P.A. Seguela:** None. **A. Shmuel:** None.

Poster

735. Synaptic Transmission, Integration, and Signal Propagation

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Topic: B.09. Network interactions

Support: ERC grant 679253
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Title: Trans-synaptically activated neurons act as temporal coders

Authors: *A. LEVI[1], S. SOMECK[1], E. STARK[2];
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Abstract: Within a neural network, information is encoded by spiking activity of multiple synaptically-connected neurons. The mechanisms of spike generation by one cell, and of transmission between cells have been studied before, yet it remains unclear whether a neuron is an integrator or a coincidence detector.
We used extra-cellular recordings and optogenetic manipulations in neocortex and hippocampus of freely-moving mice expressing light-sensitive opsins in either pyramidal cells (PYR) or parvalbumin-immunoreactive (PV) interneurons. We used Gaussian white noise (GWN) stimulation patterns while simultaneously recording spiking activity of multiple neurons. We defined spiking reliability as the correlation between spike trains during repeated stimulation trials, where every spike is convolved with a Gaussian kernel with a specific SD. To determine the dependence of reliability on the time window, we repeated the process with SDs ranging from sub-millisecond to hundreds of ms.
We found that the reliability of directly-activated units either increased with increasing kernel SD, or exhibited a single peak in the reliability vs. SD curve. The first behavior indicates higher reliability with longer integration time, corresponding to a “rate code”; whereas the second behavior corresponds to a preferred window or a “temporal code”. In some cases, the same cell was tested with multiple stimulation intensity levels of the exact same GWN pattern. Units tended to change their behavior from temporal to rate coding with increased stimulation intensity. These findings suggest that the same cell can generate spikes via two distinct dynamical mechanics: at low input levels, specific temporal windows dominate, whereas at higher input levels, the cells behaves as a monotonous integrator of its inputs.
We monitored networks in which multiple directly-activated units exhibited putative monosynaptic connections with a single unit that was not directly-activated by the GWN input. In contrast to the mixed behavior of the directly-activated units, the vast majority of indirectly activated units exhibited a single reliability peak at an SD range of 4-8 ms. This “temporal coding” behavior was observed for multiple types of indirectly-activated units, regardless of stimulation intensity. This suggests that during trans-synaptic activation, cells tend to detect coincidence events of the spike trains of their presynaptic partners.
Thus, the present results correspond to a transition from rate code/mixed-mode mechanism of spike generation in a directly-activated neuron; to a temporal/coincidence detection mechanism of spike transfer in a synaptically-activated neuron.

Disclosures: A. Levi: None. **S. Someck:** None. **E. Stark:** None.

Poster

735. Synaptic Transmission, Integration, and Signal Propagation

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Topic: B.09. Network interactions

Support: NIH U01EB017695
DOH01-C32250GG-3450000
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Title: Computer models of mouse area M1 show avalanches for full model and subcircuits defined by layer or cell type

Authors: *D. W. DOHERTY[1], S. DURA-BERNAL[2], W. W. LYTTON[3];
[1]SUNY Downstate Med. Ctr., Brooklyn, NY; [2]Physiol. and Pharmacol., State Univ. of New York Downstate Med. Ctr., Brooklyn, NY; [3]SUNY Downstate, Brooklyn, NY

Abstract: Beggs and Plentz (2003) reported avalanches in local field potential recordings from organotypic cultures and in unit recordings from acute slices of rat somatosensory cortex with a power-law value of -1.5. Since then, a range of avalanche size distribution values has been reported from about -2.05 to -1.25.
We investigated the circuitry underlying avalanche propagation in a computer model of area M1 of cerebral cortex. This allowed us to distinguish the characteristics of avalanches along different routes defined by either layer or cell type, as well as throughout the column. The M1 model is a moderately detailed simulation of a full-depth cylindrical column of 300μm diameter, containing 10,074 neurons with about 18 million connections. Activation was with an 0.57nA intracellular square-wave current applied to all cells in a 40μm cylindrical subvolume.
Avalanche sizes from all neuron types and layers of the M1 cortical column fit the power-law value -1.80. Avalanches in the population of excitatory neurons fit -1.69 and the population of M1 inhibitory neurons fit to the power-law value -1.72 for avalanche size. Avalanche sizes in layer 2/3 fit a relatively steep -1.94 and similarly in layer 5B they fit -1.90. The power-law value became sharply less negative in layer 4 at -1.75 and in layer 5A at -1.61 and layer 6 at -1.63. Excitatory neurons appeared to form two groups. One group includes three neuron types: IT2/3 neurons carried avalanche sizes that fit power-law value of -1.64, IT5A also neurons fit -1.54 and IT6 fit -1.60. Three other excitatory neurons form the second group: IT4 neurons with avalanche sizes that fit -1.75, IT5B neurons at -1.71 and PT5B neurons at -1.76. Inhibitory neurons also formed two groups. One group had very steep power-law curves and the size of their avalanches did not get very large. This group included PV2/3 neurons with a power-law value of -2.27 and SOM6 at -2.44. The second group had somewhat less steep curves and included SOM2/3 -1.84, PV5A -1.41 (small sample), and PV5B -1.65. SOM5A, SOM5B, CT6, and PV6 neurons had low

response rates and therefore did not generate enough data to determine the shape of their avalanche size distributions.
In conclusion, several excitatory neuron types, particularly IT2/3, IT5A, and IT6, may operate at criticality in our simulated M1 cortical column. Our data also suggest that some inhibitory neurons, especially PV2/3 and SOM6, may not operate in the critical state. Avalanche size distribution is differentially expressed across different layers and different cell types in our simulated M1 cortical column.

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Poster

735. Synaptic Transmission, Integration, and Signal Propagation

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Topic: B.09. Network interactions

Support: BRAIN initiative Grant U19 NS107464-01
Division of Intramural Research Program

Title: How to control a neuronal network near its critical point

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Abstract: It is now generally accepted that criticality endows neuronal networks with a variety of functional advantages including great flexibility, very large dynamic range, extreme sensitivity, optimal information processing via its long range correlations in space and time, large memory capacity, among the most relevant (Beggs & Plenz 2003, Chialvo, 2010). Despite the abundance of reports of *observed* criticality much less is known about the process that makes neuronal networks to *be there, i.e., how the system reaches and stays at criticality.* To shed light on the problem here we expand previous work on controlling criticality (Cannas et al., 2019) to the realm of neuronal networks. We make use of a generic property of the fluctuations near a point of instability: as the system approaches the critical point the temporal correlations of global variables became stronger. Our results show that it is sufficent to feedback the value of the autocorrelation to a network's control parameter (such as excitability) to drive an arbitrary neuronal network near its critical point. Numerically we show that the strategy is equally effective over a variety of networks architectures and selection of control parameters.

Experiments in real neuronal networks are currently conducted to identify the predicted shape of the autocorrelation function.

Disclosures: D.R. Chialvo: None. **S.A. Cannas:** None. **T.S. Grigera:** None. **D. Plenz:** None. **D.A. Martin:** None.

Poster

735. Synaptic Transmission, Integration, and Signal Propagation

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 735.21/B43

Topic: I.06. Computation/ Modeling/ and Simulation

Support: Whitehall Foundation Grant 17-12-114
NSF Grant 1429500
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NSF Grant 1735095
INSGC

Title: Correlation drives computation in local cortical networks at synaptically relevant timescales

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Abstract: How do neurons work cooperatively to support neural information processing? The amount of processing is widely presumed to be related to the amount of correlated information in the firing of upstream neurons. However, the amount of correlation that is most desirable remains disputed. High levels of correlation result in an abundance of redundant information, arguably reducing processing efficiency. Alternatively, low levels of correlation mean that inputs are often too uncoordinated to result in meaningful integration. Which of these paradigms is most relevant for cortical information processing is undetermined. Here, we sought to address which is more relevant by recording and analyzing the spiking activity, in organotypic cultures of mouse somatosensory cortex, from hundreds of neurons. For these recordings, we identified the effective functional network representing activity propagation through the cortical circuit at timescales relevant to synaptic communication. At each possible point of neural computation-the transformation of multiple inputs by a single neuron-we asked how the correlations between the inputs related to the computation performed by that neuron. Our results first revealed that the large majority of our networks operate in a low-correlation regime. Subsequently, we found strong positive correlations in the amount of correlation and computation across networks. This suggests that, at shorter timescales, increased correlation is preferable for driving computation.

When we considered interactions at extra-synaptic timescales, we found an increase in the mean correlation suggesting a transition to a high-correlation regime. Interestingly, at these longer timescales we also found increasingly negative relationships between correlation and computation. Together, these findings suggest that computation in these networks is optimized for intermediate levels of correlation, rather than simply minimal or maximal levels of correlation. We discuss this further in the context of multivariate transfer entropy, firing rate and Shannon entropy.

Disclosures: **S.P. Faber:** None. **N. Timme:** None. **J.M. Beggs:** None. **E.L. Newman:** None.

Poster

736. Transcription and Translation in Plasticity II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 736.01/B44

Topic: B.07. Synaptic Plasticity

Title: Histone serotonylation: A novel regulator of stress-induced neuroplasticity

Authors: *A. AL-KACHAK[1], R. BASTLE[1], S. FULTON[1], A. LEPACK[1], P. SAFOVICH[1], L. FARRELLY[1], Y. LYU[1], C. MENARD[2], A. RAMAKRISHNAN[1], A. AGUSTINUS[3], S. RUSSO[1], L. SHEN[1], Y. DAVID[3], I. MAZE[1];
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Abstract: The field of neuroepigenetics has grown rapidly over the past few decades and has recently implicated chromatin phenomena in the etiology of several psychiatric disorders including major depressive disorder (MDD). While it has been demonstrated that dysregulation of histone posttranslational modifications (PTMs) may be involved in the deleterious transcriptional processes that promote physiological maladaptations in MDD, the field still has only a limited understanding of the underlying mechanisms contributing to this disorder. While it is clear that serotonergic signaling in brain, or aberrations thereof, plays a critical role in the pathophysiology and treatment of MDD, new data from our laboratory suggest potential alternative mechanisms of action for monoamines-so-called histone serotonylation-whereby, for example, the presence of serotonin in the nucleus of dorsal raphe (DRN) neurons may directly mediate transcriptional responses related to various forms of serotonergic plasticity, and the subsequent mediation of mood. Our preliminary data indicate that histone serotonylation is significantly altered in both postmortem DRN tissues from MDD subjects and in chronically stressed rodents, phenomena that appear to be reversed by antidepressant treatments. Furthermore, potentiation of such alterations in a rodent model of MDD (e.g., chronic social defeat stress, CSDS) induced various molecular and circuit level adaptations throughout the

DRN. Our studies provide a causal link between these molecular changes and the persistence of depressive-like phenotypes.
While a majority of antidepressant treatments target dysfunction of serotonergic neurotransmission in brain, these drugs are only are only effective for ~1/3 of individuals with MDD. Therefore, it is important to establish novel approaches that specifically target histone PTMs in a cell-type specific manner *in vivo* to better understand their direct contributions to disease states for the development of future pharmacological interventions. Thus, we have developed novel intein-based chemical methodologies to synthesize specific histone PTMs to more directly assess a functional role for histone serotonylation in depressive-like behaviors.

Disclosures: **A. Al-Kachak:** None. **R. Bastle:** None. **S. Fulton:** None. **A. Lepack:** None. **P. Safovich:** None. **L. Farrelly:** None. **Y. Lyu:** None. **C. Menard:** None. **A. Ramakrishnan:** None. **A. Agustinus:** None. **S. Russo:** None. **L. Shen:** None. **Y. David:** None. **I. Maze:** None.

Poster

736. Transcription and Translation in Plasticity II

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Program #/Poster #: 736.02/B45

Topic: B.07. Synaptic Plasticity

Support: DP1 DA042078
R21 DA044767

Title: Identification of novel substrates of monoaminylation in brain, and their regulation by drugs of abuse

Authors: *A. F. STEWART[1], R. BASTLE[1], R. THOMPSON[3], A. LEPACK[1], Y. LYU[1], L. FARRELLY[4], H. MOLINA[5], T. MUIR[3], I. S. MAZE[2];
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Abstract: Monoamines are traditionally regarded as chemical signals that act extracellularly on surface bound receptors in brain. However, recent work from our lab demonstrates that non-vesicular monoamines have a neurotransmission-independent function in nuclei of monoaminergic cells, whereby they can be transamidated onto glutamine 5 of histone 3 to act as a novel epigenetic marker relevant in pathophysiological conditions, such as substance abuse disorders (SADs). Therefore, we hypothesized that non-histone proteins may similarly be monoaminylated. To selectively isolate monoaminylated proteins in brain, we developed a novel endogenous chemical tagging method to specifically immunoprecipitate (IP) dopaminylated/noradrenylated proteins. This approach utilizes the unique chemistry of the

catechol ring to selectively add biotin tags to endogenously modified proteins. Following chronic drug self-administration in rats, immunoprecipitations coupled to mass spectrometry identified novel monoaminylated proteins, including multiple isoforms of CaMKII, with their monoaminylation states regulated by drugs of abuse. We further characterized CaMKII dopaminylation utilizing *in vitro* enzymatic assays coupled to mass spectroscopy, to identify glutamine 284/285 (depending on isoform) as selective sites of monoaminylation on CaMKII. These data represent not only a possible novel biochemical mechanism of regulation of CaMKII, but also a possible shift in our conceptualization of monoaminergic transmission: monoamines would not then simply act at surface bound receptors, but also infiltrate the post-synaptic cell and modify proteins therein.

Disclosures: **A.F. Stewart:** None. **R. Bastle:** None. **R. Thompson:** None. **A. LePack:** None. **Y. Lyu:** None. **L. Farrelly:** None. **H. Molina:** None. **I.S. Maze:** None. **T. Muir:** None.

Poster

736. Transcription and Translation in Plasticity II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 736.03/B46

Topic: B.07. Synaptic Plasticity

Support: NIH Grant MH116900
NIH Grant DA044767
NIH Grant DA042078

Title: Sex-dependent roles for histone serotonylation in neurodevelopment

Authors: *J. C. CHAN, A. RAMAKRISHNAN, L. SHEN, I. MAZE;
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Abstract: Monoaminergic systems are critical for brain development, impacting cell proliferation, migration, differentiation and axonal elaboration. In particular, serotonin (5-HT) is the most widely distributed monoamine in the brain, with a dual role acting as both a neurotransmitter and trophic factor during development. For example, 5-HT can bind receptors on 5-HT terminals, negatively regulating formation of serotonergic projections to other brain regions, modulating the plasticity of these circuits. Thus, regulation of 5-HT levels during such sensitive windows of development is essential, and dysregulation of 5-HT homeostasis may contribute to increased risk of psychopathology later in life. One example is hyperserotonemia, an endophenotype consistently found in about 30% of autistic patients, where 5-HT levels are increased in whole blood but decreased in brain, resulting in the developmental hyperserotonemia hypothesis. Yet, despite substantial evidence supporting these roles of 5-HT in neurodevelopment and disease, our understanding of the cellular mechanisms by which 5-HT

dysregulation during developmental windows impacts long-term outcomes is still unclear. Recently, our lab established a novel epigenetic role for 5-HT. We have demonstrated that 5-HT is deposited on the glutamine at position 5 of the histone H3 tail (H3Q5ser) by the transglutaminase enzyme TGM2. This serotonylation reaction stabilizes the canonically transcriptionally-active lysine 4 tri-methylation (H3K4me3), resulting in the combinatorial modification H3K4me3Q5ser that correlates with permissive gene expression. Thus, we hypothesized that histone serotonylation may provide 5-HT a crucial role in chromatin regulation of neurodevelopment. We focused on the involvement of histone serotonylation in two predominant serotonergic tissues during embryogenesis: the embryonic brain and the placenta, which converts the precursor amino acid tryptophan from maternal blood to bioavailable 5-HT in the embryonic bloodstream. Using immunoblotting, we demonstrate that H3K4me3Q5ser levels differ across embryogenesis in brains and placentas of male, but not female, embryos. We also performed ChIP-seq of H3K4me3Q5ser, along with RNA-seq, in these tissues to identify the impact of sex and developmental timing on genome-wide enrichment of this mark. Ongoing experiments focus on manipulation of developmental histone serotonylation levels and long-term consequences on brain function. These studies suggest an important role for histone serotonylation in neurodevelopment that, when disrupted, may contribute to developmental origins of neuropsychiatric disorders.

Disclosures: **J.C. Chan:** None. **A. Ramakrishnan:** None. **L. Shen:** None. **I. Maze:** None.

Poster

736. Transcription and Translation in Plasticity II

Location: Hall A

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Program #/Poster #: 736.04/B47

Topic: B.07. Synaptic Plasticity

Support: National Natural Science Foundation of China, No. 31871042

Title: The effect of local translated mtIF3 on axonal pathfinding by modulating mitochondrial function

Authors: L. CHEN, L. XIANG, ***W. WANG**;
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Abstract: As previously known, axonal pathfinding is partly regulated by local protein synthesis of specific genes within axon. The role of local translation of many cytoskeleton genes such as *actin* and *cofilin1* has been studied well. A subgroup of mRNAs, which are transcribed from the nuclear-encoded mitochondrial genes, are enriched in axon terminus, however, the contribution of local translation of these mRNAs remains obscure. In our study, we found that one of them, mitochondrial translational initial factor3(mtIF3), could be locally translated in axon. As a

consequence, the deficiency of local translation of mtIF3 disrupted ATP generation and Ca2+ buffering of mitochondrions in axon, as well as axonal outgrowth. We figured out that locally synthesized mtIF3 protein regulated protein synthesis inside mitochondrion, which in turn had an effect on mitochondrial function in axon. As expected, when we exclusively inhibited protein synthesis inside mitochondrion in axon, axonal growth and axonal pathfinding in cultured neurons was also interfered. Taken together, our findings indicate that local protein synthesis in axon may impact on axonal pathfinding in a novel manner by directly modulating mitochondrial function.

Disclosures: L. chen: None. **L. xiang:** None. **W. Wang:** None.

Poster

736. Transcription and Translation in Plasticity II

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Program #/Poster #: 736.05/B48

Topic: B.07. Synaptic Plasticity

Support: NIH Grant DP1DA042078
NIH Grant T32DA007135

Title: Influence of histone H3Q5 histaminylation on WDR5-mediated H3K4 methylation and circadian rhythmicity

Authors: *R. M. BASTLE[1], S. ZHAO[2], A. RAMAKRISHNAN[1], R. THOMPSON[3], A. AL-KACHAK[1], S. FULTON[1], A. LEPACK[1], L. FARRELLY[1], Y. LYU[1], H. MOLINA[4], L. SHEN[1], T. MUIR[3], H. LI[2], I. MAZE[1];
[1]Icahn Sch. of Med. at Mount Sinai, New York, NY; [2]Tsinghua Univ., Beijing, China; [3]Princeton Univ., Princeton, NJ; [4]Rockefeller Univ., New York, NY

Abstract: Monoaminylation is a recently discovered phenomenon where intracellular, non-vesicular monoamines can be post-translationally added to glutamine (Q) residues on proteins via the tissue Transglutaminase 2 enzyme. Our laboratory has demonstrated that histone H3 is a robust substrate for monoaminylation on its fifth glutamine residue (i.e., H3Q5) within the N-terminal tail and we have uncovered roles for H3Q5 serotonylation and dopaminylation in transcriptional activation and dopaminergic neurotransmission, respectively. Given that brain histamine levels are largely rhythmic across 24 h and govern wakefulness, we sought to explore the role of H3Q5 histaminylation (i.e., H3Q5his) in regulating circadian rhythms. Upon measuring H3Q5his levels in mouse brain using site-specific antibodies, we found that H3Q5his expression is enriched in the tuberomammillary nucleus (TMN) of the hypothalamus, the source of brain histamine, and exhibits a rhythmic pattern of expression across 24 h. This expression pattern is sensitive to sleep disturbance, as delivery of zolpidem (10 mg/kg, i.p.), which rapidly

induces sleep, alters TMN H3Q5his expression. Furthermore, viral-mediated knockdown of TMN H3Q5his disrupts circadian locomotor activity in mice. To investigate the molecular mechanisms mediating these effects, we performed isothermal titration calorimetry to examine binding efficiencies of known epigenetic regulator proteins onto H3Q5his. We found that WDR5, which is involved in depositing methyl groups onto H3K4, has significantly reduced binding (~5 fold) to H3Q5his compared to unmodified H3. We found that this effect is due to the charge repulsion between the positively-charged histamine and lysine in the binding pocket of WDR5 (K259). Furthermore, using MALDI-TOF mass spectrometry we found that the presence of histamine on H3Q5 significantly decreases MLL1-mediated methyltransferase activity onto H3K4. Ongoing studies are utilizing viral vectors to manipulate the charge of WDR5 (K259) and associated H3Q5his interactions to measure its effect on circadian gene expression and behavior. These experiments promise to reveal a novel mechanism in which brain H3Q5his may influence H3K4 methylation in the context of circadian rhythms.

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Poster

736. Transcription and Translation in Plasticity II

Location: Hall A

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Program #/Poster #: 736.06/B49

Topic: B.07. Synaptic Plasticity

Support: F31 DA045428
DP1 DA042078

Title: Region specific effects of histone H3 dopaminylation in cocaine-seeking behavior

Authors: *A. LEPACK[1], S. L. FULTON[3], A. F. STEWART[1], R. M. BASTLE[2], P. J. KENNY[4], I. S. MAZE[2];
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Abstract: Substance use disorder–a persistent, relapsing illness characterized by pathological drug taking and seeking-behaviors–is hypothesized to result from a functional “rewiring” of the brain’s normal reward circuitry. Such “rewiring” is thought to be caused by long-lived changes in gene expression that promote physiological alterations implicated in addiction. Recently, we identified a role for the previously uncharacterized histone modification, H3 glutamine 5 dopaminylation (H3Q5dop), in drug-induced transcriptional plasticity. Withdrawal (WD) from

chronic cocaine self-administration (SA) in rats results in increased levels of H3Q5dop in ventral tegmental area (VTA), which correlates with a pathophysiological accumulation of intracellular dopamine (DA) during abstinence. Furthermore, by viral-mediated reduction of H3Q5dop in VTA during WD, we can attenuate cocaine-seeking behavior through reversal of gene expression patterns contributing to aberrant, cue-induced DA release. Interestingly, we also observe H3Q5dop expression in non-DAergic producing brain regions, specifically regions to which the VTA projects (e.g. prefrontal cortex [PFC] and nucleus accumbens [NAc]). Following short (24hr) WD from cocaine, we observe a robust increase in H3Q5dop in the NAc, which persists up to 30 days following abstinence from cocaine, an effect that is not seen in the PFC. In addition, viral-mediated blockade of H3Q5dop in the NAc, but not the PFC, results in decreased cocaine-seeking behaviors following prolonged WD from cocaine, suggesting a circuit-based phenomenon for H3Q5dop in regulating addictive and relapse-associated phenotypes. Taken together, these studies establish a critical neurotransmission-independent role for DA in addiction and promise to aid in our understanding as to how neurotransmission-independent DA function in brain to regulate neuronal plasticity and cocaine-mediated behaviors.

Disclosures: **A. Lepack:** None. **S.L. Fulton:** None. **A.F. Stewart:** None. **R.M. Bastle:** None. **P.J. Kenny:** None. **I.S. Maze:** None.

Poster

736. Transcription and Translation in Plasticity II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 736.07/B50

Topic: B.07. Synaptic Plasticity

Support: P50 MH096890

Title: Profiling cell-type specific chromatin accessibility in human OFC implicates astrocyte dysfunction in MDD

Authors: *S. L. FULTON[1], J. FULLARD[2], J. BENDL[2], A. LEPACK[3], R. M. BASTLE[5], A. AL-KACHAK[3], C. A. TAMMINGA[6], P. ROUSSOS[2], I. S. MAZE[4];
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Abstract: Major Depressive Disorder (MDD) is a chronic debilitating disease that arises from a complex interaction of genetics and environmental influences like stress, leading to persistent changes in frontolimbic gene expression and cellular function. However, the epigenetic mechanisms that transduce stress into coordinated gene expression changes are not well

understood. Chromatin accessibility profiling allows researchers to define the active repertoire of cis-regulatory elements for a given disease. We implemented FANs (*F*luorescence-*A*ctivated *N*uclear *S*orting) coupled with ATAC-seq (*A*ssay for *T*ransposase-*A*ccessible *C*hromatin-Sequencing) to investigate the cell type-specific regulatory landscape of human MDD. We identified over 200 MDD-specific open chromatin regions (OCRs), which were all in the non-neuronal cell population in postmortem orbitofrontal cortex (OFC) tissue, a region that processes reward-based decision-making and may mediate anhedonic symptoms in MDD. Gene set analyses of these genomic regions showed enrichment for astrocyte-mediated NF-Kb inflammatory response. These results converge with mounting evidence that inflammation stress can be a major contributor to MDD, though the specific role of astrocytes is not well characterized. We used transcription-factor motif discovery to identify ZBTB7A, a DNA-binding protein with recognition sequences significantly overrepresented in MDD-specific OCRs. ZBTB7A is a well-characterized chromatin remodeling factor, though its function in psychiatric disease has not been explored. Recently, ZBTB7A has been shown to orchestrate chromatin accessibility for a distinct subset of delayed induction NF-Kb target genes, raising the intriguing possibility that ZBTB7A may regulate the transduction of chronic NF-Kb stress signaling from adaptive to pathological**.** We found that ZBTB7A mRNA and protein are upregulated in human MDD OFC postmortem tissues. Zbtb7a mRNA is also significantly upregulated in OFC astrocytes of CSDS (chronic social defeat stress) susceptible mice. Using a cell-type specific sequencing approach, we found that over 60% of the upregulated astrocytic genes in stress-susceptible animals are Zbtb7a targets. Viral overexpression of Zbtb7a specifically in astrocytes in both the mouse and rat OFC increased vulnerability to developing stress-related behavioral deficits after an acute stressor, suggesting that upregulation of ZBTB7A in OFC astrocytes acts as a pathogenic driver of pro-inflammatory NF-Kb signaling in MDD through epigenetic modulation of chromatin accessibility at key downstream target genes, leading to MDD-related behavioral deficits.

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Poster

736. Transcription and Translation in Plasticity II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 736.08/B51

Topic: B.07. Synaptic Plasticity

Title: Chromatin profiling in human neurons reveals aberrant roles for histone H2A.Z acetylation and its associated interactions with BRD4 in schizophrenia

Authors: *L. FARRELLY[1], S. ZHANG[2], A. TOPOL[1], R. M. BASTLE[1], E. FLAHERTY[3], N. BHANU[4], B. GARCIA[4], H. LI[2], K. BRENNAND[3], I. MAZE[5];
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Abstract: Schizophrenia (SCZ) is a severe psychiatric disorder affecting ~1% of the world's population. It is largely heritable with genetic risk reflected by a combination of highly penetrant rare mutations and common variants of small effect. Most commonly prescribed antipsychotic drugs for the treatment of SCZ share antagonist activity against dopamine receptors and primarily address the positive psychotic symptoms of the disease. Unfortunately about one third of SCZ patients do not respond to treatments, indicating that better therapeutics aimed at targeting novel candidates may prove beneficial. In addition, chromatin modifications are known to play critical roles in the mediation of many neurodevelopmental processes, and, when disturbed, may also contribute to the precipitation of psychiatric disorders, such as SCZ. While a handful of candidate-based studies have measured changes in promoter-bound histone modifications, few mechanistic studies have been carried out to explore how these modifications may affect chromatin to precipitate behavioral phenotypes associated with SCZ.
We applied an unbiased and integrative approach to evaluate the epigenetic landscape of SCZ in human induced pluripotent stem cells (hiPSC), neural progenitor cells (NPCs) and neurons from schizophrenia patients *vs.* matched controls. Using proteomics-based, label free liquid chromatography mass spectrometry (LC-MS/MS) on purified histones from these cells, we specifically identified H2A.ZK4K7K11ac and H4K5K8K12ac to be significantly increased in SCZ neurons *vs.* controls, but not in hiPSCs or NPCs from the same subjects. These results were confirmed by western blotting and LC-MS/MS in postmortem SCZ cortical brain tissues. Histone interaction assays revealed the bromodomain containing protein, BRD4 (a known acetyl "reader," particularly for H4), as a novel binder of H2A.ZK4K7K11ac, data which were further confirmed by structural and biophysical assessments. Given such links between BRD4 and H2A.Z/H4 acetyl states found to be increased in SCZ neurons, we hypothesized that inhibiting BRD4 might itself help to ameliorate, SCZ-like phenotypes (e.g., aberrant gene expression and behavior) in both hiPSC neurons and rodent models of abnormal sensory-motor gating associated with SCZ. We have found that treatments with the BRD4 inhibitor, JQ1 (which inhibits BRD4 binding to both H2A.Z and H4 acetyl signatures), partially rescues the transcriptional and behavioral deficits associated with the disease. Thus, drug treatments aimed at alleviating BRD4 interactions with its acetylated histone targets may be useful in ameliorating deficits associated with SCZ.

Disclosures: L. Farrelly: None. **S. Zhang:** None. **A. Topol:** None. **R.M. Bastle:** None. **E. Flaherty:** None. **N. Bhanu:** None. **B. Garcia:** None. **H. Li:** None. **K. Brennand:** None. **I. Maze:** None.

Poster

736. Transcription and Translation in Plasticity II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 736.09/B52

Topic: B.07. Synaptic Plasticity

Support: R01AA024434
Southern Illinois University Edwardsville

Title: Nuclear RNA-seq of *Drosophila* mushroom body neurons reveals alcohol's lasting effect on transcriptional splicing

Authors: E. PETRUCCELLI[1], N. LEDRU[2], K. R. KAUN[3];
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Abstract: Understanding the dynamic transcriptional responses of specific neural cell-types is crucial for decoding behavioral plasticity. A nuclear RNA-seq approach can help reveal how experiences affect active transcriptional states. The genetic accessibility and conserved behavioral response to alcohol seen in *Drosophila* make them a great model for investigating unresolved questions in the alcohol and addiction fields. Here we addressed how alcohol hijacks memory-encoding transcriptional processes to drive maladaptive decision-making. Flies were exposed to either repeated bouts of air, ethanol, odors, or paired ethanol-odors, and then 24 hours after treatment, nuclear RNA-seq was performed on mushroom body neurons. Differential expression analysis showed significant experience-specific changes at the transcript, and not gene, level. This suggests that alternative splicing is an important mechanism by which long-term memories are encoded, and that alcohol exposure alters this process. Intriguingly, eight particular transcripts were differentially expressed when flies formed associative memories of intoxication (ethanol-odor training). One of these candidates, *Stat92E*, has known protein-protein interactions with spliceosomal proteins, which suggests a possible means through which alcohol disrupts normal splicing. Together these findings suggest a layer of molecular plasticity through which alcohol could influence memory formation and alcohol-associated behaviors.

Disclosures: E. Petruccelli: None. **N. Ledru:** None. **K.R. Kaun:** None.

Poster

736. Transcription and Translation in Plasticity II

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Program #/Poster #: 736.10/B53

Topic: B.07. Synaptic Plasticity

Support: Kansas INBRE, P20 GM103418

Title: Evaluating the role of translational efficiency in synaptogenesis in *Caenorhabditis elegans*

Authors: *K. ALIZADEH, B. D. ACKLEY;
Mol. Biosci., Univ. of Kansas, Lawrence, KS

Abstract: Nidogen is a conserved basement membrane protein required for the proper formation and organization of synapses. In *Caenorhabditis elegans*, nidogen functions to efficiently localize the presynaptic scaffold protein SYD-2/α-liprin at synaptic active zones. The synaptic phenotype in nidogen mutants is suppressed by loss-of-function in genes that encode a calcium channel (*unc-2* or *unc-36*), the calmodulin kinase (*unc-43),* or calmyrin (*calm-1*), demonstrating that calcium signaling is important in synaptic morphogenesis. Previous work identified proteins that associate with CALM-1 in a calcium-dependent fashion, including RACK-1 and multiple ribosomal proteins. Loss of function in *rack-1* results in a synaptic phenotype equivalent to the loss of nidogen, and this phenotype can be suppressed by the loss of *calm-1*. Interestingly, RACK-1 is known to be a translational inhibitor in many contexts, although whether this is how it is functioning in synaptic nidogen pathway is unclear. To test this, we are using RNAi to inactivate the ribosomal proteins isolated in our biochemical screen. The viability of RNAi in studying these genetic interactions has been validated by our previous screens. In particular, using RNAi, the *nid-1* loss-of-function phenotype was suppressed with the loss of *calm-1,* and phenocopied with the loss of *rack-1*. Furthermore, there is the question of the range of activity of RACK-1. While the role of RACK-1 in synaptic development might be through global translation inhibition, this protein could also be associated with only certain ribosomes, in which case, identifying the mRNAs associated with these ribosomes can point at new genes that are important in synaptic development. We are purifying and studying these mRNAs using immunoprecipitation and sequencing. the results from this project will shed light on the biochemistry of synapse formation and organization. This information will be important in better understanding synaptogenesis in invertebrates and vertebrates.

Disclosures: K. Alizadeh: A. Employment/Salary (full or part-time):; Kansas INBRE. **B.D. Ackley:** None.

Poster

736. Transcription and Translation in Plasticity II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 736.11/B54

Topic: B.07. Synaptic Plasticity

Support: NIH (R01 MH095948-01A1
VA 1I01BX003893-01A1

Title: Epigenetic control of a stress-induced increase in GluA2 AMPA receptor subunit expression

Authors: J. FAWCETT-PATEL[1], J.-Y. HWANG[2], S. ZUKIN[3], *J. LIU[1];
[1]LSU Hlth. Sci. Ctr., New Orleans, LA; [2]Creighton Univ. Sch. of Med., Omaha, NE; [3]Albert Einstein Col. of Med., Bronx, NY

Abstract: Transient stimuli can induce persistent alterations in synaptic function to modify both behavior and cognition. The cerebellum plays an important role in emotion, in part, *via* extensive projections to higher cortical regions. We have shown that a single exposure to predator odor promotes transcription of the AMPA receptor (AMPAR) subunit GluA2, thereby altering the AMPAR phenotype at synapses onto inhibitory interneurons in the molecular layer of the cerebellar cortex. Though AMPAR phenotype has been implicated in stress and anxiety susceptibility, the underlying molecular mechanisms governing such experience-dependent changes in excitatory signaling have yet to be elucidated. The transcriptional repressor REST binds to an RE1 recognition motif within the GluA2 proximal promoter where it acts via epigenetic remodeling to repress GluA2 expression. The present study was undertaken to examine the possibility that stress acts *via* a decrease in REST level/activity to increase GluA2 transcription in cerebellar interneurons. Using chromatin immunoprecipitation (ChIP) assays, we show that stress induces chromatin remodeling at the GluA2 promoter. Stress decreases REST occupancy and increases H3K9ac and H2K4me3, marks of epigenetic activation. Together, these changes induce a switch from a transcriptionally repressive to a permissive chromatin state. We show a requisite role for the histone acetyltransferase CBP/p300 in regulation of synaptic GluA2 content by stress, assessed electrophysiologically. Furthermore, we show a decrease in REST protein expression as assessed by immunofluorescence and Westerns. We previously found that the stress-induced increase in GluA2 transcription was ERK-dependent. This is significant in that ERK phosphorylates a degron motif within the REST carboxy-terminal domain, thereby promoting targeting of REST to the ubiquitin-based, proteosomal pathway for degradation. We further show that the stress-induced decrease in REST occurs in a proteasome-dependent manner. Collectively, our findings suggest that stress stimulates GluA2 transcription *via* ERK-

mediated degradation of REST, which increases excitatory synaptic efficacy onto interneurons, enhancing feed-forward inhibition in the cerebellar cortex.

Disclosures: **J. Liu:** None. **J. Fawcett-Patel:** None. **J. Hwang:** None. **S. Zukin:** None.

Poster

736. Transcription and Translation in Plasticity II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 736.12/B55

Topic: B.07. Synaptic Plasticity

Support: NIH Grant DA044123 to JMB
Roy J. Carver Chair in Neuroscience to TA
NIMH R01 MH087463 to TA

Title: The translin/trax microRNA-degrading complex mediates translation-dependent synaptic plasticity in the hippocampus

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Abstract: Enduring forms of synaptic plasticity require *de novo* protein synthesis which also involves local translation of mRNAs that have been pre-positioned near the synapses. As the microRNA system suppresses translation, the ability of plasticity-inducing stimuli to trigger rapid degradation of microRNAs could play a key role in driving *de novo* translation underlying persistent forms of synaptic plasticity. As recent studies have identified the translin/trax (TN/TX) complex as a microRNA-degrading enzyme that is enriched in brain, we are investigating the hypothesis that the TN/TX complex mediates translation-dependent forms of synaptic plasticity. In support of this, we have found that translin KO mice display defects in synaptic tagging and spatial object location memory (Park et al., 2017). However, since translin deletion also causes loss of trax protein, which has been shown to exert translin-independent cellular effects, it is unclear if the defects in synaptic plasticity or memory displayed by translin KO mice are due to loss of the TN/TX microRNA-degrading enzyme. To address this question, we have generated mice containing a point mutation in trax, E126A, that abolishes TN/TX RNase activity and are assessing if this mutation is sufficient to phenocopy the defects in synaptic plasticity and memory displayed by translin KO mice. In preliminary studies, we have confirmed that this mutation does not alter the expression of translin or trax proteins in the brain, nor their ability to co-precipitate. As a first step in assessing the impact of the trax(E126A) mutation on

hippocampal synaptic plasticity, we have evaluated its effect on “spaced 4-train” LTP, a plasticity paradigm that is translation-dependent and is impaired in translin KO mice. We have found that hippocampal slices prepared from adult trax(E126A) mice show a deficit in this form of late-LTP compared to the WT littermates. Thus, these findings strongly support the hypothesis that synaptic activation of the TN/TX microRNA-degrading enzyme mediates *de novo* translation critical for sustained LTP.

Disclosures: **M.S. Shetty:** None. **X. Fu:** None. **A.J. Park:** None. **T. Abel:** None. **J.M. Baraban:** None.

Poster

736. Transcription and Translation in Plasticity II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 736.13/B56

Topic: B.07. Synaptic Plasticity

Support: R01DA043361 to XZ
R21NS103159 to JD and XZ

Title: Epitranscriptomic regulation of protein synthesis, learning and memory by N^6-methyladenosine(m^6A)

Authors: J. KORANDA[1], M. J. PATEL[1], J. Y. DELGADO[1], H. SHI[2], J. THOME[1], W. FU[1], L. MO[1], L. O. VAASJO[1], A. OSUMA[1], C. HE[2], ***X. ZHUANG**[1];
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Abstract: *N^6*-methyladenosine (m^6A) is the most abundant mammalian internal mRNA modification. It profoundly regulates RNA splicing, transport, localization, translation and degradation, and may play a central role in the spatial and temporal control of protein synthesis. The emergence of m^6A research is largely facilitated by the discoveries of its key effector proteins: m^6A “writers” (methyltransferases, e.g. METTL14) install m^6A, “erasers” (demethylases) remove m^6A, and “readers” (e.g. YTHDF1, 2 and 3) recognize and bind to m^6A to determine the fate of the modified RNA. Different m^6A readers may mediate different downstream functional consequences of m^6A modification of mRNA.
Recent data suggest that m^6A deficiency impairs both neurodevelopment and adult central nervous system functions, and impairs learning and memory. Our earlier published studies have shown that conditional deletion of Mettl14 in striatal neurons impaired motor learning. Further studies by us found that conditional deletion of Mettl14 in striatonigral neurons, striatopallidal neurons or dopamine neurons altered dopamine signaling, responses to cocaine and dopamine-dependent learning. Finally, constitutive deletion of Ythdf1 impaired protein synthesis, altered synaptic transmission, and impaired many different forms of learning/memory.

However, because m^6A modifies thousands of transcripts and profoundly impacts many neuronal functions, it's been a challenge to systematically investigate how the dynamic regulation of the m^6A pathway may control specific protein synthesis with good spatial and temporal resolution to affect synaptic plasticity, learning and memory. We are using various genetic approaches to manipulate the effector proteins. What the targets of these effector proteins are, how the above manipulations may affect translation globally or translation of specific mRNAs, synaptic protein turnover, synaptic transmission, plasticity, dendritic spine morphology and behavior are being systematically examined.

Disclosures: J. Koranda: None. **M.J. Patel:** None. **J.Y. Delgado:** None. **L.O. Vaasjo:** None. **J. Thome:** None. **W. Fu:** None. **L. Mo:** None. **H. Shi:** None. **C. He:** None. **X. Zhuang:** None. **A. Osuma:** None.

Poster

736. Transcription and Translation in Plasticity II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 736.14/B57

Topic: B.07. Synaptic Plasticity

Support: NMRC/CBRG/0099/2015
NMRC-OF-IRG-2016

Title: MicroRNA-134-5p inhibition rescues long-term plasticity and synaptic tagging/capture in an Aβ (1-42)- induced model of Alzheimer's disease

Authors: *N. BABY, N. KALYANI, T. DHEEN, S. SAJIKUMAR;
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Abstract: Progressive memory loss is one of the most common characteristics of Alzheimer's disease (AD), which has been shown to be caused by several factors including accumulation of amyloid β-peptide (Aβ) plaques and neurofibrillary tangles. Synaptic plasticity and associative plasticity, the cellular basis of memory, are impaired in AD. Recent studies suggest a functional relevance of microRNAs (miRNAs) in regulating plasticity changes in AD, as its differential expression was reported in many AD brain regions. However, the specific role of these miRNAs in AD has not been elucidated. We have reported earlier that Late-Long Term Potentiation (L-LTP) and its associative mechanisms such as Synaptic Tagging and Capture (STC) were impaired in Aβ (1-42)-treated AD condition. This study demonstrates that expression of miR-134-5p, a brain specific miRNA is upregulated in Aβ (1-42)-treated AD hippocampus. Interestingly, the loss-of function of miR-134-5p restored L-LTP and STC in AD. Inhibition of miR-134-5p upregulated the expression of plasticity-related proteins, CREB-1 and BDNF in AD brains which are otherwise downregulated in AD condition. The results provide the first

evidence that the miR-134-mediated post-transcriptional regulation of CREB-1 and BDNF is an important molecular mechanism underlying the plasticity deficit in AD, thus demonstrating the critical role of miR-134-5p as a potential therapeutic target for restoring plasticity in AD condition.

Disclosures: **N. Baby:** None. **N. Kalyani:** None. **T. Dheen:** None. **S. Sajikumar:** None.

Poster

736. Transcription and Translation in Plasticity II

Location: Hall A

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Program #/Poster #: 736.15/B58

Topic: B.07. Synaptic Plasticity

Support: DFG CRC 1080
DFG CRC 902

Title: Spatio temporal dynamics of miRNA mediated regulation of local protein synthesis

Authors: ***M. WANG**[1], T. GOLDAU[2], R. KLIMEK[2], A. HECKEL[2], E. M. SCHUMAN[1]; [1]Max Planck Inst. For Brain Res., Frankfurt, Germany; [2]Inst. of Organic Chem. and Chem. Biol., Goethe-University, Frankfurt, Germany

Abstract: Local protein synthesis is required for initiation and maintenance of some forms of synaptic plasticity. The localization of messenger RNAs (mRNAs) in neuronal processes and the spatial regulation of their translation are of particular importance. One mechanism to locally control mRNA translation is via the micro RNA (miRNA) pathway, small non-coding RNAs of 19-23nt length that inhibit translation. By binding mRNAs in a sequence-dependent manner, miRISC (miRNA-induced silencing complex) leads to the translational inactivation or degradation of the target mRNA. The brain expresses a large number of tissue-specific or -enriched miRNAs. Both miRNA and the protein complexes involved in their biogenesis and functions are found in distal dendrites, where they are also subject to regulation by neuronal activity. Little is known, however, about the spatio-temporal dynamics of miRNA function and activity in neurons. To this end, we have developed and optimized a tool to control miRNA activity in space and time - a dual-fluorophore-labeled and light-inducible anti-miR. A tracking fluorophore enables the visualization and localization of the anti-miR in real time. Following photo-activation and miRNA sequestration a second fluorophore, the hybridization-sensing fluorophore, lights up. Using the anti-miR, we are investigating the role of miR-181a, a miRNA that is highly abundant in the hippocampal neuropil, on the local regulation of its targets such as Camk2a and Gria2, two proteins critical for the function and plasticity of synapses. Following transfection into primary hippocampal neurons there is rapid movement of anti-miR molecules throughout the dendrites. In order to gain insight into the correlation between miRNA activity

and its target protein expression, we are analyzing the nascent protein synthesis of candidate miR-181a targets following photo-activation. We predict that successful hybridization of the anti-miR to miR-181a should enhance translation of the target mRNAs.

Disclosures: M. Wang: None. **T. Goldau:** None. **R. Klimek:** None. **A. Heckel:** None. **E.M. Schuman:** None.

Poster

737. Dendritic Properties, Oscillations, and Plasticity

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 737.01/B59

Topic: B.08. Intrinsic Membrane Properties

Support: FNRS Grant J0148.19
University of Liege - FSR2018
R.FNRS.4129-9-F
Fondation Léon Fredericq

Title: The gating pore blocker 1-(2,4-xylyl)guanidinium inhibits the pacemaking of substantia nigra dopaminergic neurons

Authors: *K. JEHASSE[1], S. HARTMANN[3], L. MASSOTTE[1], B. LAKAYE[2], J. ROEPER[3], V. M. SEUTIN[1];
[1]Lab. of Neurophysiol. - GIGA Neurosciences, [2]Lab. of Mol. Regulation of Neurogenesis, Univ. of Liege, Liege, Belgium; [3]Inst. of Neurophysiol., Goethe Univ. Frankfurt, Frankfurt, Germany

Abstract: The exact ionic mechanisms of the slow and very regular pacemaking exhibited by midbrain dopaminergic (DA) neurons are still unclear. Several studies have shown that both voltage-gated Ca^{2+}, Na^{+} and HCN channels as well as voltage-independent Na^{+} channels open during the interspike interval (ISI). This happens to a varying extent depending on the region (substantia nigra, pars compacta [SNc] or ventral tegmental area [VTA]). In VTA DA neurons, TTX-sensitive sodium channels are necessary for generating the subthreshold membrane potential oscillations that drive pacemaking. In contrast, the subthreshold pacemaker currents in DA SN neurons are TTX-insensitive and less well defined. While HCN, Kv4 and Ca^{2+} channels all modulate pacemaker frequency, the nature of the essential current remains elusive. Given that Khaliq & Bean (2010) showed the net inward current during the ISI to be very small (in the range of 1-6 pA), we tested the hypothesis that alternative pores with very small unitary conductances (fS range) might underlie the « pacemaker current ». One type of unconventional "gating pore" has so far only been identified in channelopathies (Jiang et al., 2018). This tiny current through a pore related to the S4-voltage sensor is inhibited by 1-(2,4-xylyl)guanidinium (XG) (Sokolov et al., 2010). When we superfused midbrain slices with XG, the drug inhibited

the firing of both rat and mouse DA SNc neurons in a concentration-dependent manner (concentration of drug that inhibited the firing of rat DA neurons by 50% was ~250 µM). Identical results were obtained using extracellular, cell-attached and whole-cell recordings. GABAergic SNR neurons were only little affected by XG. A complete cessation of firing was obtained in most rat DA neurons with 1 mM XG and this concentration was chosen for further mechanistic studies. In current clamp, XG stopped firing without hyperpolarizing the membrane. Moreover, in the presence of XG, DA neurons were still able to fire upon injection of small depolarizing currents (10-30 pA). Evoked action potentials were very similar to those recorded during spontaneous pacemaking. Voltage-clamp recordings identified in SNc DA neurons a XG-sensitive current whose properties are consistent with a pacemaker current. We are currently studying the biophysical properties of this novel pacemaker current.

Disclosures: **K. Jehasse:** None. **S. Hartmann:** None. **L. Massotte:** None. **B. Lakaye:** None. **J. Roeper:** None. **V.M. Seutin:** None.

Poster

737. Dendritic Properties, Oscillations, and Plasticity

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 737.02/DP03/B60

ControlExtraData.DynamicPosterDisplay:
Dynamic Poster
Topic: B.06. Synaptic Transmission

Support: NSF No. IOS-1455527
GSU Brain and Behaviors Initiative

Title: Principles for making a half-center oscillator

Authors: ***H. JU**[1], A. Q. SHILNIKOV[2];
[1]Neurosci. Inst., [2]Neurosci. Institute, Dept. of Mathematics and Statistics, Georgia State Univ., Atlanta, GA

Abstract: Functional neural circuits regulate many crucial biological phenomena. It is of great interest for both experimental and computational neuroscientists to understand how neurons in a circuit connect to each other to produce certain activity patterns, especially rhythmic patterns. So far, it has been revealed that a fundamental building block of many neural circuits is the half-center oscillator (HCO), i.e., two identical neurons connected with reciprocal inhibitory synapses that alternately burst for the same duration; while one spikes, the other is quiescent. Well studied examples include the crustacean stomatogastric ganglion which generates the pyloric rhythm and the swim central pattern generator (CPG) of Melibe leonina. From the observation that the two neurons in a HCO stop bursting after the elimination of the synapse arises a long-lasting

question: how to make a HCO out of two intrinsically non-bursting neurons connected by a reciprocal inhibitory synapse?
More than twenty years ago, Wang and Rinzel identified two mechanisms, escape and release, to generate the oscillatory spiking pattern in two reciprocally inhibitory model neurons which are simplified and contain a special rebound current. However, until now, it is still unknown whether the escape and release mechanisms can be used to build a HCO from two intrinsically non-bursting realistic model neurons.
Since we have developed a general parameter continuation technique to study the electrical behaviors of neuron models with various time scales, we can now apply this technique combined with other computational force to examine the applicability of the escape and release mechanisms to forming a HCO out of two intrinsically non-bursting realistic model neurons and how parameters can control the bursting properties. Furthermore, we will investigate the mechanisms underlying the swim CPG in Dendronotus iris. Since it might be the simplest rhythm-generating CPG built upon HCO (comprised of only two pairs of HCOs) and the two neurons are intrinsic non-bursters, it is an ideal system to validate the principles of making HCOs in a real functional network oscillator.

Disclosures: H. Ju: None. **A.Q. Shilnikov:** None.

Poster

737. Dendritic Properties, Oscillations, and Plasticity

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 737.03/B61

Topic: B.09. Network interactions

Support: R35 NS 097343
MH 46742-29

Title: Effect of temperature on half-center oscillator networks

Authors: *E. MOROZOVA, E. MARDER;
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Abstract: The pyloric network of the crab *Cancer borealis* maintains a robust rhythm over a wide range of temperatures. Remarkably, phase relationships of the network neurons are temperature invariant. To have a better understanding of how robustness and temperature compensation of rhythmic circuits arises from the intrinsic and synaptic properties, we used the dynamic clamp to create half-center oscillator (HCO) networks of two biological neurons by connecting them via reciprocal artificial inhibitory synapses. We studied how the intrinsic properties of neurons that constitute HCOs are affected by temperature change. HCOs were built using two gastric mill (GM) neurons, which are silent in isolation with a resting potential

between -60 and -50 mV at 8^{o}C. We measured the mean membrane potential of GM neurons and their firing rates in response to 1-10 nA current steps at 8, 12, 16 and 20^{o}C. All the neurons hyperpolarized by approximately 5mV as the temperature was raised from 8^{o}C to 20^{o}C and required more current to initiate spiking. The frequency-current curves became steeper at higher temperatures. We constructed 2-cell circuits and varied synaptic and H-current conductances from 15 to 150 nS in steps, generating maps containing different combinations of these conductances at 10^{o}C and 20^{o}C. Dynamic clamp allows us to independently implement the temperature dependence of the synapses and, thus, study the contributions of the synaptic and intrinsic conductances separately to the temperature induced changes of the circuit output. Without temperature dependence in the artificial synaptic or H-currents, we observed that despite the significant effect of temperature on intrinsic properties of neurons, HCOs comprised of these neurons remain robust over a wide range of temperatures. The maps were not substantially different between 10^{o}C and 20^{o}C. There were generally a lower number of spikes per burst at higher temperature.

Disclosures: E. Morozova: None. **E. Marder:** None.

Poster

737. Dendritic Properties, Oscillations, and Plasticity

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 737.04/B62

Topic: B.08. Intrinsic Membrane Properties

Support: R01MH111107

Title: Targeting the GSK3 pathway with modulators of voltage-gated Na+ channels

Authors: A. SINGH, P. WADSWORTH, Z. LIU, J. ZHOU, ***F. LAEZZA**;
Univ. of Texas Med. Br. at Galveston, Galveston, TX

Abstract: Resilience and vulnerability to neuropsychiatric disorders are linked to molecular changes underlying neuronal excitability that are still poorly understood. In recent studies, we have shown that vulnerability to depression is mediated by a form of maladaptive plasticity consisting of increased firing of medium spiny neurons (MSNs) in the nucleus accumbens (NAc), a brain area associated with reward-related behaviors. In these cells we showed that maladaptive firing is mediated by phosphorylation of the intracellular C-tail of the voltage-gated Na^{+} channel Nav1.6 by glycogen-synthase kinase 3β (GSK3β) and that a GSK3β-Nav1.6^{T1936} competing peptide reverses maladaptive plasticity of MSNs in animal models of depression-like behaviors. Furthermore, in vivo genetic manipulations demonstrated that GSK3β and Nav1.6 are molecular determinants of MSN excitability and that silencing of GSK3β prevents this form of maladaptive plasticity of MSNs. Building on these results, we are now designing a series of

small molecules with improved drug-like properties that target specifically and selectively the GSK3β:Nav1.6 complex. One compound, ZL141, inhibits the formation of the GSK3β:Nav1.6 complex in cells as determined by the luciferase complementation assay and fluorescence spectroscopy, and binds to the Nav1.6 C-terminal tail as assessed by surface plasmon resonance. In addition, whole cell patch-clamp recordings in HEK293 cells stably expressing Nav1.6 showed that ZL141 rescues GSK3β-dependent modulation of Na+ currents and of Nav1.6 steady-state inactivation and long-term inactivation. We expect ZL141 and other small molecule analogues targeting the GSK3β:Nav1.6 channel complex to inhibit maladaptive firing of MSNs ultimately reducing susceptibility to depression and stress disorders. These studies lay groundwork for the development of compounds targeting the GSK3β signaling pathway by modulation of functionally relevant substrates such as Nav channels.

Disclosures: A. Singh: None. **P. Wadsworth:** None. **Z. Liu:** None. **J. Zhou:** None. **F. Laezza:** None.

Poster

737. Dendritic Properties, Oscillations, and Plasticity

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 737.05/B63

Topic: B.08. Intrinsic Membrane Properties

Title: A library of macaque lateral prefrontal cortex neurons electrophysiological and morphological characterization

Authors: *M. S. JIMENEZ-SOSA[1], E. S. KUEBLER[1], J. K. SUNSTRUM[1], S. MATOVIC[1], M. WIEDERMAN[1], M. KHAKI[1], N. BRAR[1], P. TRUSCHOW[2], R. GULLI[1], B. CORRIGAN[1], R. LUNA[1], M. ROUSSY[1], B. MAHMOUDIAN[1], D. BUITRAGO-PIZA[1], H. IGARASHI[1], J. JEONG[1], M. EVEREST[1], K. THOMAES[1], S. TREUE[3], J. STAIGER[2], W. INOUE[1], M. O. POULTER[1], J. C. MARTINEZ-TRUJILLO[1];
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Abstract: Since the pioneering work of Nobel Laureate from Camilo Golgi (1843-1926) and Santiago Ramon y Cajal (1852-1934), neuroscientists have sought to classify the diverse population of neurons into specific cell types. Previous studies have shown a wide-range of diversity in morphological properties and intrinsic electrophysiological properties in mouse and human neocortical neurons (Allen Institute libraries of cell types) that can be used to classify them and better understand their role in the cortical network. However, the characterization of neuron types in non-human primate (NHP) has been less systematically studied. For this study,

we have developed an experimental pipeline combining single cell patch clamp recordings, with biocytin labeling and neuronal three-dimensional reconstruction, to generate a database of cell types for neurons of the lateral prefrontal cortex (LPFC) of macaque monkeys.
We used whole cell patch clamp recordings from slices of the LPFC of 8 macaques to study the intrinsic properties of single neurons. We used a modified version of the Allen Institute electrophysiological protocol (https://celltypes.brain-map.org/). During the recording from one cell we used biocytin injection through the recording electrode, to label the neuron. We developed immunohistochemistry staining enhancing the images using anti-biocytin – streptavidin antibodies conjugated with Alexa fluor 488. We acquired high-resolution acquisition images using a 63x objective with Zeiss Laser Scanning Microscope. We conducted the 3D reconstructions using Imaris and Neurolucida 360 software. Upon completion of the reconstructions, we extract several parameters (i.e., branch order, Sholl analysis, partition asymmetry, tortuosity, etc.) to characterize each neuron. The data were stored in a database at the Robarts Institute.
We have collected 260 neurons in 8 macaque monkeys. We have processed a total of 40 neurons for imaging and reconstruction. By combining whole cell patch clamp recordings and three-dimensional reconstruction with morphological analysis, populations of neurons with similar properties can be identified in the macaque PFC contributing to the understanding of the correlation between the functional and cortical organization of single cells in the main network.

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Poster

737. Dendritic Properties, Oscillations, and Plasticity

Location: Hall A

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Program #/Poster #: 737.06/B64

Topic: B.08. Intrinsic Membrane Properties

Support: NIH grant R35 NS097343
NIH grant 5T32NS007292-31
ERC grant FLEXNEURO (716643)

Title: Compensation of size change coexists with sensitivity to channel deletion in a model of neuronal regulation

Authors: *S. GORUR-SHANDILYA[1], E. E. MARDER[1], T. O'LEARY[2];
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Abstract: Neurons can increase in size dramatically during growth, yet many kinds of neurons must also preserve their intrinsic dynamics and physiological function across several length scales. For example, neurons in the crustacean pyloric pacemaker circuit can generate similar activity patterns despite multiple-fold increases in their size and changes in morphology (Bucher *et al*. 2005). The scale invariance of neuron dynamics hints at homeostatic mechanisms that can regulate the conductance densities of multiple ion channel types in an activity-dependent manner. Using conductance-based single compartment neuron models, we asked whether a biologically plausible regulation mechanism (O'Leary *et al*. 2014) can maintain intrinsic voltage dynamics in a neuron as its surface area is varied. Despite relying only on a single sensor that measures time-averaged intracellular calcium as a proxy for activity, we found that this regulation mechanism could regulate conductance densities of ion channels, and was robust to changes in the surface area of the neuron, without having to explicitly measure cell size. By mapping changes in cell size onto perturbations in the space of conductance densities of all channels, we show that robustness to size change coexists with sensitivity to perturbations that vary the ratios of maximum conductances of different ion channel types. This difference in sensitivity can explain why ratio-preserving regulation rules that regulate ion channel densities can preserve neuron function during growth, but may also be vulnerable to perturbations like deletions or over-expressions of certain channel types. Our framework makes it possible to numerically and analytically predict which perturbations the homeostatic mechanism can compensate, and which perturbations cause pathological compensation.

Disclosures: S. Gorur-Shandilya: None. **E.E. Marder:** None. **T. O'Leary:** None.

Poster

737. Dendritic Properties, Oscillations, and Plasticity

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 737.07/B65

Topic: B.08. Intrinsic Membrane Properties

Support: ERC AdG 695709
Wellcome Trust PRF 201225
Wellcome Trust 204915
Wellcome Trust 209558/Z/17/Z

Title: Extracting signatures of dendritic spikes from Neuropixels recordings

Authors: *M. FAULKNER[1], M. JAKUBOWSKA[1], N. A. STEINMETZ[2], K. D. HARRIS[1], M. CARANDINI[1], A. ROTH[1], M. HAUSSER[1];

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Abstract: Dendritic spikes in apical dendrites of cortical pyramidal neurons have been proposed to play a critical role in coincidence detection and synaptic plasticity. Calcium signals have also been observed during sensory detection tasks, suggesting active dendrites may contribute to sensory processing. Dendritic calcium spikes and somatic burst activity are reciprocally causally related; backpropagation of somatic bursts above a critical frequency can generate calcium spikes which in turn can generate further somatic burst firing. We are using Neuropixels recordings of somatic and dendritic signals in awake head-fixed mice performing a behavioral task to detect active dendritic events and investigate how their properties are modulated by behavioral state.
Neuropixels probes were placed parallel to the apical dendrites of layer 5 pyramidal neurons in primary visual cortex. Recordings were obtained while mice were exposed to sparse noise visual stimuli or darkness and their forepaws rested on a wheel whose movements were recorded. By analyzing both low frequency (LFP) and high frequency signals from the Neuropixels probe, electrical signals corresponding to somatic action potentials and dendritic spikes could be identified. Following spike sorting based on signals of putatively somatic origin, the dendritic signatures of well-isolated units were examined in a spatiotemporal spike-triggered average of the extracellular potentials. Units were selected for further study if they exhibited backpropagation or had a sink corresponding to the timescale and location of expected putative dendritic calcium spikes. Through subtraction of single spike events from burst spike events, we can identify non-linear signatures that match anticipated putative calcium spiking both in duration and location. We are currently examining differences in the dendritic signatures during behavioral state by using simultaneously collected wheel movement, visual stimulus and eye pupil diameter data. These results indicate that Neuropixels recordings could be used to detect dendritic spikes in vivo, allowing simultaneous capture of dendritic and somatic spiking activity during behavior.

Disclosures: M. Faulkner: None. **M. Jakubowska:** None. **N.A. Steinmetz:** None. **K.D. Harris:** None. **M. Carandini:** None. **A. Roth:** None. **M. Hausser:** None.

Poster

737. Dendritic Properties, Oscillations, and Plasticity

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 737.08/B66

Topic: B.08. Intrinsic Membrane Properties

Support: NIH R01 grant MH115832

Title: Cholinergic modulation of responses to depolarizing current ramps in CA1 hippocampal pyramidal neurons

Authors: *C. L. COMBE[1], T. MAZAHERI[2], C. C. CANAVIER[2], S. GASPARINI[1];
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Abstract: *In vivo* measurements of CA1 place cell firing have demonstrated that firing rates are influenced by novelty and previous exposure to the environment, resulting in modulation of firing rate responses within the place field. Although synaptic plasticity likely contributes to modulation, the intrinsic properties of CA1 pyramidal neurons, such as adaptation, also influence the firing rate. To isolate these intrinsic contributions, we injected triangular depolarizing current ramps of various durations (1-10 s) to approximate the spatially-tuned, temporally-diffuse depolarizing synaptic input received by these neurons while traversing a place field. These ramps were applied to CA1 pyramidal neurons *in vitro* (slice electrophysiology) and *in silico* (multicompartmental model).
We found that, under control conditions, CA1 neurons responded with decelerating rate responses, firing more action potentials and at higher frequencies on the ascending phase than the descending phase of the depolarizing ramps, producing clockwise f-I plots. This decelerating response was more prominent when the ramps were injected in the dendrites versus the soma, especially for shorter ramps (1-2 s), representing a faster running speed, compared to longer ramps (10 s). On the other hand, the cholinergic agonist carbachol (2 μM) caused the rate responses to accelerate during the ramp, with more action potentials fired on the descending phase of the ramps (counter-clockwise f-I plots). Computer simulations were employed to dissect the mechanisms responsible for the observed asymmetry. The model was calibrated to fit the steady-state I-V curve; a persistent Na^+ current was added in and near the soma to reproduce the tetrodotoxin-sensitive region of negative slope conductance revealed by experiments. The model suggests a prominent role for the accumulation of Na^+ channel inactivation in modulating the rate responses. The classic *h* inactivation variable accounts for the weak asymmetry of somatic ramps, but a second, slower component of inactivation is required to capture the greater asymmetry of the dendritic ramps. The slow component of inactivation is prominent for dendritic channels and increases with the distance from the soma, both in the apical trunk and in the oblique dendrites of CA1 neurons. This component is also responsible for the attenuation of spike height in our simulated dendritic recordings, consistent with the literature on these neurons. Our results suggest that modulation of intrinsic ion channels by experience and novelty-related fluctuations in cholinergic activity may contribute to the shifts observed *in vivo* in peak firing rate as the place field is traversed.

Disclosures: C.L. Combe: None. **T. Mazaheri:** None. **C.C. Canavier:** None. **S. Gasparini:** None.

Poster

737. Dendritic Properties, Oscillations, and Plasticity

Location: Hall A

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Topic: B.08. Intrinsic Membrane Properties

Support: NHMRC APP1085708
NHMRC APP1086082
ARC DP160103047
Viertel Senior Medical Research Fellowship

Title: Influence of cocaine on sensory processing in cortical dendrites

Authors: *S. MURPHY, L. GODENZINI, R. GUZULAITIS, D. LATERRA, A. LAWRENCE, L. PALMER;
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Abstract: Cocaine exposure causes dramatic changes to the structure and functioning of individual neurons, leading to extensive remapping of brain connectivity. These changes alter the processing of synaptic input and overall brain functioning. Despite the prevalence and known detrimental effects of cocaine use on sensory processing, the modulation of cortical activity during cocaine exposure are poorly understood and are the focus of this study. Here, somatic and dendritic activity in layer 2/3 pyramidal neuron dendrites within the somatosensory cortex was investigated using two-photon Ca^{2+} imaging and whole cell patch clamp electrophysiology. During single exposure to cocaine, Ca^{2+} activity in tuft dendrites was enhanced during both spontaneous and sensory tactile stimulation. Somatic voltage was also altered in response to cocaine, leading to dramatic changes in up- and down-states in the anaesthetized mouse. These results illustrate the cellular basis of altered sensory perception during cocaine exposure, providing invaluable insight into the effects of cocaine on cortical processing of sensory information.

Disclosures: S. Murphy: None. **L. Godenzini:** None. **R. Guzulaitis:** None. **D. LaTerra:** None. **A. Lawrence:** None. **L. Palmer:** None.

Poster

737. Dendritic Properties, Oscillations, and Plasticity

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 737.10/B68

Topic: B.08. Intrinsic Membrane Properties

Title: Biophysical scaling rules for layer 5 pyramidal neurons across species

Authors: *L. BEAULIEU-LAROCHE[1], M. M. HANSEN[1], N. BROWN[1], Z. WILLIAMS[2], M. P. FROSCH[3], S. S. CASH[4], M. T. HARNETT[1];
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Abstract: The size of dendritic arbors varies greatly across species, but it remains unclear how this impacts the integrative properties of cortical neurons. Here, we compare input-output relationships and associated ion channel distributions for mouse, rat, and human layer 5B pyramidal neuron somas and dendrites. Outside-out recordings demonstrated that intermediate-sized rat neurons have uniformly higher HCN and voltage-gated potassium channel densities compared to both the smaller mouse neurons and larger human neurons. Furthermore, extrapolated total conductance across the dendritic tree increased greatly from mouse to rat, but only minimally from rat to human. Despite these prominent differences in ion channel distributions, whole-cell recordings revealed that a variety of input-output properties, such as local impedance profile, were surprisingly well conserved across species. However, other functional features, including input resistance and spike properties, were substantially more variable. Our results suggest that some highly-conserved biophysical features are crucial for maintaining optimal functional set points, while other less stable features may simply reflect neuronal size. Future experiments will assess additional mammalian species and cell types to reveal what scaling rules control the electrical properties of cortical neurons across the phylogenetic tree.

Disclosures: L. Beaulieu-Laroche: None. **M.M. Hansen:** None. **N. Brown:** None. **Z. Williams:** None. **M.P. Frosch:** None. **S.S. Cash:** None. **M.T. Harnett:** None.

Poster

737. Dendritic Properties, Oscillations, and Plasticity

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Topic: B.08. Intrinsic Membrane Properties

Support: NIH Grant NS044163
Epilepsy Center of Excellence, Veterans Administration, Seattle, WA.

Title: Layer 5 pyramidal neuron subtypes differ in plasticity in response to conditioning with repeated action potentials

Authors: D. GUAN[1], W. J. SPAIN[2], ***R. C. FOEHRING**[1];
[1]Anat. and Neurobio., Univ. Tennessee Hlth. Sci. Ctr., Memphis, TN; [2]Physiol. & Biophysics Box 357290, Univ. of Washington Dept. of Physiol. and Biophysics, Seattle, WA

Abstract: Activity can cause long term strengthening (LTP) or weakening (LTD) of synaptic connections. Activity also induces changes in the intrinsic excitability of neurons, a process referred to as LTP-IE by Cudmore and Turrigiano (2004, *J Neurophysiol* 92: 341). They found that LTP-IE was induced in L5 Pyramidal neurons (PNs) in visual cortex by a conditioning protocol (CP): a leftward shift in the f-I curve (no change in slope) and decreased AP voltage threshold (AP_{th}) and rheobase. LTP-IE occurred in L5 PNs but not L2/3 PNs or FS interneurons. To test for cell type specificity for LTP-IE within L5 PNs, we used 3 mouse lines that express GFP (*etv1, glt*) or YFP (*thy1-h*) in subsets of L5 PNs. *Thy1-h* and *glt* PNs send projections out of the telencephalon and projections of *etv1* PNs are restricted to the telencephalon. Whole cell current clamp recordings were performed upon PNs from somatosensory (*etv1, glt*) or motor cortex (*thy1-h*) under conditions where fast synaptic transmission was blocked to ensure any changes observed were intrinsic to the cell recorded from. We tested cell excitability with a family of 500 ms DC current steps and measured rheobase, firing rate, and f-I slope. This was performed at break in and repeated every 10 minutes. After excitability became stable (1-3 repeats), we used the CP of Cudmore and Turrigiano (2004; 15 supra-threshold 5ms current injections at 40Hz, repeated at 4 s intervals for 5 min). In a control group of 8 *thy1-h* PNs (no CP), excitability remained stable for >60 min. In all *thy1-h* cells (n = 10) the CP enhanced cell excitability. At 30 minutes after the CP, f-I curves showed a parallel left shift of > 8Hz, rheobase was significantly reduced, and firing rates were significantly increased (LTP-IE). In contrast, when the same CP was applied to *glt* PNs, there were no changes in rheobase, firing rate, or f-I curves (n = 8). All *etv1* PNs showed excitability changes after the CP. In 6 of 10 *etv1* PNs there was enhanced excitability (LTP-IE): no change in rheobase, increased firing rate, and increased F-I slope. In the other 4 *etv1* PNs, the CP decreased excitability: no change in rheobase, lower firing rate, and a rightward parallel shift of f-I (no slope change). This later effect is a previously undescribed long-term depression of intrinsic excitability (LTD-IE). Further experiments systematically vary the properties of the CP (frequency, number of APs) to define how these parameters influence the direction and magnitude of plasticity. We are also investigating the ionic basis for the observed excitability changes. These data show that PN types differ in their sensitivity to conditioning and may express LTP-IE or LTD-IE.

Disclosures: D. Guan: None. **W.J. Spain:** None. **R.C. Foehring:** None.

Poster

737. Dendritic Properties, Oscillations, and Plasticity

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 737.12/B70

Topic: E.04. Voluntary Movements

Support: Zuckerman STEM Fellowship

Title: Dendritic coordination in layer 5 tuft dendrites in awake, behaving mice

Authors: *N. CERMAK[1], J. SCHILLER[2];
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Abstract: The role of dendrites in *in vivo* biophysical behavior of neurons is unclear. Studies in brain slices have clearly shown that dendrites of pyramidal neurons can utilize active conductances to perform local, nonlinear computations. However, *in vivo* evidence of such local nonlinear computations is lacking. We used two-photon microscopy to study calcium dynamics in many separate branches of tuft dendrites (within 50um of the pia) of single layer 5 pyramidal neurons in primary motor cortex. During imaging, mice were awake and running on either a freely-moving or motorized treadmill. After experiments, we also determined the structure of the full dendritic arbor, enabling us to relate calcium imaging ROIs to specific locations on the dendritic tree. To accurately determine the structure of dendritic trees we found it was necessary to use extremely sparse labelling (10-100 neurons/mm^3). Additionally, we used an AAV carrying both mRuby2 and GcaMP6f, so that the mRuby2 signal could be used for structural determination. We found that most calcium activity was shared across many branches of dendritic tree, despite distances sometimes exceeding 500 um between imaged segments. We typically did not observe single-branch activity in the absence of other branches. Dendritic activity tended to be enriched around starts or stops of freely-initiated movement bouts, as well as the duration of forced (motorized) movement. We are currently investigating the origins of these whole-tuft activity patterns, and whether they are consistent with backpropagating action potentials. Additionally, we are continuing to investigate the effect of other behavioral paradigms on branch coordination.

Disclosures: **N. Cermak:** None. **J. Schiller:** None.

Poster

737. Dendritic Properties, Oscillations, and Plasticity

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 737.13/B71

Topic: B.06. Synaptic Transmission

Support: Israel/US Binational Science Foundation Grant 2009341

Title: Conditions that maximize the dimensionality of dendritic spatial computation

Authors: L. JIN[1], ***B. W. MEL**[2];
[1]Neurosci. Grad. Program, [2]Biomed. Engin., USC, Los Angeles, CA

Abstract: Dendrites are sensitive to the spatial patterning of their synaptic inputs, which can significantly increase a neuron's processing power. The limits of a single dendrite's spatial computing capabilities are unknown, however, so we asked two questions for pyramidal neurons (PNs), the main cell type of the cerebral cortex: (1) What biophysical parameter settings maximize a dendrite's nonlinear spatial processing power? And (2), for these optimal settings, what is the maximum "dimensionality" of the dendrite's nonlinear i/o function? To answer #1, we used a detailed compartmental model of a PN and a new method to quantify a single dendrite's raw nonlinear spatial processing power. We found a dendrite's ability to distinguish spatially articulated input patterns is maximized when (1) the dendrite is ~200um in length - roughly the natural length of a PN thin dendrite - whereas shorter (100um) or longer (400um) dendrites behaved more linearly; and (2) dendritic spine neck resistance was low (<50 MOhms), which is currently a matter of controversy.
To answer #2, we developed an improved method to quantify the "dimensionality" of dendritic spatial computation, building on previous observations that a dendrite's i/o function can be modeled as an asymmetric multi-dimensional sigmoid function. We found a dendrite's responses to arbitrary spatial patterns of excitation is predicted (i) poorly by a conventional 1-D i/o function, which considers only each input's "weight" while ignoring its location; (ii) moderately well by a 3-D i/o function, which measures excitation within proximal, mid, and distal compartments; and (iii) asymptotically well with 5 spatial compartments. Thus, whereas the integrative units found in conventional artificial neural networks use 1-D (sigmoid or ReLU) activation functions, that distinguish inputs only by their synaptic weights, a PN dendrite provides a higher-dimensional nonlinear i/o function that also depends on the absolute and relative locations of its inputs. An example will illustrate where multi-dimensional activation functions may be useful in natural computing contexts.

Disclosures: **B.W. Mel:** None. **L. Jin:** None.

Poster

737. Dendritic Properties, Oscillations, and Plasticity

Location: Hall A

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Program #/Poster #: 737.14/B72

Topic: B.06. Synaptic Transmission

Support: JSPS Grant-in-Aid for JSPS Fellows 18J00589

Title: Role of GABAergic inhibitory inputs on dendritic integration for wind direction-selectivity in the insect's mechanosensory projection neurons

Authors: *H. SHIDARA, H. OGAWA;
Dept. of Biol. Sciences, Fac. of Sci., Hokkaido Univ., Sapporo, Japan

Abstract: Individual neurons receive large number of excitatory and inhibitory synaptic inputs on their dendrites and integrate them to output the processed result as spikes to postsynaptic neurons. Many studies on mammals have shown that the relationship between dendritic location of the excitatory inputs and their contribution to final outputs. In addition, recent research revealed that the local inhibitory inputs modulate the output of the neural activity, leading the change in the sensitivity for recognition. These results indicate that the dendritic integration of synaptic inputs have a crucial role for the brain function regulating animal behavior. However, the detailed relationship between the dendritic integration in individual neurons and behaviors remains unclear because the individual neurons' function does not necessarily have a direct link to the behavior due to too complicated neural system in mammals. Thus, to reveal the relationship, we focused on the simple and well-studied neural system, the crickets' cercal sensory system to detect airflow. The crickets exhibit the wind-elicited escape behavior, of which moving orientation depends on the airflow direction. The neural processing of the stimulus direction is conducted by local circuits including the identified interneurons, the giant interneurons (GIs), within the terminal abdominal ganglion. Each GI has unique dendrites, which receive directional selective inputs from sensory afferents region-specifically. Although the inhibitory inputs also have a crucial role for forming the directional selectivity, it remains unclear where and how they contribute the integration of the sensory information on GI's dendrites. Here, to examine the integration mechanism of excitatory and inhibitory inputs in GIs, we recorded the local inputs as dendritic Ca^{2+} signal and the final outputs as spiking activity by electrophysiology, respectively. The Ca^{2+} imaging results indicated that three distinct branches of dendrites in 10-3, one of the GIs, received different direction-selective inputs. Then, to investigate the effect of region-specific inhibitory inputs, we also recorded the spiking activity and Ca^{2+} responses in 10-3 with bath application of GABA-A receptor antagonist, PTX. The PTX application enhanced the spiking responses to airflow from all direction, but the preferred angle did not even change. It means the inhibitory inputs will be involved in sharpening the

directional selectivity, but not contribute to directional preference. These results showed that the relationship between the excitatory and inhibitory inputs is important for formation of directional selectivity in 10-3.

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

Poster

737. Dendritic Properties, Oscillations, and Plasticity

Location: Hall A

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Program #/Poster #: 737.15/B73

Topic: B.06. Synaptic Transmission

Support: NIH Grant MH106906
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Title: Summation of subthreshold signals at individual glutamatergic synapses on dendritic spines

Authors: C. A. CELIS[1], J.-Y. WENG[2], *D. ZECEVIC[3];
[1]Yale Univ. Sch. of Med., New Haven, CT; [2]Dept. of Cell. and Mol. Biol., Yale Univ., New Haven, CT; [3]Yale Univ. Sch. Med., New Haven, CT

Abstract: The capacity of single excitatory synapses on individual dendritic spines to influence electrical signaling of individual nerve cells is not fully understood. This question is important because nonclustered, widely distributed spines are active in vivo, as documented repeatedly (e.g. Chen, Rochefort, Sakmann and Konnerth, 2013). To investigate this question, we used a combination of electrophysiology techniques, pharmacological tools, 2-photon photolysis of caged glutamate, and voltage-sensitive dye recordings from dendritic spines in rat brain cortical slices. The goal was to analyse temporal summation of excitatory postsynaptic potentials (EPSPs) generated at individual synapses. We have shown previously, in several classes of principal cortical neurons, that optical recording with voltage-sensitive dyes has the adequate sensitivity and spatiotemporal resolution to monitor synaptic signalling in individual dendritic spines, including temporal summation of uncaging evoked responses that mimic unitary EPSPs. We found that the excitatory postsynaptic currents (EPSCs) recorded electrically from the soma as well as EPSP signals recorded optically at the site of origin (dendritic spines) do not exhibit temporal summation up to the frequencies similar to 50 Hz. This is because local EPSP signals in spines return to the baseline in 10-20 ms. Thus, at common physiological frequencies (below 50 Hz), the synaptic driving force is maintained during repetitive activation of synapses preventing synaptic saturation. In contrast, the somatic electrical recordings revealed a clear sublinear summation of EPSPs at these frequencies based on widening of the synaptic signals due to cable RC filtering in the dendrites. At higher frequency of synaptic activation (100 and 200 Hz), both

the electrical EPSC signal recorded from the soma and the local optical EPSP signal from spines exhibit temporal summation. The summating signals saturated at a range of values from 15 - 80 pA for EPSCs and from 3 - 17 mv for local EPSPs. The NMDA receptors were not activated significantly by sub-linearly summated repetitive quantal EPSPs. Here, we provide evidence that the saturation of local EPSP response in spines is not due to postsynaptic glutamate receptor saturation. Instead, the sublinear response is controlled by powerful AMPA receptor desensitization.

Disclosures: D. Zecevic: None. **C.A. Celis:** None. **J. Weng:** None.

Poster

737. Dendritic Properties, Oscillations, and Plasticity

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 737.16/B74

Topic: B.06. Synaptic Transmission

Support: NIH Grant NS122820

Title: Rapid synaptically activated calcium transients in dendritic spines using electrical stimulation and low affinity indicators

Authors: K. MIYAZAKI, *W. N. ROSS;
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Abstract: Calcium imaging from dendritic spines is an important tool for examining synaptic physiology. While there are many reports of these measurements there are still some controversies about these signals. These controversies may relate to the different sources of calcium, different methods of stimulation, and different choice of indicator. It is also possible that some differences may relate to the heterogeneity among spines on the same cell and to differences in age or species of the preparation.
To examine these questions in pyramidal neurons in rat and mouse hippocampal slices we used an apparatus where the fluorescence of the indicator was excited by a laser spot focused to a region of about 12 µm diameter around the expected synaptic region and the emitted light was detected with a sensitive RedShirtImaging CCD camera recording at 1000 Hz. Neurons were filled from patch electrodes on the soma and were stimulated in current clamp with theta-glass electrodes placed on the slice near the dendrite of interest. Following single stimuli we searched for localized, all-or-none responses in the camera field. In many cases these spots corresponded to spines projecting to the side of the dendrite; in others a clear spine was not visible, possibly because it projected vertically. Using an ROI of about 1 μm^2 centered over this spot we could detect clear calcium transients using a range of indicators including the very low affinity and weak buffering OGB-5N, which has a Kd of 20-40 µM. In most experiments we also

simultaneously detected sodium transients from co-injected SBFI using a high speed multiplexing technique (Miyazaki et al., 2019).
In most cases the synaptically activated calcium transient had a fast rise time (< 10 ms) and a fast decay time (half amplitude in ~25 ms) using 150 µM OGB-5N as the calcium indicator. Even though the recovery time was fast it was still slightly slower than the signal from a backpropagating action potential (bAP) detected on the same trial. The amplitude was similar to the amplitude of the bAP signal from the same location when detected in the proximal dendritic field. A large part of the signal was blocked by APV or CPP confirming that it was due to entry through the NMDA receptor, as previously reported by many investigators. Most of the signal was also blocked by NBQX, consistent with it being due to relief of the Mg block by the fast AMPA mediated EPSP. In many cases a small, slower calcium signal could be detected in NBQX. This signal was more visible following repetitive stimulation (three shocks at 20 ms intervals) or in experiments using higher affinity indicators.

Disclosures: K. Miyazaki: None. **W.N. Ross:** None.

Poster

737. Dendritic Properties, Oscillations, and Plasticity

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Topic: B.06. Synaptic Transmission

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Title: Mechanisms constraining the recruitment of perisomatic and dendritic innervating interneurons in hippocampal CA1

Authors: *E. R. NEBET, S. CHAMBERLAND, R. W. TSIEN;
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Abstract: Information processing in the brain requires precise coordination across individual neuronal elements. Functionally distinct GABAergic interneurons control activity propagation within neuronal circuits by targeting precise spatial domains of pyramidal cells. However, the main determinants gating the recruitment of GABAergic interneurons remain generally unknown.
We performed electrophysiological recordings in CA1 of acute hippocampal slices while stimulating CA3 Schaffer's collaterals (SC). Genetically labeled parvalbumin-positive (PV+) and somatostatin-positive (SST+) interneurons were recorded from and anatomically identified.
We find that segregation of direct (CA3) and indirect (CA1) excitatory inputs contributes to cell

type-specific recruitment of three interneuron classes. PV+ perisomatic-targeting interneurons were recruited mainly via direct excitation, leading to feedforward (FF) inhibition, while SST+ oriens-lacunosum moleculare (OLM) interneurons were exclusively recruited by indirect excitation to execute feedback (FB) inhibition. Interestingly, PV+ bistratified interneurons with axons terminating on the proximal dendrites of pyramidal neurons were excited by both direct and indirect afferents to a similar extent. Thus, these interneurons map onto pyramidal cells along a spatial continuum, defined by direct and indirect recruitment. Repetitive high-frequency SC stimulation led to cell type-specific changes in their relative contribution to inhibitory activity. Perisomatic-targeting cells decreased their firing probability during repetitive stimulation while OLM cells were initially silent but later increased their activity. Bistratified cells demonstrated an elevated firing probability, which gradually decreased. Notably, these three classes of interneurons preserved their timing of AP discharge during repetitive activity. Altogether, our data highlight the main circuit determinants gating interneuron type-specific recruitment during synaptic activity. These processes might allow GABAergic interneurons to modulate their relative contribution to the net inhibitory drive in CA1 while preserving their relative timing of activation.

Disclosures: **E.R. Nebet:** None. **S. Chamberland:** None. **R.W. Tsien:** None.

Poster

737. Dendritic Properties, Oscillations, and Plasticity

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Program #/Poster #: 737.18/B76

Topic: B.06. Synaptic Transmission

Support: ERC Advanced Grant 694829 'neuroXscales'
China Scholarship Council

Title: Investigating dendritic signals evoked by natural patterns of presynaptic activity

Authors: *X. XUE, T. LUMMEN, A. HIERLEMANN, J. BARTRAM;
Dept. of Biosystems Sci. and Engin., ETH Zurich, Basel, Switzerland

Abstract: Dendrites are complex neuronal structures specialized for receiving synaptic inputs. Moreover, dendritic properties enable synaptic inputs to interact, which gives rise to a diverse repertoire of localized input processing options. Whether a specific dendritic event is evoked by such interactions is often highly dependent on the precise input activation patterns. Despite the functional significance of these events, their study is a challenging task. For example, synaptic activation sequences generated with existing chemical or optogenetic tools may not be comparable to natural ones, while the inference of innate input activation patterns with Ca^{2+} imaging is currently hindered by the slow Ca^{2+}-indicator response.

In this *in vitro* study, we developed an approach that provides, for localized synapses, precise spiking sequences of the respective presynaptic cells, while it also allows for imaging the evoked dendritic signals. To achieve this, we performed simultaneous high-density microelectrode array (HD-MEA) recordings and Ca^{2+}/voltage imaging in primary neuronal cultures. By correlating unit activity with Ca^{2+} signals in dendritic spines we were able to associate synapses with the corresponding presynaptic cells. With this information, presynaptic activation patterns could be linked to specific dendritic events. We propose that the combination of large-scale recordings of network spiking by HD-MEAs with simultaneous imaging of dendrites is a powerful approach to examine a variety of important topics including dendrite development and synaptic plasticity.

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Poster

737. Dendritic Properties, Oscillations, and Plasticity

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Topic: B.08. Intrinsic Membrane Properties

Support: NIMH - MH111768

Title: Opposing changes in dendritic-soma electrical coupling underlie ES-potentiation

Authors: *J. K. CLARK, D. V. MADISON;
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Abstract: EPSP-Spike (ES) Potentiation occurs alongside synaptic Long-Term Potentiation (LTP) as a result of high frequency stimulation (HFS). ES-potentiation is the change in excitability that is not accounted for by changes in synaptic strength after the induction of LTP. While previous studies suggest ES-Potentiation may be influenced by GABAergic signaling; ES-Potentiation does not occur in the presence of the $GABA_A$ channel blocker Picrotoxin, the underlying mechanisms regarding the expression of ES-Potentiation remain unclear. We seek to understand these mechanisms by recording simultaneous input/output (I/O) relationships of dendritic field EPSPs, somatic EPSP fields, and resultant Population Spikes before and after the induction of LTP/ES-potentiation in area CA1 of hippocampal slices. In our current study, we show that electrical coupling between dendrite and soma is decreased by an HFS-induced increase in $GABA_B$ signaling. Such a change would be expected to decrease dendritic EPSP-spike coupling, but despite this reduction, ES-Potentiation occurs, i.e. the coupling between the EPSP and the action potential is increased. These data suggest that there are two distinct and opposing changes that occur as a result of HFS: 1) a decrease in passive dendritic-somatic electrical coupling, and 2), an increase in coupling between the somatic EPSP and action potential generation. The decrease in the first of these, dendritic-somatic coupling is mediated by

a persistent increase in post HFS $GABA_B$-mediated dendritic synaptic transmission, while the second may be related to a decrease in somatic $GABA_A$-mediated transmission. These two opposing influences may function as a homeostatic mechanism to balance the excitatory/inhibitory relationship between primary neurons and interneurons, and to exert dual control on the magnitude of ES-potentiation.

Disclosures: J.K. Clark: None. **D.V. Madison:** None.

Poster

738. Epilepsy, Ion Channels, and Mechanism of Action

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 738.01/B78

Topic: B.10. Epilepsy

Support: Israel Science Foundation 1454/17
Fritz Thyssen Stiftung Foundation 10.17.1.023MN
ERA-NET E-Rare 2017, 3-14671

Title: Developmental changes in the activity of inhibitory neurons in Dravet syndrome

Authors: *Y. ALMOG[1], K. ANDERSON[2], M. RUBINSTEIN[1];
[1]Sackler Sch. of Med., Tel Aviv Univ., Tel Aviv, Israel; [2]Goldschleger Eye Res. Inst., Ramat Gan, Israel

Abstract: Dravet syndrome (DS) is an epileptic encephalopathy caused by mutations in the *SCN1A* gene, encoding for the voltage-gated sodium channel $Na_V1.1$. The disease starts with febrile seizures occurring around six months of age and progresses to recurrent refractory seizures with frequent episodes of status epilepticus. Toward adolescence, epilepsy improves and seizure frequency is reduced. DS mice recapitulate this disease progression. Previous electrophysiological studies in DS mice demonstrated reduced excitability in multiple types of GABAergic inhibitory interneurons at the onset of spontaneous seizures, at postnatal day (P)21. However, the neuronal changes occurring during the febrile stage and later, when epilepsy improves, are less clear. We examined the excitability of CA1 hippocampal stratum oriens interneurons (O-LM) at three age points: P14 - during the febrile stage; P21 - at the onset of spontaneous seizures; P35 - following the improvement of epilepsy. Measurements of intrinsic firing properties showed a transient reduction in excitability occurring only at the onset of spontaneous seizures (P21). In contrast, examination of synaptically-evoked excitatory post-synaptic potentials (eEPSPs) and action potentials (eAPs) revealed reduced function of inhibitory neurons at all stages. At P14, the threshold for eAPs was increased (WT: -44.76±0.38 mV, DS: -42.26±0.29 mV; n=14-17; $p<0.001$) and in agreement, so was the amplitude of the eEPSPs (WT: 11.82±0.36 mV, DS: 13.2±0.47 mV; $p<0.05$). Additionally, the eAPs' max rise slope was

decreased (WT: 272.41±6.95 mV/ms^2, DS: 241.37±8.68 mV/ms^2; p<0.01), suggesting reduced sodium conductance. At P21, in addition to increased eAP threshold and eEPSPs' amplitude, and reduced max rise slope, we also observed a marked reduction in eEPSPs' duration (half-width: WT: 26.07±2.32 ms, DS: 13.72±1.03 ms; p<0.001) and as a result, shorter latency to spike (WT: 12.11±0.41 ms, DS: 9.92±0.33 ms; p<0.001). At P35, in correlation with the improvement of epilepsy, the duration of eEPSPs was increased (half-width: WT: 21.79±1.54 ms, DS: 30.89±2.67 ms; p<0.01), along with correction of latency to spike (WT: 14.79±0.57 ms, DS: 14.29±0.51 ms; p=0.51). Nevertheless, increased eAP threshold (WT: -45.52±0.51 mV, DS: -43.44±0.53 mV; p<0.01), increased eEPSPs' amplitude (WT: 9.63±0.5 mV, DS: 12.22±0.65 mV; p<0.01) and reduced max rise slope (WT: 349.59±14.51 mV/ms^2, DS: 295.97±8.65 mV/ms^2; p<0.01) persisted. Together, the examination of synaptically-evoked activity demonstrates a close correlation between the severity of Dravet epilepsy and the level of dysfunction of inhibitory neurons.

Disclosures: Y. Almog: None. **K. Anderson:** None. **M. Rubinstein:** None.

Poster

738. Epilepsy, Ion Channels, and Mechanism of Action

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 738.02/B79

Topic: B.10. Epilepsy

Support: Wellcome Trust Grant 105203/Z/14/Z
Royal Society UF140596

Title: Investigating the pathogenic effects of mutation in Kv3.1 causative for progressive myoclonic epilepsy

Authors: *J. C. CARPENTER[1], J. HENEINE[1], M. SAMPEDRO CASTANEDA[1], R. MANNIKKO[1], G. LIGNANI[1], S. SCHORGE[2];
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Abstract: Progressive myoclonic epilepsy (PME) is a rare and severe epilepsy syndrome that is caused by single gene mutations. The syndrome is characterised by the core symptoms of myoclonus (involuntary muscle jerks), epilepsy and progressive neurological dysfunction, usually in the form of dementia and ataxia. Although the genetic causes of PME have been well studied, the underlying mechanisms remain poorly understood. In particular, it is not known how mutations in several different genes, of apparently unrelated and diverse biological function, give rise to this distinct epilepsy syndrome. Recently, a recurrent, *de novo* p.Arg320His mutation in KCNC1, which encodes K_V3.1, was discovered as a novel cause of PME without dementia, since

termed ‘Myoclonic epilepsy and ataxia caused by mutation of K^+ channel’ or (MEAK). Kv3.1 is a voltage-gated potassium channel that is highly expressed in parvalbumin-positive interneurons and fast-spiking neurons of the cerebellum and is important for high frequency neuronal firing. Previous biophysical studies have found the p.Arg320His mutation in Kv3.1 to be a loss-of-function with a dominant negative effect. Until now, however, the effects of this mutant channel on neuronal function have not been investigated.
Here we used transfection and lentiviral-mediated transgene delivery to express WT and mutant Kv3.1b channels in primary cortical neuronal cultures prepared from C57BL/6 neonatal mice. We carried out whole-cell current-clamp electrophysiological recordings of transduced neurons at 32°C, at 14-16 DIV, in order to assess the impact of mutant Kv3.1b channel expression on interneuronal firing. We also performed a biophysical characterisation of mutant Kv3.1b channels in *Xenopus laevis* oocytes and two-electrode voltage-clamp recordings of oocytes expressing Kv3.1b alpha-pore mutants, in order to investigate whether the p.R320H mutation results in the introduction of pathogenic gating pore currents. Our results exclude H^+-carried gating-pore currents as a mechanism of pathogenicity and reveal alterations in firing frequency for cortical interneurons expressing Kv3.1b p.R320H mutant channels. Overall, these data contribute to a greater mechanistic understanding of MEAK with implications for other forms of PME caused by different gene mutations. Our findings are important because mechanistic insights into PME are sorely lacking, yet are essential for the development of therapeutics for these devastating diseases, for which none currently exist.

Disclosures: J.C. Carpenter: None. **J. Heneine:** None. **M. Sampedro Castaneda:** None. **R. Mannikko:** None. **G. Lignani:** None. **S. Schorge:** None.

Poster

738. Epilepsy, Ion Channels, and Mechanism of Action

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 738.03/B80

Topic: B.10. Epilepsy

Support: DFG grant HE8155/1-1
DFG grant LE1030/16-1
Eva Luise und Horst Köhler Stiftung

Title: Pathophysiological mechanisms and treatment options for KCNA2-related developmental and epileptic encephalopathies

Authors: *U. B. S. HEDRICH[1], H. PANNIKKAVEETTIL ASHRAF[1], H. KOCH[1], H. LERCHE[1], T. V. WUTTKE[1,2];
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[2]Dept. of Neurosurg., Tuebingen, Germany

Abstract: Developmental and epileptic encephalopathies (DEE) are fatal disorders characterized by epilepsy, intellectual disability and other neuropsychiatric symptoms. Available treatments are largely ineffective and the development of new treatment strategies is hampered by the lack of knowledge about the mechanisms of seizure generation. Recently, we identified *de novo* mutations in the *KCNA2* gene encoding the voltage-gated potassium channel $K_V1.2$ as a causative factor for DEE (Syrbe et al., 2015; Masnada et al., 2017). Functional studies revealed mutations with only loss-of-function (LOF) effects, only gain-of-function (GOF) effects or GOF which were diminished by additional LOF effects. The electrophysiological findings correlated with distinct phenotypic features.
To understand the pathophysiological mechanisms of different *KCNA2* mutations on the morphological and electrophysiological properties of single neurons, we used the *in utero* electroporation technique and overexpressed wildtype (WT), GOF or LOF $K_V1.2$ channels in layer 2/3 pyramidal cells. Overexpression of both WT and mutant GOF channels caused a reduction in the total length and complexity of the dendritic trees of neurons analyzed in 12-15 day old cells. Additionally, whole cell patch clamp recordings revealed a reduced firing frequency of pyramidal cells overexpressing WT or mutant GOF channels compared to control cells. In contrast, pyramidal cells expressing mutant LOF channels did not show morphological alterations, but also exhibited a hypoexcitable activity.
Since treatments are often ineffective in patients carrying *KCNA2* mutations, we investigated the effect of 4-Aminopyridine (4-AP), a specific blocker of K_V1 potassium channels, on WT and mutant channels expressing cells. Further studies are needed to gain insight if pharmacological treatment with 4-AP in intact animals can also antagonize the pathophysiological consequences of *KCNA2* mutations *in vivo*.

Disclosures: U.B.S. Hedrich: None. **H. Pannikkaveettil Ashraf:** None. **H. Koch:** None. **H. Lerche:** None. **T.V. Wuttke:** None.

Poster

738. Epilepsy, Ion Channels, and Mechanism of Action

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 738.04/B81

Topic: B.10. Epilepsy

Support: DFG Research Unit FOR2715

Title: Relationship of clinical phenotypes and functional studies in neurons in SCN8A-related disorders

Authors: *Y. LIU[1], K. M. JOHANNESEN[2], M. KOKO[1], J. SCHUBERT[1], C. HØI-HANSEN[3], M. RANNAP[1], E. GARDELLA[2], G. NIELS[4], E. BRILSTRA[5], R. S. MØLLER[2], H. LERCHE[1]; [1]Dept. of Neurol. and Epileptology, Hertie-Institute For Clin. Brain Res., Tuebingen, Germany;

[2]Inst. for Regional Hlth. Services, Odense, Denmark; [3]Dept. of Pediatrics, Copenhagen, Denmark; [4]Dept. of Pediatrics, Arnhem, Netherlands; [5]Univ. Med. Ctr. Utrecht, Utrecht, Netherlands

Abstract: SCN8A encodes the voltage-gated sodium channel Nav1.6, one of four Na^+ channels expressed in the mammalian brain, which are essential for neuronal activity and involved in several neuropsychiatric diseases. More than 100 mutations in the SCN8A gene have been found in patients with broad clinical phenotypes ranging from severe early onset epileptic encephalopathy, benign familial infantile epilepsy with movement disorders, to intellectual disability without epilepsy. To correlate the genotype with the clinical phenotype, we selected several SCN8A mutations causing distinct phenotypes and performed functional analysis in both neuroblastoma cells and primary cultured mouse hippocampal neurons. A patient carrying the p.Ile1654Asn mutation suffered from absence seizures, ataxia and was refractory to valproic acid. This mutant led to barely measurable Na^+ currents in transfected neuroblastoma cells and no neuronal firing in primary cultured neurons when endogenous channels were blocked with TTX, indicating a clear loss-of-function effect. In contrast, the p.Phe846Ser mutation, which caused severe and pharmacoresistant early onset epileptic encephalopathy (including to high dosages of phenytoin), induced a large hyperpolarizing shift of the activation curve in neuroblastoma cells and robustly increased neuronal firing in primary neurons. Interestingly, it has been described, that the p.Arg1629His mutation is associated with episodic ataxia, whereas its corresponding mutation in *SCN1A* (p.Arg1648His) causes febrile and afebrile seizures. This former mutant induced both gain-and loss-of-function biophysical changes, which led to stronger neuronal firing and broader half-width of action potentials. These results suggest distinct neuronal mechanisms for different clinical phenotypes caused by *SCN8A* mutations and the importance of studies in neurons to understand disease mechanisms and to translate these findings into treatment of *SCN8A*-related disorders.

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Poster

738. Epilepsy, Ion Channels, and Mechanism of Action

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 738.05/B82

Topic: B.10. Epilepsy

Support: NIH grant U54-NS108874
American Epilepsy Society Predoctoral Fellowship

Title: Impact of developmentally-regulated alternative splicing on functional consequences of an SCN2A mutation (R853Q) associated with epileptic encephalopathy

Authors: *S. GANGULY, C. H. THOMPSON, A. L. GEORGE, Jr.;
Pharmacol., Northwestern Univ., Chicago, IL

Abstract: Mutations in genes encoding voltage-gated sodium channels (Na_V), including *SCN2A* ($Na_V1.2$), are associated with epilepsy with a wide range of clinical severity, variable age-of-onset, and different degrees of pharmacoresponsiveness. Determining the functional properties of mutant $Na_V1.2$ channels is valuable for establishing molecular mechanisms and genotype-phenotype relationships. Because epilepsy associated with $Na_V1.2$ mutations can have its onset in early life, we hypothesized that developmentally-regulated alternative splicing of the gene may influence the functional and pharmacological consequences of mutations. Therefore, we investigated the biophysical properties of *SCN2A*-R853Q mutant channels in two developmentally-regulated splice isoforms of $Na_V1.2$, one primarily expressed during early neurodevelopment and the other expressed during adulthood. We engineered the R853Q mutation into the neonatal and adult isoforms of $Na_V1.2$ and expressed both in tsA201 cells co-transfected with human β1 and β2 auxiliary subunits. Whole-cell patch clamp was used to record from transfected cells to compare voltage- and time-dependent properties of mutant and wildtype (WT) channels. Cells transfected with the R853Q mutation exhibited a smaller current density, less steep voltage-dependence of activation, enhanced frequency-dependent channel inactivation, and altered recovery from fast inactivation. The neonatal splice variant potentiated these effects of the mutant, and caused a hyperpolarizing shift in voltage-dependence of fast inactivation. Findings concerning recovery from, and onset of, slow inactivation also show considerable differences both when comparing R853Q to WT, and between adult and neonatal splice variants. In conclusion, $Na_V1.2$ R853Q exhibits functional properties consistent with loss-of-function, the degree of which is altered when expressed in the neonatal splice isoform. We conclude that developmentally-regulated alternative splicing contributes to the severity and possibly early age-of-onset observed for *SCN2A*-associated epileptic encephalopathy, and this could affect the degree of pharmacoresponsiveness at different stages of neurodevelopment.

Disclosures: S. Ganguly: None. **C.H. Thompson:** None. **A.L. George:** None.

Poster

738. Epilepsy, Ion Channels, and Mechanism of Action

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

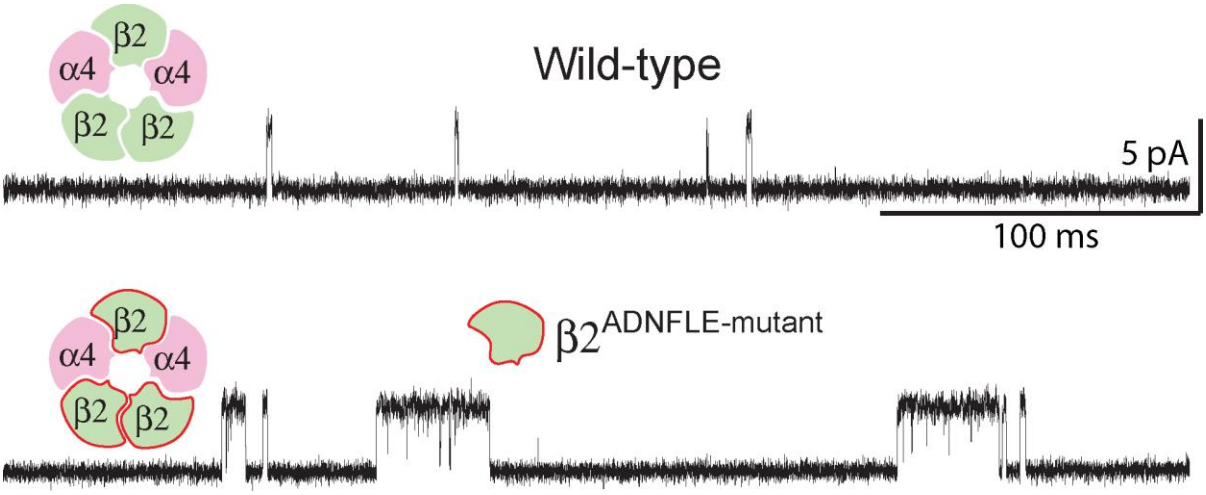
Program #/Poster #: 738.06/B83

Topic: B.10. Epilepsy

Title: Mechanistic consequences and stoichiometry-selectivity of mutations in α4β2 nicotinic acetylcholine receptors in ADNFLE epilepsy

Authors: *S. MAZZAFERRO, S. M. SINE;
Mayo Clin., Rochester, MN

Abstract: Some 30% of monogenic epilepsies are caused by defects in genes encoding ion channels. The monogenic epilepsy known as Autosomal Dominant Nocturnal Frontal Lobe Epilepsy (ADNFLE) is caused by mutations in the α4 or in the β2 subunits of the α4β2 nicotinic acetylcholine receptor (nAChR). The α4β2 nAChR localizes to both pre- and post-synaptic regions throughout the CNS where nerve-released ACh either excites the postsynaptic neuron or enhances release of excitatory or inhibitory neurotransmitters. ADNFLE mutations identified so far cause gain of function where sensitivity and efficacy of the α4β2 nAChR to ACh are enhanced. The α4β2 nAChR is found in two stoichiometric forms, one with three α4 and two β2 subunits, and the other with two α4 and three β2 subunits, denoted $(\alpha4)_3(\beta2)_2$ and $(\alpha4)_2(\beta2)_3$, respectively. However, whether ADNFLE mutations enhance function of both stoichiometric forms is not clear. A selective effect on one stoichiometric form would be significant because the two forms diverge dramatically in their sensitivity to ACh and to allosteric modulators. To determine whether ADNFLE mutations are stoichiometry-selective, we recorded single channel currents from α4β2 nAChRs expressed in 293 HEK cells, and distinguished the two stoichiometries based on their distinct single channel current amplitudes. For the two ADNFLE mutations investigated, we observe dramatically prolonged channel openings, indicating stabilization of the open channel state. However, stabilization of the open state is significantly greater for the $(\alpha4)_2(\beta2)_3$ than the $(\alpha4)_3(\beta2)_2$ stoichiometry. Thus combined with recent cryo-EM structures of the two stoichiometric forms, the stoichiometry selective effects on receptor activation kinetics provide important insights toward drug development for therapy of ADNFLE.



Disclosures: S. Mazzaferro: None. **S.M. Sine:** None.

Poster

738. Epilepsy, Ion Channels, and Mechanism of Action

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 738.07/B84

Topic: B.10. Epilepsy

Support: CIHR MOP-133611
NSERC RGPIN 341942-13

Title: Hyperexcitability of hippocampal CA1 pyramidal neurons due to Kv7 channel dysfunction in a NHE6 KO model of Christianson syndrome

Authors: *A. Y. GAO, T. JAMES, R. A. MCKINNEY;
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Abstract: Christianson syndrome (CS) is a rare X-linked neurodevelopmental disorder characterized by intellectual disability, epilepsy, and ataxia. Of these symptoms, seizures are one of the most significant issues impacting all known CS patients, with affected individuals experiencing multiple types (e.g. tonic-clonic, myoclonic, absence) of episodes each day. This phenotype is suggestive of an imbalance in excitatory/inhibitory (E/I) neurotransmission within their neural circuitry. CS is the result of mutations in the *SLC9A6* gene encoding the organellar Na^+/H^+ exchanger isoform 6 (NHE6), an endosomal pH regulator that is essential for endosomal trafficking. In neurons, such trafficking mechanisms allow for the transport of molecules responsible for maintaining E/I balance. Thus, we investigated whether a complete loss of NHE6 could result in excitatory neuron hyperexcitability in male NHE6 knock-out (KO) mice. We first subjected hippocampal area cornu ammonis 1 (CA1) pyramidal neurons to current injections of increasingly positive magnitude in the presence of synaptic blockers and found that while CA1 neurons from age- and sex-matched wild-type (WT) mice eventually ceased action potential (AP) firing in response to more positive current steps, KO cells instead persisted in their spiking. The data signified that KO neurons were indeed intrinsically hyperexcitable. Interestingly, other active and passive properties remained unchanged between WT and KO neurons. Speculating that this phenotype was due to a loss or dysfunction of a negative regulator of AP firing, we investigated Kv7 channels, voltage-activated, non-inactivating, outwardly-rectifying K^+ channels that mediate the M-current and are partially responsible for spike-frequency adaptation. Molecular biology and immunostaining experiments revealed that among the two highly expressed neuronal Kv7 channel subunits, Kv7.2 and Kv7.3, Kv7.2 levels remained unaffected while Kv7.3 expression and localization were perturbed in KO hippocampi. Using a Kv7-specific antagonist, XE-991, we found that Kv7-mediated currents were also reduced in KO CA1 cells. Finally, by applying a Kv7 channel agonist, retigabine, we could significantly reduce AP spiking in NHE6 KO neurons, further implying an impairment of Kv7 function. Overall, the data

suggest that in NHE6 KO hippocampal neurons, alterations in Kv7 channel function result in their intrinsic hyperexcitability. Combined with other mechanisms, this could potentially leading to E/I imbalance in overall hippocampal circuitry.

Disclosures: A.Y. Gao: None. **T. James:** None. **R.A. McKinney:** None.

Poster

738. Epilepsy, Ion Channels, and Mechanism of Action

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 738.08/B85

Topic: B.10. Epilepsy

Support: NINDS NS29709

Title: Mice with adult-onset P/Q calcium channel deletion recapitulates childhood absence epilepsy

Authors: *Q. M. MIAO, J. NOEBELS;
Dept. of Neurol., Baylor Col. of Med., Houston, TX

Abstract: Inborn errors of CACNA1A-encoded P/Q type voltage-gated calcium ion channels impair synaptic transmission, producing early and lifelong lasting neurological deficits. However, whether these pediatric syndromes depend on remodeled brain networks during a developmental critical remains unclear. Here P/Q channel alpha subunits were ablated by activating an ER-cre-Cacna1a/flox model in mature brain. We show that mice with adult-onset deletion of P/Q channel alpha subunits display identical patterns of absence epilepsy, ataxia, and episodic dystonia, replicating the inborn error. These data demonstrate that P/Q channels remain critical for normal function of adult brain, and that spike-wave absence seizures, the most common form of childhood epilepsy, can be generated in the adult brain due to dysfunction of P/Q channels. Uncoupling the neuronal synchronization disease phenotype from downstream neonatal remodeling during vulnerable developmental periods holds significant promise for gene-guided precision rescue strategies at later stages of the disorder. We would further explore the mechanisms of how P/Q channels' deficiency in adult mice leads to absence seizures.

Disclosures: Q.M. Miao: None. **J. Noebels:** None.

Poster

738. Epilepsy, Ion Channels, and Mechanism of Action

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 738.09/B86

Topic: B.10. Epilepsy

Support: Ontario Brain Institute Grant 410010422
CIHR Grant 119603
NSERC Grant 04487

Title: Characteristics of seizure-like events during a functional lack of pannexin-1 activity

Authors: *M. S. AQUILINO[1,2], P. WHYTE-FAGUNDES[4], M. K. LUKEWICH[1,3], L. ZHANG[1], B. L. BARDAKJIAN[2], G. ZOIDL[4], P. L. CARLEN[1,3,2];
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Abstract: Objective Recent evidence has highlighted a connection between Pannexin-1 (Panx-1) and modulation of neuronal excitability. This work assesses the changes in behavioral and electrophysiological markers of seizure, across three distinct models of epilepsy, with and without the functional presence of Panx-1.
Methods Four groups of C57Bl6 mice were used: Panx-1 genetic knockout, strain-matched controls, controls pretreated with Brilliant Blue-FCF, and controls pretreated with Probenecid. Animals of both sexes were subjected to either acute injection of pentylenetetrazol (PTZ), acute electrical kindling of the CA3, or *in vitro* brain slice incubation with 4-aminopyridine.
Results Panx-1 knockout or pharmacological blockade of Panx-1 suppressed the severity and incidence of seizure-like responses across all models of seizure-induction. In mice subjected to acute intraperitoneal injection of PTZ, the control group had more severe seizures compared to Panx-1 deficient mice, spending a greater proportion of time following injection in higher Racine scale stages. Panx-1 knockouts outperformed controls when subjected to a paradigm of rapid kindling, having shorter after-discharges and fewer seizure-like events. Furthermore, brain slices of Panx-1 knockouts demonstrated fewer electrographic seizures when subjected to bath incubation with 4-AP than their control counterparts. Pretreatment with Brilliant Blue-FCF or Probenecid recapitulated the knockout phenotype. Cross-frequency coupling features of layer 2/3 neocortical field potentials highlight differential patterns in the control and knockout groups, suggesting Panx-1 plays a role in maintaining certain neurophysiological rhythms.
Significance Neuronal excitability is significantly impacted by the functional absence of Panx-1. Genetic, pharmacological, or stimulation-based paradigms of targeting Panx-1 function may have a therapeutic effect in the treatment of seizures and epilepsy.

Disclosures: **M.S. Aquilino:** None. **P. Whyte-Fagundes:** None. **M.K. Lukewich:** None. **L. Zhang:** None. **B.L. Bardakjian:** None. **G. Zoidl:** None. **P.L. Carlen:** None.

Poster

738. Epilepsy, Ion Channels, and Mechanism of Action

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 738.10/B87

Topic: B.10. Epilepsy

Support: NIH NS092786

Title: Cell-type specific role of pannexin1 to distinct seizure parameters

Authors: *P. OBOT, L. VELISEK, E. SCEMES, J. VELISKOVA;
New York Med. Col., Valhalla, NY

Abstract: Epileptic seizure is not solely dependent on neuronal activity but also upon the release of excitatory mediators from glial cells. Pannexin 1 (Panx1) is a plasma membrane channel present in both neurons and glial cells that when activated releases the excitatory molecule ATP. We have previously shown that blockade or deletion of Panx1 has seizure-limiting effects using the kainic acid (KA)-induced status epilepticus (SE) model in juvenile mice. Moreover, we showed that astrocyte and neuronal Panx1 contribute distinctly to KA-induced seizures: While neuronal Panx1 accelerated seizure progression and severity, astrocyte Panx1 improved the seizure outcome. The electroencephalographic (EEG) recordings confirmed that in GFAPCre:Panx1$^{f/f}$ mice the KA-induced continuous ictal activity (SE) occurred significantly faster compared to NFH-Cre:Panx1$^{f/f}$ mice. Here we further characterized the contribution of astrocyte and neuronal Panx1 to seizures using EEG and hippocampal field potential recordings. Three-weeks old male and female Panx1$^{f/f}$, GFAP-Cre:Panx1$^{f/f}$, and NFH-Cre:Panx1$^{f/f}$ mice were injected with 30 mg/kg of KA i.p. and EEG recordings were performed using an EEG-video system (Pinnacle Technology). The temporal progression of seizures from the onset of first spike, then first ictal event to the occurrence of SE was evaluated. Acute hippocampal slices prepared from the three mouse genotypes were exposed to 1 µM KA and epileptiform discharges recorded were recorded in the interface chamber (Fine Science Tools, AxoScope 10.3). Evaluation of the severity of epileptiform activity included the total duration of overall activity, number of ictal events and the fraction of ictal activity obtained within 20-min recordings. EEG recordings revealed that GFAPCre:Panx1$^{f/f}$ had delayed onset of KA-induced first spike ($p < 0.01$) as well as first ictal event ($p < 0.05$), but these animals showed faster onset of SE compared to either Panx1$^{f/f}$ or NFH-Cre:Panx1$^{f/f}$ mice ($p< 0.05$). *In vitro* field-potential recordings showed that slices from GFAPCre:Panx1$^{f/f}$ mice spent less time in epileptiform activity ($p < 0.05$), and that the fraction of ictal activity ($p < 0.01$) and the number of ictal events was decreased ($p < 0.01$) compared to slices from NFH-Cre:Panx1$^{f/f}$ and from Panx1$^{f/f}$. Our study reveals that

neuronal Panx1 accelerates the initial phases of KA-seizures, while astrocyte Panx1 delays the last phase (SE). However, during the initial 20 min, astrocyte Panx1 exacerbates epileptiform activity. Overall, these results indicate a complex interplay between Panx1 in these two cell-types in seizures.

Disclosures: P. Obot: None. **L. Velisek:** None. **E. Scemes:** None. **J. Veliskova:** None.

Poster

738. Epilepsy, Ion Channels, and Mechanism of Action

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 738.11/DP02/B88

ControlExtraData.DynamicPosterDisplay:
Dynamic Poster
Topic: B.02. Ligand-Gated Ion Channels

Support: Wellcome Trust Grant 209164/Z/17/Z
Wellcome Trust Grant: 204788/Z/16/Z

Title: Whole-brain seizure networks in zebrafish models of GABRA1 and GABRG2-related epilepsies

Authors: *R. E. ROSCH[1], D. BURROWS[1], E. SAMARUT[2], M. P. MEYER[1];
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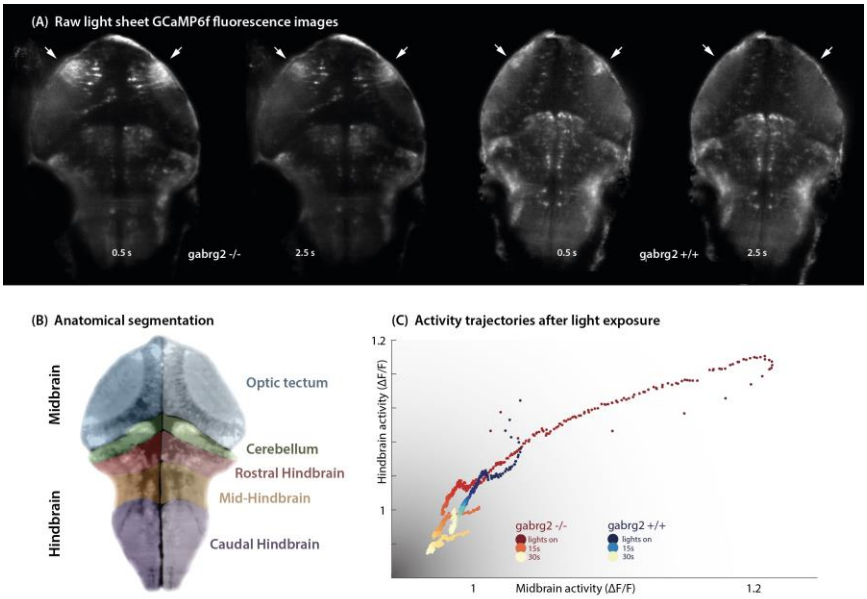
Abstract: Mutation in genes encoding GABA receptor subunits are a well-recognised cause of epilepsy in human patients with phenotypes ranging from familial forms of generalised epilepsies to devastating early infantile epileptic encephalopathies. Two key genes that are affected by deleterious mutations in human epilepsy patients are GABRA1 and GABRG2.Recently zebrafish have emerged as an important vertebrate model to study such genetic epilepsies *in vivo*. Even early in larval development, zebrafish carrying knock-outs of a number of human ‘epilepsy genes’ can show paroxysmal convulsions and electrophysiological markers of epilepsy seizures. Furthermore, there are now tools available that allow functional imaging of whole-brain dynamics at near single-neuron scale. Here we report whole-brain calcium imaging in larval zebrafish using light sheet and two-photon microscopy and genetically encoded calcium indicators (GCaMP6f). We record light-induced whole-brain activity in fish carrying homozygous knock-outs of either the gabra1, or the gabrg2 gene. Both fish lines show light-inducible reflex seizures, with evidence of localised neuronal hyperexcitability compared to their wild-type sibs (Figure 1 shows raw fluorescence images after light exposure and relative changes in dF/F in midbrain and hindbrain for gabrg2 knock-outs and wild type controls). Using non-negative matrix factorisation on the whole-brain calcium recording, we identify key brain

areas that are involved in the different stages of these reflex seizures and evaluate how seizures differ between the two mutant lines.The combination of genetic modification and detailed imaging of neuronal function highlight the role of zebrafish in translational epilepsy research. Our results add to the wider effort in understanding the genotype-phenotype relationship in genetic epilepsies. A better multi-scale mechanistic understanding may then be a first step towards translating novel genetic diagnoses into urgently needed new therapies.



Disclosures: **R.E. Rosch:** None. **D. Burrows:** None. **E. Samarut:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); DanioDesign, Modelis inc.. **M.P. Meyer:** None.

Poster

739. Epilepsy: Pharmacology

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 739.01/B89

Topic: B.10. Epilepsy

Support: Zogenix/Univ. Montpellier contract #180370

Title: Neurosteroids modulate the *in vivo* responses to fenfluramine at the sigma-1 receptor in mice

Authors: *T. MAURICE[1], A. GAMMAITONI[2], B. S. GALER[2], P. MARTIN[2];
[1]INSERM Umr_s1198, Montpellier, France; [2]Zogenix Inc, Emeryville, CA

Abstract: Fenfluramine (N-ethyl-α-methl-3-(trifluoromethyl)-benzeneethanamine, FFA) has been shown in two randomized, double-blind, placebo-controlled clinical trials to substantially reduce the frequency of convulsive seizures in patients with Dravet syndrome, a severe, treatment-resistant epileptic encephalopathy. In addition to the well-known action of fenfluramine as a releaser of neuronal serotonin, we have recently shown that FFA contributes to its antiseizure activity by acting as a potent positive modulator of the sigma-1 receptor (S1R) in in vitro tests and in vivo behavioral responses. Here, we examined whether the modulation of S1R extends to behavioral responses seen after exposure to the neuroactive steroids dehydroepiandrosterone sulfate (DHEAS) and pregnenolone sulfate (PREGS), which are S1R agonists, while progesterone acts as a S1R antagonist. The effects of the steroids on the FFA racemate or the dextro-rotary isomer (+)-FFA were evaluated in the mouse model of dizocilpine-induced learning impairment (Maurice et al. *Brain Res.* 1994;647(1):44-56). Two behavioral tests were used: spontaneous alternation in Y-maze (spatial working memory) and passive avoidance (contextual long-term memory). FFA racemate or (+)-FFA attenuated dizocilpine-induced learning impairment in both responses, in the 0.1-1 mg/kg intraperitoneal (IP) dose range. This effect was prevented by pre-administration of the S1R antagonist NE-100 (1 mg/kg IP), confirming that both the FFA racemate and the dextro-rotary isomer (+)-FFA activated S1R in vivo. DHEAS or PREGS attenuated dizocilpine-induced learning deficits in the 5-20 mg/kg IP dose range. Coadministration of DHEAS or PREGS and FFA, particularly at the lowest active dose (5 mg/kg) together with either the FFA racemate or (+)-FFA (0.1 mg/kg) resulted in an additive or synergistic effect on behavioral responses. These observations confirmed positive modulation of FFA on S1R by showing that, in physiological conditions, the drug potentiates the action of endogenous modulators of S1R as neuroactive steroids. The latter are potent modulators of the excitatory/inhibitory balance in the brain, and this effect must be considered in the anti-epileptic action of FFA.

Disclosures: **T. Maurice:** F. Consulting Fees (e.g., advisory boards); Zogenix Inc. **A. Gammaitoni:** A. Employment/Salary (full or part-time):; Zogenix Inc. **B.S. Galer:** A. Employment/Salary (full or part-time):; Zogenix Inc. **P. Martin:** A. Employment/Salary (full or part-time):; Zogenix Inc..

Poster

739. Epilepsy: Pharmacology

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 739.02/B90

Topic: B.10. Epilepsy

Support: NS 110863
NS 040337
NS 044370

Title: Progesterone receptor regulation of seizures

Authors: S. SHIONO, J. WILLIAMSON, J. KAPUR, ***S. JOSHI**;
Univ. of Virginia, Charlottesville, VA

Abstract: Menstrual cycle-linked hormonal fluctuations regulate seizure frequency. We tested whether progesterone receptors (PRs) regulated progesterone withdrawal seizures and susceptibility to status epilepticus (SE).
Adult female Sprague Dawley rats that developed epilepsy following cholinergic SE were studied. Seizures were monitored via hippocampal and cortical EEG and behavior. Basal seizure frequency was monitored for two weeks and then animals were daily treated with progesterone (P, 50 mg/kg/day, ip) for a week. The effect of P withdrawal on seizure frequency was determined during the subsequent week. To block PRs, half of the animals were treated with anti-progestin RU-486 (10 mg/kg/day, P+RU) during the week of progesterone. Control animals were treated with vehicle instead of RU-486 (P+V). RU-486 and vehicle were administered 30 min before progesterone. An animal that experienced twice as many seizures during withdrawal week as during pretreatment week was considered to have catamenial seizure exacerbation. RU-486 treatment protected animals from catamenial seizures (15% P+RU-treated, n=13 vs 57% P+V-treated animals, n=14, $p<0.05$, Fisher's exact test). The weekly average seizures of animals in P+V group were 30±9 and this number increased to 57±16 during withdrawal (n=14, p=0.023, paired t-test). In contrast average weekly seizures at baseline and during withdrawal remained stable in P+RU group animals (41±16 and 43±13 respectively, p=0.37, paired t-test). Thus, progesterone withdrawal-induced seizures were suppressed wit RU-486. However, inhibitory actions of RU-486 on glucocorticoid and androgen receptors may have contaminated the effect on PRs. Hence subsequent studies were performed in animals with global deletion of PRs (KO). We first determined whether global deletion of PRs (KO) affected susceptibility to prolonged seizures of SE. PR KO and littermate WT animals experienced 4-5 day-long estrous cycles and associated hormonal fluctuations. To ensure uniform hormonal milieu, SE was induced on the day of estrus in 5 KO animals and 4 WT littermates. The latency to seizure onset was similar in the WT and KO animals (756 ± 50 s, n=4 vs 646 ± 78 s, n=5). The duration of electrographic SE also appeared to be comparable between WT (458 ± 109 min, n=4) and KO animals (381 ± 89 min, n=5). However, the power of EEG in delta to gamma frequencies ended to be lower in the KO animals tan that in the WT animals. Thus, lack of PRs may reduce the severity of SE. Studies are ongoing to confirm and extend these findings.

Disclosures: S. Shiono: None. **J. Williamson:** None. **J. Kapur:** None. **S. Joshi:** None.

Poster

739. Epilepsy: Pharmacology

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 739.03/B91

Topic: B.10. Epilepsy

Title: Neuromodulatory effects of dydrogesterone against anxiety and chemically-induced seizures in male rats

Authors: A. KAUR, *P. E. ALELE;
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Abstract: Current treatment of epilepsy, a common and debilitating neurological disorder, is hampered by serious adverse effects and the incomplete control of seizure activity by standard antiepileptic drugs (AEDs). Some AEDs have been associated with suicide-related events, major congenital malformations when used in pregnancy, an incomplete efficacy that may lead to poor patient non-adherence, and increased morbidity and mortality. Dydrogesterone (DYG), a stereoisomer of natural progesterone, has been shown to significantly increase allopregnanolone levels in the frontal lobe, hippocampus, and the hypothalamus. Presumably, increased allopregnanolone increases the inhibitory effect of gamma-aminobutyric acid (GABA) in the brain. Our goal was to determine if the presumed neuromodulatory effect of DYG would impart an antianxiety effect and protect against chemically-induced seizures in adult male rats. We administered three doses of DYG (0.2, 0.6, and 1 mg/kg body weight) for 14 days. We then used the elevated plus maze to test for effects of DYG on anxiety, followed by administration of pentylenetetrazol (PTZ), a chemical convulsant, to test for seizure latency, severity, and duration in response to the treatments. Trunk blood was collected to measure serum levels of estradiol, progesterone and testosterone. All three doses of DYG significantly reduced the time animals spent on the open arm compared to diazepam ($p<0.05$). The 0.2 mg/kg DYG dose was comparable to diazepam in increasing seizure latency ($p>0.05$), whereas the 1 mg/kg DYG dose and the saline-treatment significantly reduced the seizure latency compared to diazepam ($p<0.05$). Saline treatment, 0.6 mg, and 1 mg/kg DYG treatment significantly increased seizure duration compared to diazepam treatment ($p<0.05$). Conversely, the 0.6 mg and the 1 mg/kg DYG treatments significantly reduced the seizure severity compared to the saline-treated controls ($p<0.05$). Diazepam also significantly reduced seizure severity compared to controls ($p<0.05$). No significant alterations occurred among the DYG-treated, and control groups in the serum levels of estradiol, progesterone, and testosterone after two weeks' treatment. These data support previous findings that DYG is a potent neuromodulator against seizure activity and suggest further studies to explore its therapeutic potential as an adjunct for tonic-clonic and other seizure types.

Disclosures: A. Kaur: None. **P.E. Alele:** None.

Poster

739. Epilepsy: Pharmacology

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 739.04/B92

Topic: B.10. Epilepsy

Support: NINDS grant #1U54NS079202

Title: Combination of allopregnanolone and midazolam administered intramuscularly terminates tetramethylenedisulfotetramine-induced status epilepticus in mice

Authors: *D. ZOLKOWSKA, N. GARIBAY, C. W. FLAMM, M. A. ROGAWSKI;
Dept. of Neurol., Sch. of Med., Univ. of California, Davis, Sacramento, CA

Abstract: Tetramethylenedisulfotetramine (TETS) is a highly lethal neurotoxic rodenticide that acts as a noncompetitive GABA-A receptor. The National Institutes of Health considers TETS to be a high priority chemical threat agent. Severe TETS intoxication causes convulsive status epilepticus (SE) that is refractory to treatment. Benzodiazepines, the standard of care for initial treatment of SE, are often ineffective in managing SE, especially when therapy is delayed. Allopregnanolone (5α,3α-P), a neurosteroid positive modulator of synaptic and extrasynaptic GABA-A receptors, may provide a superior treatment option. According to current treatment algorithms, midazolam is expected to be the first seizure therapy that will be administered in a chemical exposure emergency. It is therefore of interest to assess the efficacy of 5α,3α-P in conjunction with this initial therapy. In the present study, we determined whether intramuscular (IM) 5α,3α-P (3 mg/kg) added to IM midazolam (MDZ, 1.8 mg/kg) was more effective than IM midazolam alone in terminating SE in mice exposed to TETS. To create a model mimicking the SE produced by TETS in humans, mice were pretreated with a single dose of riluzole (10 mg/kg, IP) and 10 min later received a lethal dose of TETS (0.2 mg/kg, IP). Riluzole does not inhibit TETS-induced SE but does protect against the rapidly lethal effects of TETS in mice, providing a model of persistent seizure activity. Behavioral seizure activity was assessed by visual observation and the latency to cessation of SE was recorded. Animals were monitored for 72 h after seizure termination and the incidence of mortality was recorded. Latency to cessation of SE was defined as the interval between the first behavioral myoclonic body twitch and termination of behavioral seizure activity. 5α,3α-P (6 mg/ml) was dissolved in a 24% Captisol in 0.9% saline. MDZ at human equivalent dose of 1.8 mg/kg (IM) was administered at 40 min after the first myoclonic twitch. Some animals received 5α,3α-P (3 mg/kg IM) together with MDZ. Addition of 5α,3α-P reduced the time to cessation of SE from 7.23 ± 1.75 min (MDZ alone) to 4.02 ± 1.18 min and increased 72 h survival from 86.6% (MDZ alone) to 100%. The addition of 5α,3α-P caused a transient increase in sedation in the majority of animals receiving the dual therapy compared with MDZ alone, but all animals fully recovered. Our results demonstrate that

addition of 5α,3α-P to standard of care MDZ more rapidly and more effectively terminates TETS-induced behavioral seizures than does MDZ alone. Importantly, 100% animals treated with the dual therapy were protected from mortality.

Disclosures: D. Zolkowska: None. **N. Garibay:** None. **C.W. Flamm:** None. **M.A. Rogawski:** None.

Poster

739. Epilepsy: Pharmacology

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 739.05/B93

Topic: B.10. Epilepsy

Title: Metyrapone reduces seizures in GAERS: Role of corticosterone

Authors: G. DEZSI[1], E. OZTURK[1], ***N. C. J. JONES**[2];
[1]Monash, Melbourne, Australia; [2]Monash Univ., Melbourne, Australia

Abstract: Introduction: Epilepsy is a common neurological disorder characterised by the occurrence of spontaneous unprovoked seizures. People with epilepsy are treated with anti-epileptic medications, and the vast majority of these drugs target ion channels. However, one third of patients with epilepsy have inadequate control of their seizures with existing medications, sparking a need to develop new therapies targeting alternative mechanisms. Here we explored whether metyrapone, an 11-b-hydroxylase inhibitor, can influence seizures in a rat model of epilepsy. Methods: We performed a series of pharmacological studies in different cohorts of rats (n>8/group). Adult epileptic GAERS (Genetic Absence Epilepsy Rats from Strasbourg) were surgically implanted with extradural recording electrodes to facilitate EEG recording and seizure quantification, and allowed to recover. Rats were connected to the EEG amplifiers, and treated with the corticosterone synthesis inhibitor metyrapone (5-100mg/kg); corticosterone (3-30mg/kg); or the neurosteroid DOC (10-50mg/kg); or their respective vehicles. Recordings persisted for 2 hours, and resulting EEG was analysed for the frequency of spike-wave discharge seizures using semi-automated software Spike-Wave finder. Drugs were delivered in random order using a repeated measures design, whereby each animal in the cohort was exposed to all doses of drug, with at least 48 hours in between treatments, and data analysis was conducted in a blinded fashion. Results: Metyrapone completely and dose-dependently suppressed spike-wave discharges in GAERS. In this study, vehicle-treated rats experienced 77+/- 8 seizures/hour whereas rats treated with 100mg/kg metyrapone experienced 8+/- 2 per hour ($P<0.0001$). In contrast, corticosterone treatment significantly enhanced seizure frequency ($P<0.01$), whereas the neurosteroid DOC did not influence seizure frequency at the doses used. Conclusions: Here we show that the 11-b-hydroxylase inhibitor metyrapone dose-dependently reduces seizures in GAERS. This is likely mediated by inhibition of corticosterone, since

exogenous corticosterone increased seizures, but the precursor DOC did not impact seizures. Metyrapone may therefore represent a new therapy for seizures with a novel mechanism of action.

Disclosures: G. Dezsi: None. **E. Ozturk:** None. **N.C.J. Jones:** None.

Poster

739. Epilepsy: Pharmacology

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 739.06/B94

Topic: B.10. Epilepsy

Support: F30-NS095578 awarded to Wulsin AC
NS-062806 awarded to Danzer SC
T32-GM063483 awarded to Wulsin AC
NS-065020 awarded to Herman JP

Title: AAV-Cre mediated deletion of hippocampal glucocorticoid receptors reduces status epilepticus severity

Authors: *K. L. KRAUS[1,3], A. C. WULSIN[4], J. P. HERMAN[2], S. C. DANZER[3];
[2]Dept Pharmacol. and Systems Physiol., [1]Univ. of Cincinnati, Cincinnati, OH; [3]Dept Anesthesia, [4]Pediatric Neurol., Cincinnati Children's Hsptl Med. Cntr, Cincinnati, OH

Abstract: Status epilepticus (SE) is a medical emergency with a high mortality rate. Many patients are refractory to anti-convulsive therapy; even when successfully treated, patients are usually left with disabling morbidity. Histological evidence in both human and animal tissue demonstrates significant hippocampal neuron loss and synaptic rearrangements that are thought to play a role in the subsequent development of epilepsy, as well as the cognitive deficits associated with SE. We and others have shown that epileptic activity, particularly during SE, results in hyperactivation of the HPA axis. This is evidenced by elevated glucocorticoid secretion within hours of SE as well as a state of chronic glucocorticoid hypersecretion that persists for months after the initial insult (Wulsin, A.C., 2016). Furthermore, exposure to elevated glucocorticoids can increase neuronal activity and produce neuronal injury. Therefore, *we hypothesize that glucocorticoid receptor (GR) signaling contributes to SE-induced neuronal death and injury.* To assess the role of hippocampal GRs in SE, a Cre-mediated viral deletion strategy was developed to knockdown hippocampal GR expression. Adult male and female $GR^{fl/fl}$ mice on a C57BL6 background undergo bilateral intrahippocampal viral injections of either AAV9.CamkII.Cre.eGFP (AAV9-Cre-GFP; 1µL, 3e1011 vg/mL) or AAV9.CamkII.eGFP (AAV9-GFP; 1µL, 2.4e1011 vg/mL) as control. To characterize the viral spread in each mouse, a Nikon TiE inverted microscope and lumencor SpectraX light source is used for high-speed

imaging of all hippocampal sections. Imaging confirmed robust GFP-labeling of dentate granule cells throughout the rostral-caudal extent of the hippocampus with this approach. GR immunostaining of the tissue confirmed deletion of GRs in AAV9-Cre-GFP-expressing cells. Histological stains and probing for activated caspase-3 revealed no evidence of viral toxicity. In initial experiments, we induced SE by systemic administration of the mAchR agonist pilocarpine (vs. saline control) two weeks after viral infusion. Hippocampal GR knockdown increased the latency to first seizure after injection and reduced SE-induced mortality (n=14 control, n= 13 GR knockout; $p < 0.01$, t-test). These studies establish the utility of a new approach to selectively eliminate GRs from adult hippocampal neurons and demonstrate that hippocampal GR activation contributes to SE severity and mortality.

Disclosures: K.L. Kraus: None. **A.C. Wulsin:** None. **J.P. Herman:** None. **S.C. Danzer:** None.

Poster

739. Epilepsy: Pharmacology

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 739.07/B95

Topic: B.10. Epilepsy

Title: Inhibition of NMDA currents in dissociated neurons derived from kindled rat hippocampus

Authors: *J. MARTINEZ-LAZCANO[1], E. G. GUEVARA[3], E. LARA-GONZALEZ[4], E. RENDON-OCHOA[4], J. BARGAS[5], C. PAZ[2];
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Abstract: The epilepsy is characterized by sustained depolarization and rapid frequency discharges attributed to over-stimulation of N-methyl-D-aspartate (NMDAr)receptors, several studies suggest the regulation of NMDAr activity through inhibition of P-glycoprotein activity and drug-resistance protein-1 (MRP1). Our group has hypothesis that Probenecid, an inhibitor of the activity and expression of some ABC-type transporters, can modify the activity of the NMDA receptor. Whereby, our aim was evaluated the effect of probenecid on NMDA-induced currents in dissociated hippocampal cells from control and kindled rats. Material and Methods: The rats were decapitated to extract the brain and place it in a Krebs solution at 25 ° C; pH: 7.4, 300 ± 5 mOsm / l and saturated with 95% O2 and 5% CO2. Subsequently, sagittal slices of the hippocampal CA region of 300 μm thickness were obtained and enzymatic and mechanical cell dissociation was performed. The cell suspension was placed in a petri dish with solution at room temperature, after 15 min the neurons were adhered to the base of the petri-box to perform

voltage-clamp records of currents evoked by NMDA. The records were made using an electrode with resistance of 4-7 MΩ, applying a 100 μM solution of NMDA and different concentrations of probenecid (0.2, 2, and 20 mM) to the record plate and obtained with an Axopatch 200B amplifier and controlled and monitored with pClamp-8.2. Results: Probenecid produces a dose-dependent reduction in the current evoked by NMDA, in neurons derived from the hippocampus of the CA region of control rats. In the case of neurons obtained from kindled rats, our observed that the NMDA current residuals were less compared against control neurons. In neurons from kindled rats the NMDA current was reduced compared to neurons from control rats in present of 20 mM of Probenecid. Discussion and Conclusions: Probenecid inhibits currents evoked by NMDA in dissociated neurons from control rats and kindled rats.

Disclosures: J. Martinez-Lazcano: None. **E.G. Guevara:** None. **E. Lara-Gonzalez:** None. **E. Rendon-Ochoa:** None. **J. Bargas:** None. **C. Paz:** None.

Poster

739. Epilepsy: Pharmacology

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 739.08/B96

Topic: B.10. Epilepsy

Support: EBS Innovation Initiative

Title: Carbamazepine and GABA have distinct effects on seizure onset dynamics

Authors: *D. N. CRISP[1], R. PARENT[2], G. G. MURPHY[3], W. C. STACEY[4];
[1]Biomed. Engin., [2]Mol. and Behavioral Neurosciences Inst., [3]MBNI/Physiology, [4]Neurol., Univ. of Michigan, Ann Arbor, MI

Abstract: Intro:
Our recent work has demonstrated that seizures can be classified according to the dynamics of their onset transitions and that these transitional dynamics can be an indicator for changes in brain state during epileptogenesis. Future research into epilepsy treatment could benefit from understanding if these dynamic classifications are linked to specific biological mechanisms. We investigated the effect different anticonvulsants have on the type of seizure onset bifurcation *in vitro* using acutely prepared mouse brain slices.
Methods:
In vitro horizontal brain slices (n = 100) containing hippocampus, amygdala, and entorhinal cortex regions were prepared and extracellular field potentials were recorded in the presence of the pro-convulsant high potassium/low magnesium (HPLM) aCSF to produce ictal-like activity. The control group (40/100) received no anticonvulsants, while the two experimental groups were treated with HPLM + 50 uM carbamazepine (30/100) or HPLM + 10 uM GABA (30/100). The

concentration of HPLM was high enough to induce seizures in all slices despite anticonvulsants. Ictal onset bifurcations from hippocampal recordings were labeled by three independent reviewers. Label validity was confirmed with both Fleiss Kappa testing and rigorous machine learning feature analysis.
Results:
Three out of four possible onset dynamics (supercritical Hopf, subcritical Hopf, and SNIC bifurcations) were present in all three experimental conditions. The control group had mostly SNIC bifurcations (23/40), followed by subcritical Hopf (12/40), then supercritical Hopf (5/40). Both experimental conditions (Carbamazepine and GABA) deviated from this distribution significantly.
Interpretation:
This result suggests that the pathway to seizure onset is modulated by the different mechanisms of the two anticonvulsants. Dynamics theory suggests that this effect occurs because the anticonvulsants modulate the preictal brain state and change the potential pathway into seizure.

Disclosures: D.N. Crisp: None. **R. Parent:** None. **G.G. Murphy:** None. **W.C. Stacey:** None.

Poster

739. Epilepsy: Pharmacology

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 739.09/B97

Topic: B.10. Epilepsy

Title: Antisense oligonucleotide therapy for scn2a gain-of-function epilepsies

Authors: *M. LI[1], N. JANCOVSKI[1], P. JAFAR-NAJAD[2], L. E. BURBANO[1], A. NEMIROFF[3], K. DALBY[3], S. MALJEVIC[1], C. A. REID[1], F. RIGO[2], S. PETROU[1,3];
[1]Florey Inst. of Neurosci. and Mental Hlth., Melbourne, Australia; [2]Ionis Pharmaceuticals, Carlsbad, CA; [3]RogCon Biosci., Miami, FL

Abstract: OBJECTIVE: To establish the therapeutic potential of antisense oligonucleotides (ASOs) in *SCN2A* gain-of-function developmental and epileptic encephalopathy (DEE) by evaluating its efficacy in a mouse model containing a recurrent *SCN2A* variant identified in patients with early-onset DEE.
BACKGROUND: *SCN2A* encodes for a voltage-gated sodium channel and *de novo* variants are the cause of a spectrum of early-onset DEE. There is growing evidence showing early disease onset correlates with gain-of-function variants, but therapies using conventional sodium channel blockers can be complicated by low selectivity. To improve selectivity, we employed the ASO technology and identified a lead ASO that specifically downregulates mouse *Scn2a* expression.
DESIGN: Mice heterozygous for *Scn2a* R1883Q (equivalent to human *SCN2A* R1882Q) displayed spontaneous seizure as early as postnatal (P) day 1 and lethality from P13. ASO was

injected into the ventricle and efficacy was assessed by slice electrophysiology, survival, seizure counts, EEG and behavioural tests.
RESULTS: A single dose of ASO significantly extended survival, with 90.2 % of the ASO group surviving on P30, while none from control group survived. Further monitoring found 68.9 % of ASO group lived until P80. A subset of mice received second ASO injection at P25 and resulted in survival beyond P180. ASO treatment not only prolonged lifespan but also abolished behavioural seizure and EEG interictal activity. Recordings from excitatory neurons revealed increased action potential firing, which was normalized to wildtype level with ASO treatment. Performance in a battery of motor and psychosocial behavioural tests revealed alteration in anxiety-like traits that was rectified by lowering the ASO dose.
CONCLUSIONS: *Scn2a* downregulatory ASO significantly improved survival and mitigated seizure in a mouse model of *Scn2a* gain-of-function DEE. Therapeutic window can be maximised by dose titration and repeated dosing. This study demonstrates ASO is a viable therapeutic strategy for *SCN2*A gain-of-function epilepsy.

Disclosures: M. Li: None. **N. Jancovski:** None. **P. Jafar-najad:** None. **L.E. Burbano:** None. **A. Nemiroff:** None. **K. Dalby:** None. **S. Maljevic:** None. **C.A. Reid:** None. **F. Rigo:** None. **S. Petrou:** None.

Poster

739. Epilepsy: Pharmacology

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 739.10/B98

Topic: B.10. Epilepsy

Title: Blockade of PD-1/PD-L1 suppressed epileptiform activities in both *in-vivo* and *in-vitro* seizure models

Authors: *Z. CHEN;
Fudan Univ., Shanghai, China

Abstract: PD-1 receptor and its ligand PD-L1 are important in immunotherapy particular in cancer therapy. Although PD-1/PD-L1 have been found to also exist in neurons, the function of PD-1/PD-L1 in the central never system, particularly in relation with epilepsy, is still unexplored. In this study, we studied the relationship and the influence of PD-1/PD-L1 pathway on epileptogenesis. Either pentylenetetrazole (PTZ) or cyclothezide (CTZ) induced *in vivo* and *in vitro* epilepsy model were used in this study. SHR-1210 (PD-1 antibody) and SHR-1316 (PD-L1 antibody) applied intracerebraventricular (i.c.v.) significantly inhibited PTZ (50 mg/kg. i.p.) induced seizure behavior and epileptiform like EEG activities in both rat and mice seizure model. *In vitro,* SHR-1210 and SHR-1316 also significantly inhibited CTZ induced epileptiform burst discharges in cultured hippocampal neurons. In conclusion, our results suggest that

blockade of PD-1/PD-L1 could interference with the occurrence of the burst activities suppress seizure behavior.

Key waords
PD-1; PD-L1; Epilepsy; Epileptiform discharges; CTZ; PTZ

Disclosures: Z. Chen: None.

Poster

739. Epilepsy: Pharmacology

Location: Hall A

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Program #/Poster #: 739.11/B99

Topic: B.10. Epilepsy

Support: NIH NS050229

Title: Selective hyperactivation of JNK2 in an animal model of chronic epilepsy

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Abstract: c-Jun N-terminal kinases (JNKs) are members of the mitogen-activated protein kinase (MAPK) family. Hyperactivation of JNKs by phosphorylation (pJNK) is associated with debilitating neurodegenerative diseases, including Alzheimer's and Parkinson's. In a rat model of epilepsy produced by chemoconvulsant-induced status epilepticus, we previously reported elevated pJNK levels during chronic epilepsy, and showed that pharmacological JNK inhibition reduced seizure frequency (Tai TY et al, *Neuroscience*, 2017). We also have described the time course of JNK activation during the development of epilepsy in our animal model and found that JNK hyperactivation only occurred in the chronic epilepsy phase of spontaneously recurring seizures and not during the earlier stages of epileptogenesis (Parikh AN et al., *Soc. Neurosci. Abstr*., 2017). In this current study, we sought to identify which of the JNK isoforms (JNK1, JNK2, or JNK3) contributes to the overall increased pJNK levels seen in chronic epilepsy in our animal model. After pJNK enrichment by immunoprecipitating CA1 hippocampal homogenates with an anti-pJNK antibody (Ab), the ratios of individual JNK isoforms between the chronically epilepsy rats and their naïve, age-matched controls were determined by Western blotting for the two JNK electrophoretic bands at 54 kDa and 46 kDa. Subsequent Western blotting with the anti-pJNK Ab was used to normalize protein loading between experimental and control samples. These experiments revealed a significant increase in pJNK2 levels in chronic epilepsy when compared to naïve controls (54 kDa: 142 ± 12.4%, n=8, p=0.012; 45 kDa: 114 ± 5.9%, n=8, p=0.048). No changes in phosphorylation/activation levels were observed for either JNK1 (54 kDa band: 99 ± 7.5%, n=8, p=0.883; 45 kDa band: 104 ± 4.8%, n=8, p=0.415) or brain specific

JNK3 (54 kDa band: 109 ± 17.1%, n=8, p=0.609; 45 kDa band: 106 ± 13.9%, n=8, p=0.682). However, analysis of total levels (phosphorylated and nonphosphorylated) of JNK isoforms showed no significant changes in the total expression of any JNK isoform, including JNK2. This suggests that elevated levels of pJNK2 in epilepsy arise from activation by upstream signaling pathways, not from increased protein expression of JNK2. In summary, our results show that JNK2 is selectively hyperactivated in chronic epilepsy. Given our previous observation that overall JNK inhibition reduces seizure frequency, this investigation suggests that selective JNK2 inhibition may be a potential antiepileptic strategy.

Disclosures: F.A. Concepcion: None. **A.N. Parikh:** None. **M.N. Khan:** None. **R.D. Boehm:** None. **A. Dhami:** None. **N.P. Poolos:** None.

Poster

739. Epilepsy: Pharmacology

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 739.12/B100

Topic: B.10. Epilepsy

Support: NIH grant 1R21HD093033
NIH NCATS Award UL1 TR001425
NARSAD Independent Investigator Grant from the Brain & Behavior Research Foundation

Title: P110β-selective inhibition in a PTEN-deficient mouse model for epilepsy rescues molecular and behavioral phenotypes

Authors: A. R. WHITE, D. TIWARI, M. MACLEOD, A. SNIDER, S. C. DANZER, *C. GROSS;
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Abstract: Approximately 2.2 to 3 million people in the US have been diagnosed with epilepsy, affecting all ages, races, genders, and socioeconomic groups. Studies have shown that epilepsy in about one third of patients is uncontrolled with current medications, leaving a vast need for improved therapies.
The causes of epilepsy are diverse and not always known but one prominent gene mutated in a small subpopulation of patients is Phosphatase and Tensin homolog (PTEN) [1]. PTEN has been extensively studied in cancer biology, as it is commonly mutated in a host of cancers. Phosphoinositide 3-kinases (PI3Ks) are the enzymatic counter actors of PTEN. There are three class 1A PI3K catalytic isoforms, p110α, β and δ. Inhibition of only one of these PI3K catalytic isoforms, p110β, but not p110α and δ, reduces tumor progression in prostate cancer [2]. P110β-selective inhibitors are currently being evaluated in clinical trials for PTEN-deficient cancers.

Our lab has shown that the same PI3K isoform, p110β is upregulated in the inherited intellectual disability and autism spectrum disorder (ASD) Fragile X Syndrome (FXS) and that inhibition of p110β rescues many FXS phenotypes, including audiogenic seizures, in a FXS mouse model [3,4]. This work collectively leads to the hypothesis that inhibition of p110β will reduce PI3K signaling and subsequently rescue seizure and behavioral phenotypes in neuron-specific PTEN KO mice.
In the present study, we have used the p110β-selective inhibitor GSK6A to assess both molecular and clinical phenotypes in the context of PTEN deficiency. In CamKIIα-Cre;Ptenfl/fl mice, GSK6A significantly reduces aberrant protein synthesis and cell signaling to levels comparable to littermate controls. In this mouse model, GSK6A is also able to restore nesting behavior to littermate control range. Additionally, ongoing seizure assessment suggests a decrease in seizure quantity after one week of GSK6A administration as compared to vehicle controls. Each study utilizes both female and male mice, with littermate controls, and experimenters were blinded during analysis. All molecular experiments were subjected to power analysis to guarantee rigor. Seizure assessments are ongoing in order to successfully realize analogous rigor. In summary, our results suggest that selective inhibition of the PI3K isoform p110β rescues a broad spectrum of neuronal phenotypes in PTEN-deficient mice.
References:
1. Song, M.S., et al. Nat Rev Mol Cell Biol, 2012. 13(5):283-296.
2. Wee, S. PNAS. 2008. 105(35):13057-13062.
3. Gross, C., et al. Cell Rep, 2015. 11(5):681-688.
4. Gross, C. et al. Neuropsychopharmacology, 2019. 44(2):324-333.

Disclosures: A.R. White: None. **D. Tiwari:** None. **M. MacLeod:** None. **A. Snider:** None. **S.C. Danzer:** None. **C. Gross:** None.

Poster

739. Epilepsy: Pharmacology

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 739.13/B101

Topic: B.10. Epilepsy

Title: [E/Z] isoxylitones as JAK-STAT inhibitor: The promise of a new drug class

Authors: *S. U. SIMJEE, U. NISAR, F. SHAHEEN, A.-U.-R. RAHMAN, M. I. CHOUDHARY;
H.E.J. Res. Inst. of Chemistry, Intl. Ctr. for Chem. and Biol. Sciences, Univ. of Karachi, Karachi, Pakistan

Abstract: Purpose: Epilepsy is a neurological disorder marked by recurring seizures. Despite availability of a broad category of AEDs, over one-third of the epileptic patients do not respond

to these drugs. Thus finding new therapeutics to overcome the untreatable epilepsy is needed. Activation of Janus Kinase (JAK)/Signal Transducer and Activator of Transcription (STAT) signaling pathway has been reported to link with epilepsy and thus can be use as a target molecular pathway to interrupt the process of epileptogenesis. In the present study, we targeted the JAK/STAT pathway using [*E/Z*] isoxylitones in order to inhibit epileptogenesis following a brain insult in an animal model. The outcome of these studies could lead to new therapies that can be used to prevent or inhibit development of epilepsy. **Methods:** Pentylenetetrazole (PTZ)-induced kindling in mice was used as a model of epileptogenesis. Seizure-related behaviors were monitored following PTZ administration. JAK/STAT were analyzed in mice brain samples using RT-PCR and immunohistochemistry. **Results:** It was observed that [*E/Z*] isoxylitones, a sodium channel blocker not only halt the epileptogenesis in PTZ-kindled mice but also effectively reduces the JAK-1, JAK-3, and STAT-5a expression in cortex and hippocampus of the treated mice brain. **Conclusion:** The present data suggests that isoxylitones act at the underlying molecular mechanism to control the seizure pattern, such as the downregulation of JAK/STAT treated mice brain. These findings uncover a potential effect of the JAK/STAT pathway in epileptogenesis and may provide a new therapeutic target that can be harnessed for the prevention of epilepsy development and/or progression. At this stage we propose to examine isoxylitones to determine 1) its potency to inhibit JAK/STAT pathway and cellular toxicity in primary hippocampal neurons, 2) ability to block acute seizure- induced JAK/STAT pathway activation and off-target effects on other kinases. The expected outcome is identification of lead JAK/STAT inhibitors that can be advanced towards clinical testing for epilepsy disease modification.

Disclosures: S.U. Simjee: None. **U. Nisar:** None. **F. Shaheen:** None. **A. Rahman:** None. **M.I. Choudhary:** None.

Poster

739. Epilepsy: Pharmacology

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 739.14/B102

Topic: B.10. Epilepsy

Title: Targeting overexpressed TGF-β linked MAPK pathway to halt pentylenetetrazole-induced epileptogenesis in mice

Authors: *M. SHAHID[1], U. NISAR[1], F. SHAHEEN[1], M. ASKANI[1], S. U. SIMJEE[1,2];
[1]H.E.J. Res. Inst. of Chem., Intl. Ctr. For Chem. and Biol. Sci., Karachi, Pakistan; [2]Dr. Panjwani Ctr. for Mol. Med. and Drug Res., Intl. Ctr. for Chem. and Biol. Sci., Karachi, Pakistan

Abstract: Epilepsy is illustrated by persistent predisposition of the brain to generate seizures and considered as one of the most common, chronic, neurological disorder affecting around 1% of

the individuals worldwide. A growing body of advanced researches now points a link between inflammation and various epilepsy syndromes, reflecting both an inflammatory state inside the epileptic brain along with increased permeability of the blood-brain barrier, heading towards enhanced neuronal excitability. The probable contribution of TGF-β in epileptogenesis is reinforced by animal studies viewing TGF-β up-regulation as measure of inflammatory reaction in the brains of kindled animals that are exposed to status epilepticus. The main focus of this study was to investigate the potential relationship between the TGF-β associated MAPK pathway and epilepsy which will aid in confirming that up regulation of TGF-β genes might be one of the underlying cause of epilepsy. A novel anticonvulsant [E/Z] isoxylitones was used to treat epileptic seizures along with standard antiepileptic drugs (AEDs) diazepam and valproic acid in pentylenetetrazole-induced kindling model of mice. To confirm aforementioned evidences, expression levels of TGF-β, TRAF6 and JNK3 genes along with inflammatory cytokine interleukin-1β (IL-1β) were analyzed. It was observed that as compared to the PTZ-control group, there was a significant decrease in the response of seizures observed in [E/Z] isoxylitones treated group. Furthermore, expressions of these genes were significantly reduced in [E/Z] isoxylitones and standard AEDs treated groups. It is concluded that, TGF-β signaling pathway can be a potential subcellular target for reducing seizure duration and associated neuronal death in epilepsy and [E/Z] isoxylitones is an effective way to achieve this therapeutic target.

Disclosures: **M. Shahid:** None. **U. Nisar:** None. **F. Shaheen:** None. **M. Askani:** None. **S.U. Simjee:** None.

Poster

739. Epilepsy: Pharmacology

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 739.15/C1

Topic: B.10. Epilepsy

Support: Italian MoH
Novartis Pharma Grant Agreement 43010

Title: Neuroprotective and anti-inflammatory effect of fingolimod (FYT720) in a rat model of epileptogenic cortical dysplasia

Authors: *F. COLCIAGHI[1], B. CIPELLETTI[1], A. CATTALINI[1], E. RINALDI[2], A. CONSONNI[2], F. BAGGI[2], C. CAGNOLI[1], R. MANTEGAZZA[2], M. DE CURTIS[1], G. S. BATTAGLIA[1];
[1]Epilepsy Unit, [2]Neuroimmunology and Neuromuscular Dis. Unit, Fondazione IRCCS Inst. Neurologico Carlo Besta, Milano, Italy

Abstract: Clinical and experimental evidence provided support that both innate and adaptive immunity may be crucial in the pathophysiology of epilepsy. The methylazoxymethanol/pilocarpine (MP) rat is a convulsive model of human cortical dysplasia (CD), the most common developmental malformation that causes refractory epilepsy. We showed that pilocarpine-induced status epilepticus (SE) and subsequent seizures (SRS) in MP rats lead to progressive cortical/hippocampal neurodegeneration and neuroinflammation (Colciaghi 2001, 2014; Nobili 2015). More recently we observed increased blood-brain-barrier (BBB) leakage, infiltration of $CD8^+$ cells and increased expression of sphingosine 1-phosphate receptors (S1Ps) in the cortex of MP rats in the course of epilepsy. Fingolimod (FYT720) the first oral disease-modifying therapy approved by FDA and EMA for relapsing-remitting multiple sclerosis, is able to cross the BBB and to bind S1P receptors expressed on CNS resident cells. Here we verified whether FYT720 could be protective for both neurons and glia and modulate seizure activity in MP rats. Rats with cortical dysgeneses were generated by prenatal injection (E15) of MAM (15 mg/kg i.p.) in pregnant rats. N=20 adult MAM rats were implanted with EEG cortical electrodes. One week later, rats received pilocarpine (270 mg/kg i.p.) for induction of the SE and SRS. N=5 MP rats that survived SE received FYT720 formulated in pellet (2 mg/kg body weight/day) for 20 days, starting from the 5^{th} day after SE. Additional n=5 MP rats received conventional pellets and were used as proper epileptic untreated controls. In both groups we performed: i) GFAP/Iba-1/CD8 IHC analysis to assess gliosis/cytotoxic T cell infiltrates ii) FluoroJade (FJ^+) assay to assess neurodegeneration iii) EEG analysis to assess seizure activity. Here we show that fingolimod exerts robust neuroprotective (↓FJ^+ cells) and anti-inflammatory (↓GFAP/Iba-1/$CD8^+$ cells) effects in the cerebral cortex and hippocampus of FYT720-MP *vs* untreated-MP rats. Although seizure analysis is currently underway, our data suggest that fingolimod could be a new therapeutic approach for the prevention of epileptogenesis in CD rat model.

Disclosures: F. Colciaghi: None. **B. Cipelletti:** None. **A. Cattalini:** None. **E. Rinaldi:** None. **A. Consonni:** None. **F. Baggi:** None. **C. Cagnoli:** None. **R. Mantegazza:** None. **M. de Curtis:** None. **G.S. Battaglia:** None.

Poster

739. Epilepsy: Pharmacology

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 739.16/C2

Topic: B.10. Epilepsy

Support: CONCAYT-SEP-CB 250930
UDG-PTC-1500
PRO-SIN 2018

Title: Muscarinic receptor type 2 and 4 modulate the anticonvulsive effect of sparteine in status epilepticus murine model

Authors: *F. V. VILLALPANDO VARGAS[1], S. RODRÍGUEZ MERCADO[3], A. M. MALDONADO MORA[3], S. ARELLANO LEYVA[3], L. G. MEDINA-CEJA[2];
[1]Univ. of Guadalajara, Guadalajara, Mexico; [2]Univ. of Guadalajara, Zapopan, Jalisco, Mexico, Mexico; [3]Guadalajara Univ., Guadalajara, Mexico

Abstract: In order to determinate the anticonvulsive effect of Sparteine (Sp) through the activation or inactivation of the M2 and M4 subtype of muscarinic acetylcholine receptor (mAChR) we used male Wistar ratas (200-350 g) with cannula implantation in the right ventricle to inject drugs (i.c.v., total volumen per drug 2.5µl) . All animals were behavioral recorder using racine scale 30 min before drugs and continually during and after drugs administration until 3 h after kainic acid (AK). Control groups (n=6, per group): saline solution (SS, 0.9%, i.p.), dimethyl sulfoxide (DMSO, i.c.v.), KA (9 mg/kg, i.p.) and Sp+KA (30 mg/kg, i.p., Sp was administrated 30 minutes before KA). Experimental groups (n=6, per group): were pre-treated one hour before Sp and one and a half hour before KA administration (i.c.v.) with the antagonist of M2 AF-DX 116 (AF; 4.74µM) or M4 PD102807 (PD; 100µM) and agonist of M2 Arecaidine but-2-ynyl ester tosylate (Ar; 20nM) or M4 VU10010 (VU; 10µM). Results are showed in figure 1. Mean ± Standar Error of Mean (SEM) are showed, Kruskal-Wallis test plus Dunn´s multiple comparación test was performance, significance $p<0.05$.

Disclosures: F.V. Villalpando Vargas: None. **S. Rodríguez Mercado:** None. **A.M. Maldonado Mora:** None. **S. Arellano Leyva:** None. **L.G. Medina-Ceja:** None.

Poster

739. Epilepsy: Pharmacology

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 739.17/C3

Topic: B.10. Epilepsy

Support: IPN SIP 20171379
IPN 20181021

Title: Effect of cerebrolysin on cognitive impairment and dendritic morphology of granular neurons in the dentate gyrus of rats with temporal lobe epilepsy

Authors: *L. A. PICHARDO-MACIAS, V. DÍAZ-VILLEGAS, I. L. FLORES-NAVARRETE, S. GUZMÁN-VELÁZQUEZ, D. A. ÁLVAREZ GARCÉS, S. R. ZAMUDIO;
Fisiología, Inst. Politécnico Nacional, CDMX, Mexico

Abstract: Temporal lobe epilepsy (TLE) is characterized by an abnormal increase and synchronization of neuronal electrical activity, which is manifested by spontaneous recurrent seizures (SRS). Studies of patients with TLE suggest that cognitive impairments are a common comorbidity frequently associated with changes in hippocampal synaptic plasticity. Cerebrolysin (CBL) is a biologically active mixture of peptides with low molecular weight and with neuroprotective and neurotrophic effects. Therefore, the objective of this study was to determine whether CBL treatment reduces the number of SRS, improves cognitive deficits (learning and spatial memory) and reduces dendritic alterations of granular dentate neurons in rats with TLE. For this purpose, male Wistar rats were divided into the following groups: a) control, b) control + CBL c) epileptic and d) epileptic + CBL. TLE was induced by systemic administration of lithium and pilocarpine, epilepsy was determined by monitoring of behavioral in video recordings. CBL (538 mg/kg) or vehicle (i.p.) were administered for 5 consecutive days per week for 3 weeks. After treatment, the Barnes maze test (BMT) was used to assess spatial navigational learning and memory. The dendritic morphology of the dentate gyrus was evaluated by the Golgi-Cox staining method. The results of this study did not support an antiepileptic effect of CBL; epileptic animals treated with this agent showed secondarily generalized seizures similar in frequency and intensity to those of epileptic animals treated with vehicle. However, we observed that CBL attenuated the dendritic deterioration caused by epilepsy, which was related to improved cognitive performance of CBL-treated animals in the BMT compared to epileptic rats. In conclusion, CBL did not show an anticonvulsant effect on secondarily generalized seizures; however, CBL can be proposed as an add-on therapy in the management of epilepsy to prevent neuronal alterations and to improve memory and learning processes.

Disclosures: L.A. Pichardo-Macias: None. **V. Díaz-Villegas:** None. **I.L. Flores-Navarrete:** None. **S. Guzmán-Velázquez:** None. **D.A. Álvarez Garcés:** None. **S.R. Zamudio:** None.

Poster

739. Epilepsy: Pharmacology

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 739.18/C4

Topic: B.10. Epilepsy

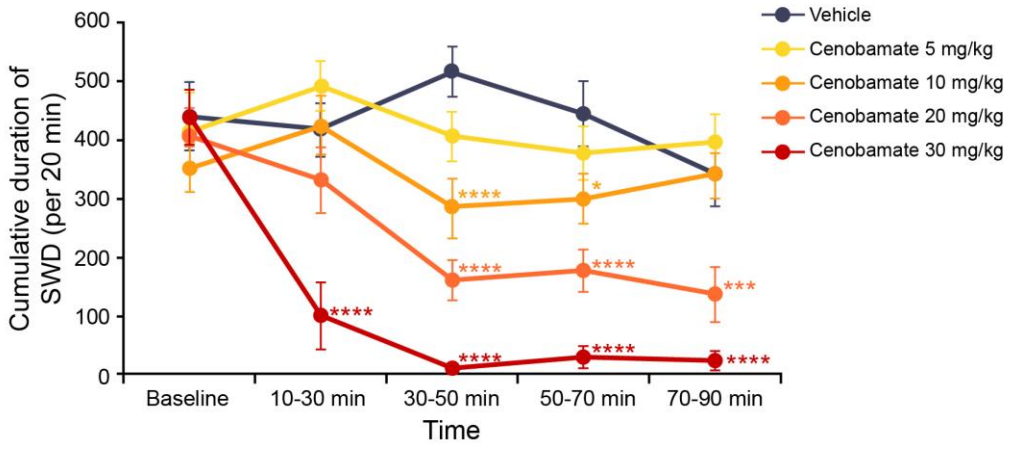
Support: Funding from SK Life Science, Inc. (Paramus, NJ)

Title: Cenobamate (YKP3089) dose-dependently reduced spike-and-wave discharges in the genetic absence epilepsy rats from Strasbourg (GAERS) animal model

Authors: *S. M. MELNICK[1], H. SHIN[2], C. ROUCARD[3], K. GLENN[1];
[1]SK Life Science, Inc., Paramus, NJ; [2]SK Biopharmaceuticals, Co., Ltd., Seongnam, Gyeonggi, Korea, Republic of; [3]Synapcell, Saint Ismier, France

Abstract: Background: The GAERS animal model shows behavioral and pharmacological features of absence seizures and the characteristic spike-and-wave discharges (SWD) on electroencephalograms (EEG). Cenobamate is a novel antiepileptic drug in development for treatment of focal (partial-onset) seizures. Its potentially unique dual mechanism of action may include 1) enhancement of fast and slow inactivation of sodium channels and inhibition of the persistent component and 2) positive allosteric modulation of $GABA_A$-mediated ion channels. This study assessed dose-dependent effects of cenobamate on SWD in the GAERS model. **Methods:** Male GAERS animals received EEG electrode implants at 3 months old. After 1-week recovery and screening EEG, rats were randomized in a crossover design to 5, 10, 20 or 30 mg/kg cenobamate, vehicle (30% PEG300), or 150 or 200 mg/kg valproate via intraperitoneal injection with 3-day washouts. EEGs were performed on freely moving rats for 20 min pre-injection (baseline) and 90 min post-injection. Blinded experts analyzed EEGs to identify SWD. Time course of number and cumulative duration of SWD were analyzed by 2-way repeated measures ANOVA, then Bonferroni-paired comparisons vs baseline, vehicle, and valproate. **Results:** Both valproate doses led to significant reductions in the number and cumulative duration of SWD vs vehicle, with peak effects in cumulative duration at 30-50 min, followed by a diminished effect to 90 min. The lowest cenobamate dose showed no significant effects on either parameter. Increasing cenobamate doses showed significant, dose-dependent reductions in the number and cumulative duration of SWD vs vehicle (**Figure**), with maximal effects at 30-50 min that were sustained to 90 min. **Conclusions:** Cenobamate induced a dose-dependent reduction in the number and cumulative duration of SWD in the GAERS model with a near maximal reduction at 30 mg/kg cenobamate. The effect of cenobamate was more prolonged than that of valproate. These data suggest that cenobamate may be effective in treating patients with absence seizures.

Figure. Cumulative Duration of Spike-and-Wave Discharges (SWD) with Cenobamate (YKP3089)



*P<0.05; ***P<0.001; ****P<0.0001 vs same time point for vehicle

Disclosures: **S.M. Melnick:** A. Employment/Salary (full or part-time):; SK Life Science, Inc. **H. Shin:** A. Employment/Salary (full or part-time):; SK Biopharmaceuticals, Co., Ltd. **C. Roucard:** 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.; CEO of CRO hired by SK Life Science, Inc. **K. Glenn:** A. Employment/Salary (full or part-time):; SK Life Science, Inc..

Poster

739. Epilepsy: Pharmacology

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 739.19/C5

Topic: B.10. Epilepsy

Support: NIH Grant 5R01NS024067
NIH Grant 5R37MH071739
FACES: Finding a Cure for Epilepsy and Seizures
FRQS: Fonds de recherche du Quebec - Sante

Title: Cannabidiol elevates the ratio of feedforward to feedback inhibition to dampen hippocampal activity propagation

Authors: *S. CHAMBERLAND[1], E. R. NEBET[1], E. C. ROSENBERG[1], O. DEVINSKY[2], R. W. TSIEN[1];
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Abstract: *Cannabis sativa* L. derivatives are emerging as therapeutics for some forms of epilepsy, with one formulation being FDA approved (Devinsky et al., 2017, 2018). Cannabidiol (CBD) administration to patients with certain treatment-resistant epilepsies significantly decreases the number and severity of seizures. However, the effects of CBD on neuronal activity and neuronal circuits remain obscure. We combined electrophysiology, optogenetics and single-cell anatomical tracing in acute hippocampal slices to dissect the effects of CBD at the neuronal and circuit levels. Our results show that CBD decreases the propagation of high-frequency activity from region CA3 to region CA1 region of the mouse hippocampus. This CBD action is abolished by GPR55 deletion or block of GABAergic transmission. The dampening of high-frequency activity was traced to disparate CBD effects on perisomatic-targeting parvalbumin+ (PV) and dendritic-targeting somatostatin+ (SST) interneurons (INs): enhanced feedforward recruitment of PV-INs but attenuated feedback recruitment of SST-INs. This countermodulation of PV- and SST-INs was shown to be due to alterations in the intrinsic excitability of PV- and SST-INs. Notably, the CBD-induced attenuation of high frequency spike throughput was mimicked by optogenetic drive of PV-INs, but not of SST-INs. Finally, CBD quieting of SST-INs further disinhibits PV-INs through a novel synaptic mechanism controlling the firing of PV-INs. Thus, in hippocampal CA1, increased recruitment of PV-INs suffices to dampen high-frequency activity propagation. Altogether, these mechanisms may contribute to the anti-seizure effects of CBD.

Disclosures: **S. Chamberland:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); GW Pharmaceuticals. **E.R. Nebet:** None. **E.C. Rosenberg:** None. **O. Devinsky:** None. **R.W. Tsien:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); GW Pharmaceuticals.

Poster

739. Epilepsy: Pharmacology

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 739.20/C6

Topic: B.10. Epilepsy

Support: European Union's Horizon 2020 Research and Innovation Programme under the Marie Sklodowska-Curie grant agreement no. 642881 (ECMED)
European Union's Seventh Framework Programme (FP7/2007-2013) under grant agreement no. 602102 (EPITARGET)
Dutch Epilepsy Foundation, project number 16-05

Title: The novel matrix metalloproteinase inhibitor IPR-179 has disease-modifying effects in rodent models of epilepsy

Authors: *D. W. M. BROEKAART[1], A. BERTRAN[3], S. JIA[4], C. M. DRION[5], A. KOROTKOV[1], O. SENKOV[4], A. BONGAARTS[1], J. D. MILLS[1], J. J. ANINK[1], J. SECO[3], J. C. BAAYEN[2], S. IDEMA[2], E. CHABROL[6], A. J. BECKER[7], W. WADMAN[5], T. TARRAGÓ[3], J. A. GORTER[5], E. ARONICA[1,8], R. PRADES[3], A. DITYATEV[4,9,10], E. A. VAN VLIET[1,5];
[1](Neuro)Pathology, [2]Neurosurg., Amsterdam Univ. Med. Centers, Amsterdam, Netherlands; [3]Iproteos S.L., Barcelona, Spain; [4]Mol. Neuroplasticity, German Ctr. for Neurodegenerative Dis. (DZNE), Magdeburg, Germany; [5]Swammerdam Inst. for Life Sciences, Ctr. for Neurosci., Univ. of Amsterdam, Amsterdam, Netherlands; [6]UCL, London, United Kingdom; [7]Neuropathology, Univ. of Bonn Med. Ctr., Bonn, Germany; [8]Stichting Epilepsie Instellingen Nederland (SEIN), Heemstede, Netherlands; [9]Med. Fac., Otto-von-Guericke Univ. Magdeburg, Magdeburg, Germany; [10]Ctr. for Behavioral Brain Sci. (CBBS) Magdeburg, Magdeburg, Germany

Abstract: Matrix metalloproteinases (MMPs) are synthetized by neurons and glia and delivered into the extracellular space, where they act as modulators of neuroplasticity, but also as neuroinflammatory agents. They are responsible for the degradation of cell adhesion molecules and extracellular matrix proteins through proteolytic cleavage. We have previously shown that in human as well as experimental temporal lobe epilepsy (TLE), the development of epilepsy (epileptogenesis) is associated with increased expression of MMPs. Therefore, they form a novel therapeutic drug target to treat or even prevent epilepsy. Unfortunately, currently available MMP inhibitors are not selective and cause side effects and toxicity, thus limiting their therapeutic use. The aim of the present study is to determine whether the newly-developed selective

MMP2/MMP9 inhibitor IPR-179 can modify epileptogenesis without side effects in two rodent models of TLE. The effects of IPR-179 (6 mg/day i.p.) were studied on the development of electrically-induced seizures using the rat rapid kindling model as well as on the development of spontaneous recurrent seizures using the intrahippocampal kainic acid mouse model. Furthermore, cognitive function was assessed using the novel object recognition task, spatial navigation using a labyrinth test and locomotion/anxiety using the open field test. In the rapid kindling model, rats treated with IPR-179 (n=8) showed reduced seizure severity over the course of kindling compared to vehicle-treated animals (n=8). In the intrahippocampal kainic acid mouse model, treatment with IPR-179 (n=10) resulted in reduced frequency and duration of spontaneous seizures as compared to vehicle-treated mice (n=8). Furthermore, cognitive decline was attenuated after IPR-179 treatment. Importantly, IPR-179 did not cause toxic effects or behavioral abnormalities in both animal models. These data show that IPR-179 has disease-modifying effects in two rodent models of epilepsy and attenuates seizure-induced cognitive decline. Since side effects were not observed in these experiments and increased expression of MMPs is also evident in resected brain tissue of patients with TLE, this novel MMP inhibitor deserves further investigation in clinical trials.

Disclosures: **D.W.M. Broekaart:** None. **A. Bertran:** A. Employment/Salary (full or part-time):; Iproteos S.L.. **S. Jia:** None. **C.M. Drion:** None. **A. Korotkov:** None. **O. Senkov:** None. **A. Bongaarts:** None. **J.D. Mills:** None. **J.J. Anink:** None. **J. Seco:** None. **J.C. Baayen:** None. **S. Idema:** None. **E. Chabrol:** None. **A.J. Becker:** None. **W. Wadman:** None. **T. Tarragó:** A. Employment/Salary (full or part-time):; Iproteos S.L.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Iproteos S.L., Patent WO2017/085034 A1, “Gelatinase inhibitors and use thereof”. **J.A. Gorter:** None. **E. Aronica:** None. **R. Prades:** A. Employment/Salary (full or part-time):; Iproteos S.L.. **A. Dityatev:** None. **E.A. van Vliet:** None.

Poster

739. Epilepsy: Pharmacology

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 739.21/C7

Topic: B.10. Epilepsy

Support: CONACYT 902327

Title: Effect of WIN 55,212-2 administered alone in a kainic acid-induced status epilepticus model

Authors: ***M. D. BURELO**[1], C. RIOS[1], A. DIAZ-RUIZ[2], V. BARON-FLORES[1];
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Abstract: Status epilepticus (SE) is a neurologic and medical emergency condition where continuous generalized seizures are manifested without full recovery of consciousness resulting in irreversible brain damage, significant disability and may be fatal. The early escalation to anesthetic agents for refractory generalized convulsive status epilepticus, to prevent neuronal injury and pharmaco-resistance associated with prolonged seizures is increasingly used, although morbidity and mortality are improved by this approach. Additional trials for new anti-epileptic drugs should be performed in order to achieve prompt recognition, early seizure termination, and simultaneous evaluation for any potentially treatable cause in the patient with SE. The aim of this study was to evaluate the effect of the synthetic cannabinoid WIN 55,212-2 (WIN) administered in a single dose during the SE induced by kainic acid to assess the control of seizures. For this, we used 12 male Wistar rats weighing 250-350g that were randomly allocated to either one of our two groups, group 1: Kainic acid (KA) + Vehicle (n = 6), Group 2: KA + WIN (3 mg/kg, ip, n = 6). Seven days before SE-induction, rats were surgically implanted with three stainless-steel electrodes into the motor cortex (MCx) of each animal. We performed the behavioral and electroencephalographic (EEG) recordings, using a video-EEG device. We ensured the exact moment of SE installation, by looking at the recordings, both behaviorally and electroencephalographically. Such signals were recorded at five different times: T1: baseline; T2: in SE; T3: 1 h; T4: 2 h and T5: 24 h after presenting SE. 10-secs epochs were selected avoiding signal artifacts and containing the epileptiform EEG activity. An automated analysis based on the fast-Fourier transformation method to estimate the total spectral power (μV^2) and the mean frequency (Hz) was applied to the EEG signals. The results showed no difference between the two groups on the intensity of the electrographic SE, but when assessing behavioral seizures during SE based on the Racine scale, we noticed WIN had a reducing effect. We are currently working on the Histology assay to complement this study to observe the severity of neuronal damage after SE.

Disclosures: M.D. Burelo: None. **C. Rios:** None. **A. Diaz-Ruiz:** None. **V. Baron-Flores:** None.

Poster

739. Epilepsy: Pharmacology

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 739.22/C8

Topic: B.10. Epilepsy

Support: NIH grant R01NS106688

Title: Regulation of indoleamine 2,3-dioxygenase 1 and 2 expression by microglia, relevance to acquired epilepsy

Authors: *Z. A. MACDOWELL KASWAN[1], M. HURTADO[2], A. J. STEELMAN[2], G. G. FREUND[3], R. H. MCCUSKER[2];
[1]Neurosci. Program, [2]Dept. of Animal Sci., [3]Dept. of Pathology, Univ. of Illinois At Urbana-Champaign, Urbana, IL

Abstract: Indoleamine 2,3-dioxygenases (Ido1 and Ido2) are the first and rate-limiting enzymes for the conversion of tryptophan to kynurenine (Kyn). Kyn production, following Ido1/2 upregulation in response to inflammatory signals, promotes immunosuppression. Additionally, microglia convert Kyn into the seizure-inducing metabolite quinolinic acid. Thus, Kyn production via Ido1/2 is postulated to play a role during neuroinflammation, ictogenesis and acquired epilepsy. Intracerebral injection of C57BL/6 mice with Theiler's murine encephalomyelitis virus (TMEV) is used as a preclinical model of ictogenesis and acquired epilepsy. Infected mice have increased Ido1 and Ido2 expression by microglia and IFNγ expression within the hippocampus. Our preliminary data show that TMEV-infected Ido1 knockout mice have increased seizure incidence compared to C57BL/6 mice, while Ido2 knockout mice have reduced seizure incidence, clearly implicating opposing roles for the Ido's in ictogenesis. While it is not known how TMEV induces Ido1/2 expression *in vivo*, TMEV ssRNA and dsRNA are capable of activating toll-like receptor (TLR7) and pattern recognition receptors MDA5/RIG-1, respectively. To assess the mechanism by which TMEV induces Ido1/2, we treated microglial cells with TLR7 agonists (resiquimod and gardiquimod), MDA5/RIG-1 agonists (poly(I:C) HMW/LyoVec and poly(I:C) LMW/LyoVec) and the pro-inflammatory cytokine interferon (IFNγ). We also tested the effects of the 2-propanolol analogue VIS351 (which increases Ido-dependent tolerogenic activity) and cannabidiol (CBD, an anti-epileptic agent). Our results show that the viral mimetics do not directly enhance expression of either Ido1 or Ido2, but IFNγ strongly enhances Ido1 expression. These data indicate that the changes in Ido1 expression my microglia *in vivo* are likely indirectly mediated by IFNγ. In contrast, the tolerogenic compound VIS351 increases Ido2 expression. VIS351 also increases microglial expression of the cytokines interleukin (IL) 6 and tumor necrosis factor (TNFα). CBD did not change Ido1/2 expression, but induced expression of another enzyme capable of converting tryptophan to kynurenine, tryptophan 2,3-dioxygenase (Tdo2). CBD also induced cytokine expression (IFNγ, IL-10, IL-1β and TNFα). Taken together, these data suggest that Ido1 and Ido2 are induced in microglia, but by distinct mechanisms. Their opposing roles during acquired epilepsy strongly suggests that it is possible to attenuate seizures by independently regulating Ido1 and Ido2.

Disclosures: Z.A. Macdowell Kaswan: None. **M. Hurtado:** None. **A.J. Steelman:** None. **G.G. Freund:** None. **R.H. McCusker:** None.

Poster

739. Epilepsy: Pharmacology

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 739.23/C9

Topic: B.10. Epilepsy

Support: NIH R01NS106688

Title: Regulation of indoleamine 2,3-dioxygenase expression by dendritic cells, relevance to viral-induced seizures

Authors: M. HURTADO[1], Z. A. MACDOWELL KASWAN[2], A. J. STEELMAN[1], G. G. FREUND[3], *R. H. MCCUSKER[1];
[1]Animal Sci., [2]Neurosci., [3]Dept. of Pathology, Univ. of Illinois at Urbana-Champaign, Urbana, IL

Abstract: Epilepsy is one of the most prevalent neurological disorders and affects about 3 million people in the United States. Approximately 50% of cases are a result of acquired epilepsy, which can be caused by a number of risk factors, including viral encephalitis and the ensuing persistent neuroinflammation. Neuroinflammation has been implicated to play a role in neurodegeneration and ictogenesis via the induction of indoleamine 2,3-dioxygenases (Ido1 and Ido2); enzymes that initiate tryptophan metabolism to kynurenine (Kyn) and Kyn metabolites of which several are ictogenic. Previous studies have demonstrated that mice infected intracerebrally with Theiler's murine encephalomyelitis virus (TMEV) have increased Ido1 and Ido2 associated with seizure incidence. We have demonstrated that Ido1 knockout mice have a higher seizure incidence compared to C57BL/6 mice, whereas Ido2 KO mice have diminished seizure incidence, indicating an opposing role for the two enzymes. Thus, Ido's involvement in ictogenesis requires further examination. Our exciting new 10x single-cell sequencing data identified dendritic cells within the TMEV-infected mouse hippocampus. These infiltrating immune cells were the major source of downstream enzymes (Kmo, Kynu and Haao) that generate ictogenic Kyn metabolites. Dendritic cell activation is implicated in seizure susceptibility as they modulate the immune response in an Ido1/2 dependent manner. Thus, we examined how treatment with immune-inducing agents affected Ido1/2 expression by dendritic cells. TMEV ssRNA and dsRNA induce inflammation by their interaction with toll-like receptor (TLR7) and pattern recognition receptors (MDA-5/RIG-1), respectively. Thus, we treated bone-marrow derived dendritic cells with interferon (IFNγ) and agents that act as viral mimetics (MDA-5/RIG-1 agonists poly(I:C) HMW/LyoVec and poly(I:C) LMW/LyoVec; TLR7 agonists resiquimod (R848) and gardiquimod (Gard)). We also investigated a 2-propanolol analogue, VIS351 with Ido-dependent tolerogenic activity. IFNγ increased Ido1 expression, an effect that was diminished by VIS351. In contrast, Ido2 expression was increased by R848 and Gard in

addition to IFNγ, but also decreased by VIS351. MDA-5/RIG-1 agonists did not alter Ido1 or Ido2 expression. Thus, Ido1 and Ido2 expression are differentially regulated by the viral mimetics. Based on differential effects of Ido1 KO and Ido2 KO on ictogenesis, it should be possible to modulate seizures by differentially modulating Ido1 and Ido2 expression.

Disclosures: R.H. McCusker: None. **M. Hurtado:** None. **Z.A. MacDowell Kaswan:** None. **A.J. Steelman:** None. **G.G. Freund:** None.

Poster

739. Epilepsy: Pharmacology

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 739.24/C10

Topic: B.10. Epilepsy

Support: ITF Grant MRP/101/17X
RGC GRF Grant 11102417M
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Title: Application of CCKb receptor antagonist on the treatment of kainic acid-induced epileptic mice

Authors: *A. TAN[1], J. HE[2];
[1]City Univ. of Hong Kong, Hong Kong, Hong Kong; [2]City Univ. of Hong Kong, Hong Kong, China

Abstract: Epilepsy is a group of long-term neurological disorders characterized by seizures and it causes unconscious changes in body movement, body function and sensation awareness. Epileptic seizure affects over 50 million people worldwide and it is difficult to cure. The excitation/inhibition imbalance of neuronal network will lead to the generation of epilepsy. Most seizures involve neocortex and hippocampus, which are associated with neuronal plasticity. The entorhinal cortex is part of the medial temporal lobe or hippocampal memory system and constitutes the major gateway between the hippocampal formation and neocortex. Cholecystokinin (CCK) from the entorhinal cortex enables neural plasticity in the neocortex. In the present study, we investigated the relationship between neuroplasticity and epilepsy. Our previous studies showed that long-term potentiation (LTP) was blocked with the infusion of CCKb antagonist *in vitro*. In our experiment, we explored the treatment strategy for the kainic acid-induced epileptic mice. C57BL/6 mice with kainic acid application developed daily seizures

at a frequency of 1-8 times and at the stage of 3-5. We have adopted a new scale for seizure measurement. We calculated the seizures in twelve hours every day and evaluated the severity of seizures via the accumulative scores. The seizure scale was reduced after the one-time intraperitoneal injection of CCKb antagonist. Our results imply that the application of kainic acid in the hippocampus temporally activates the temporal lobe, possibly facilitating CCK release in the brain. With the injection of CCKb antagonist, further enhancement of the excitatory circuitry can be blocked.

Disclosures: **A. Tan:** None. **J. He:** None.

Poster

739. Epilepsy: Pharmacology

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 739.25/C11

Topic: B.10. Epilepsy

Support: FWO grant 1S84218N
Scientific Fund Willy Gepts
Queen Elizabeth Medical Foundation (ING prize)
Strategic research program of the VUB (SRP49)

Title: Characterization of the effects of a ghrelin receptor agonist on cell viability in excitotoxic conditions

Authors: *A. BUCKINX, A. DE SMET, D. DE BUNDEL, R. KOOIJMAN, I. SMOLDERS; Vrije Univ. Brussel, Brussels, Belgium

Abstract: Temporal lobe epilepsy is the most common form of pharmacoresistant epilepsy, a disease often featured by neuroinflammation, excitoxicity and neuronal loss in the hippocampus. Ghrelin receptor agonists, such as JMV-1843, have been shown to exert anticonvulsant, anti-inflammatory and neuroprotective effects, rendering these compounds highly interesting drug candidates for new therapeutic strategies for epilepsy. However, the molecular mechanisms-of-action of these agonists remain unexplored. Therefore, we aimed to study the effect of JMV-1843 on cell death, inflammation and autophagy in hippocampal cell cultures treated with excitotoxic concentrations of the neurotransmitter glutamate.
Experiments were conducted using the mHippoE14 cell line, consisting of hippocampal neurons, astrocytes and microglia, the SH-SY5Y neuronal cell line, the 1321N1 astrocytic cell line, and the BV2 microglial cell line. The specific culture medium for each cell type was refreshed every 2-4 days, and cells were kept under standard conditions (37°C, 95% O_2/ 5% CO_2). For evaluating cell viability, cells were seeded at a density of 100,000 cells/ 0.5 mL culture medium in a 24-well plate. The next day, cells were exposed to glutamate in the presence or absence of JMV-1843

and harvested 24 hours later for cell counting with trypan blue.
First, we established that the optimal glutamate concentration required to induce approximately 40% cell death in the mHippoE14 cell line after 24 hours was 20 mM, corresponding to what has been described in literature. Preliminary experiments (n=4) reveal that JMV-1843 exerts a trend towards a neuroprotective effect at the highest dose tested (1 μM). However, JMV-1843 did not completely abolish neuronal cell death induced by glutamate administration. The same dose of JMV-1843 significantly increased cell viability of astrocytes.
JMV-1843 was demonstrated to be anticonvulsant, however, how it exerts such effects at the molecular level remains up to now unknown. This study already suggests that JMV-1843 can enhance astrocyte survival in the central nervous system and it remains to be established if and how other processes such as autophagy and inflammation take part in modulation of cell survival in different types of neurons and glial cells. Although caution is required when extrapolating *in vitro* results to *in vivo* observations, these results may potentially aid in understanding the possible molecular mechanism-of-action behind JMV-1843's anticonvulsant effects.

Disclosures: A. Buckinx: None. **A. De Smet:** None. **D. De Bundel:** None. **R. Kooijman:** None. **I. Smolders:** None.

Poster

739. Epilepsy: Pharmacology

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 739.26/C12

Topic: B.10. Epilepsy

Support: CURE Epilepsy Foundation

Title: LPS induced peripheral inflammation prevents SUDEP in DBA/1 mice

Authors: *Y. P. ADHIKARI[1], X. JIN[2];
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Abstract: Sudden Unexpected Death in Epilepsy patients (SUDEP) is the sudden and unanticipated death of a relatively healthy person with epilepsy where no structural or toxicological cause of death can be identified after post mortem analysis. SUDEP is the cause of premature death of 50% patients with chronic refractory epilepsy. Respiratory failure during seizures is regarded as an important mechanism of SUDEP. 5-HT neurotransmission is important to prevent respiratory failure during seizure. Previous studies showed that abnormal 5-HT neurotransmission is involved in the pathogenesis of SUDEP and that enhancing 5-HT neurotransmission in the brain-stem suppresses SUDEP. Although peripheral inflammation is known to enhance 5-HT neuron activation and, 5-HT synthesis and release, the effect of

peripheral inflammation on SUDEP susceptibility has not been investigated so far. We investigated the effect of LPS-induced peripheral inflammation on SUDEP susceptibility in DBA/1 mice. The DBA/1 mice exhibit tonic seizures in response to loud sound stimulation which lead to seizure induced respiratory arrest (S-IRA) and result in SUDEP. We found that intraperitoneal administration of LPS significantly reduced the incidence of S-IRA in DBA/1 mice in response to audiogenic stimulation. This protective effect peaked at 8-12 hours after LPS injection and could be attenuated by blocking TLR4 or RAGE receptors prior to LPS administration or by administration of 5-HT3 receptor antagonist -Ondansetron. The results suggest that LPS induced peripheral inflammation is effective in preventing SUDEP through the activation of TLR4/ RAGE signaling and enhancing 5-HT neurotransmission.

Disclosures: Y.P. Adhikari: None. **X. Jin:** None.

Poster

739. Epilepsy: Pharmacology

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 739.27/C13

Topic: B.10. Epilepsy

Support: Posttraumatic Epilepsy Award, CURE Epilepsy Foundation
Indiana Spinal Cord and Brain Injury Research Fund from the Indiana State Department of Health

Title: Blocking receptor for advanced glycation end-products (RAGE) or toll like receptor 4 (TLR4) attenuates posttraumatic epileptogenesis in mice

Authors: *X. PING[1], M. S. RIPSCH[1], F. A. WHITE[2], X. JIN[3];
[1]Stark Neurosci. Res. Inst., Indianapolis, IN; [2]Anesthesia, Indiana Univ. Sch. Med., Indianapolis, IN; [3]IUPUI Stark Neurosci. Res. Inst., Indianapolis, IN

Abstract: Development of posttraumatic epilepsy occurs in a complicated neurobiological environment including on-going secondary injury caused by traumatic brain injury (TBI). Neuroinflammation is an important factor that contributes to posttraumatic epileptogenesis. However, the mechanism remains poorly understood. High mobility group box 1(HMGB1) signaling pathways have been implicated in inflammatory responses and epileptogenesis. In this study, we tested the hypothesis that blocking RAGE or TLR4 signaling pathways may prevent posttraumatic epileptogenesis in a mouse model of partial cortical isolation (undercut). Adult mice that underwent undercut surgery received daily injections of saline, RAGE antibody, or a TLR4 inhibitor TAK-242 for 1 week and were tested for seizure susceptibility in 2 weeks after injury. Undercut animals treated with RAGE antibody or TAK-242 showed significantly higher seizure threshold than saline-treated undercut mice in a pentylenetetrazol (PTZ) test.

Consistently, undercut injury in RAGE knockout mice didn't cause a reduction in seizure threshold in PTZ test, suggesting a preventative effect on posttraumatic epileptogenesis. We further used continuous video and wireless electroencephalographic (EEG) recordings to monitor spontaneous seizure activity between 2-6 weeks after undercut injury and found a significant decrease in frequency of spontaneous seizures in RAGE antibody or TAK-242 treated group (0.46 ± 0.30, 0.18 ± 0.23, and 0.09 ± 0.15 seizures/day for saline, RAGE antibody, and TAK-242 groups respectively. $p < 0.05$ in RAGE antibody and TAK-242 groups vs saline group). Histological analyses of lesioned cortical tissues showed higher neuronal densities in Nissl staining and higher densities of GAD67-immunoreactive interneurons in RAGE antibody or TAK-242 treated groups than the control undercut group. Immunostaining to GFAP and Iba-1 revealed lower densities of astrocytes and microglia in cortex of the treatment groups, suggesting reduced glia activation. These results suggest that blocking RAGE or TLR4 signaling pathways is a promising strategy for preventing posttraumatic epilepsy in TBI patients.

Disclosures: X. Ping: None. **M.S. Ripsch:** None. **F.A. White:** None. **X. Jin:** None.

Poster

739. Epilepsy: Pharmacology

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 739.28/C14

Topic: B.10. Epilepsy

Title: Neuroprotective profile assessment of lacosamide in the kindling model induced by pentylenotetrazole in mice

Authors: *P. PEREIRA[1], P. PFLÜGER[1], F. SANTOS[1], D. AGUIRRE[1], D. MOURA[2], J. PICADA[3], G. LEIPNITZ[1], L. LAZZAROTTO[1];
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Abstract: Lacosamide (LCM) is an anticonvulsant drug approved as adjuvant therapy in the treatment of partial seizures with or without secondary generalization in patients 17 years of age or older. LCM acts by increasing the slow inactivation of voltage-dependent sodium channels, producing stabilization of the hyperexcitable neural membranes. The goal of this study was to evaluate the LCM effect in the pentylenotetrazole (PTZ)-induced kindling model, as well as, some biochemical parameters. Male mice CF-1 were divided into the following experimental groups: saline, saline-PTZ, diazepam-PTZ, LCM 20 mg/kg-PTZ, LCM 30 mg/kg-PTZ and LCM 40 mg/kg-PTZ. Diazepam (2mg/kg) was used as a positive control. On alternate days, animals received LCM or controls and after 30 minutes they received PTZ (50 mg/kg), totaling 11 days of treatment. After PTZ administration, animals were observed for 30 minutes regarding latency time for the first seizure (LFS) lasting more than 3 seconds and occurrence of clonic seizures.

After the last day of treatment, animals were euthanized and hippocampus, bone marrow and peripheral blood samples were collected for biochemical analyzes. ROS production, SOD and CAT activity, complexes I-III, II and II-III activity, genotoxicity (Alkaline Comet Assay), mutagenicity (Micronucleus test) and COX-2 and Bcl-2 expression (Western blotting) were performed. The seizures occurrence was analyzed by Fisher Exact test. LFS by Generalized Estimating Equations. Biochemical data were analyzed by one-way ANOVA ($P \leq 0.05$). This project was approved by the UFRGS Committee on Ethics in the Use of Animals (CEUA; N. 34134). The results demonstrated that LCM did not decrease the percentage of seizures and it did not increase the latency time for the first seizure in the kindling model. However, LCM 30 and 40 mg/kg reestablished the mitochondrial complex I-III activity. ROS production was reduced by the 3 doses of LCM and SOD also had its activity reduced. LCM did not induce chromosomal mutations and doses of 20 and 30 mg/kg prevented the genotoxic damage caused by PTZ in the hippocampus. COX-2 levels decreased in animals treated with LCM 30 and 40mg/kg and Bcl-2 levels increased with LCM 40mg/kg. Although LCM did not reduce the convulsive behavior in the kindling model, our findings provide evidence that LCM has an important neuroprotective profile on biochemical parameters associated with epilepsy.

Disclosures: **P. Pereira:** None. **P. Pflüger:** None. **F. Santos:** None. **D. Aguirre:** None. **D. Moura:** None. **J. Picada:** None. **G. Leipnitz:** None. **L. Lazzarotto:** None.

Poster

739. Epilepsy: Pharmacology

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 739.29/C15

Topic: B.10. Epilepsy

Support: SIP Grant 20195797

Title: Chiral hydroxyamides as anticonvulsants

Authors: *S. E. MEZA TOLEDO, J. ESQUIVEL-VARGAS, J. A. MARTÍNEZ-RODRÍGUEZ, J. PERALTA-CRUZ, M. GONZÁLEZ-FLORES;
Biochem., Inst. Politécnico Nacional, Esc.Nac.Cien.Biol, Mexico City, Mexico

Abstract: Compound DL-3-hydroxy-3-ethyl-3-phenyl propionamide (DL-HEPP) has a broad profile of anticonvulsant activity. However, the mechanism underlying the anticonvulsant action of DL-HEPP is not known. In order to study if GABAergic mechanisms are involved in the anticonvulsant action of HEPP, we resolved its enantiomers and measured their protection against convulsant drugs acting at GABAergic system such as bicuculline, a competitive $GABA_A$ receptor antagonist, and thiosemicarbazide, a glutamate decarboxylase inhibitor. The racemate was resolved from the (+) and (-) 1-phenyelthylamine salts of the acids. The optically

active acids were then esterified and reacted with ammonia to give (+) HEPP and (-) HEPP. Optical purity of amides was greater than 99% enantiomeric excess determined by chiral high performance liquid chromatography. Pharmacologically, (+) HEPP, (-) HEPP and DL-HEPP have a similar significant anticonvulsant activity against bicuculline and thiosemicarbazide-induced seizures in mice, but the time course of the anticonvulsant activity was different. These results suggest that (+) HEPP and (-) HEPP may be acting through GABAergic mechanisms. The anticonvulsant activity of DL-HEPP and its enantiomers was greater than that of sodium valproate, an antiepileptic used in clinic. This study shows that (+) HEPP and (-) HEPP represent a new class of anticonvulsant compounds worthy of further development for potential antiepileptic therapy.

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Poster

740. Central and Peripheral Myelinating Cells II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 740.01/C16

Topic: B.11. Glial Mechanisms

Title: Altered human oligodendrocyte heterogeneity in multiple sclerosis

Authors: *S. JAEKEL[1], E. AGIRRE[2], A. MENDANHA FALCAO[2], D. VAN BRUGGEN[2], K. WAI LEE[2], I. KNUESEL[3], D. MALHOTRA[4], C. FFRENCH-CONSTANT[5], A. WILLIAMS[5], G. CASTELO-BRANCO[2];
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Abstract: Oligodendrocyte pathology is increasingly implicated in neurodegenerative diseases as oligodendrocytes both myelinate and provide metabolic support to axons. In multiple sclerosis (MS), demyelination in the central nervous system thus leads to neurodegeneration, but the severity of MS between patients is very variable. Disability does not correlate well with the extent of demyelination, which suggests that other factors contribute to this variability. One such factor may be oligodendrocyte heterogeneity. Not all oligodendrocytes are the same—those from the mouse spinal cord inherently produce longer myelin sheaths than those from the cortex, and single-cell analysis of the mouse central nervous system identified further differences. However, the extent of human oligodendrocyte heterogeneity and its possible contribution to MS pathology remain unknown. Here we performed single-nucleus RNA sequencing from white matter areas of post-mortem human brain from patients with MS and from unaffected controls. We identified

subclusters of oligodendroglia in control human white matter, some with similarities to mouse, and defined new markers for these cell states. Notably, some subclusters were underrepresented in MS tissue, whereas others were more prevalent. These differences in mature oligodendrocyte subclusters may indicate different functional states of oligodendrocytes in MS lesions. We found similar changes in normal-appearing white matter, showing that MS is a more diffuse disease than its focal demyelination suggests. Our findings of an altered oligodendroglial heterogeneity in MS may be important for understanding disease progression and developing therapeutic approaches.

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Poster

740. Central and Peripheral Myelinating Cells II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 740.02/C17

Topic: B.11. Glial Mechanisms

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Title: Oligodendrocytes support neuronal glutamatergic transmission via expression of glutamine synthetase

Authors: *W. XIN[1,2,3], Y. A. MIRONOVA[2], H. SHEN[3], R. MARINO[3], A. WAISMAN[4], W. H. LAMERS[5], D. E. BERGLES[2], A. BONCI[3,2];
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Abstract: Glutamate has been implicated in a wide range of brain pathologies and is thought to be metabolized via the astrocyte-specific enzyme glutamine synthetase (GS). We show here that oligodendrocytes, the myelinating glia of the central nervous system, also express high levels of GS in caudal regions like midbrain and spinal cord. Selective removal of oligodendrocyte GS in mice led to reduced brain glutamate and glutamine levels and impaired glutamatergic synaptic transmission without disrupting myelination. Furthermore, animals lacking oligodendrocyte GS displayed deficits in cocaine-induced locomotor sensitization, a behavior that is dependent on

glutamatergic signaling in the midbrain. Thus, oligodendrocytes support glutamatergic transmission through the actions of GS and may represent a therapeutic target for pathological conditions related to brain glutamate dysregulation.

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Poster

740. Central and Peripheral Myelinating Cells II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 740.03/C18

Topic: A.08. Development of Motor/ Sensory/ and Limbic Systems

Support: National Multiple Sclerosis Society Grant RG3367
NIH Grant R01NS052741
Mayo Clinic Center for Biomedical Discovery

Title: Mass spectral analysis of developmental changes in the lipid composition of myelin membranes

Authors: *E. M. TRIPLET[1], H. YOON[2], I. LANZA[3], I. A. SCARISBRICK[2];
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Abstract: Lipids are key structural and signaling molecules in the CNS. Lipid synthesis is required for neurite outgrowth, synaptogenesis, the formation of myelin and the establishment of salutatory conduction. Lipid composition across neurons and glia is very different and underpins their functional properties. For example, myelin membranes are enriched in cholesterol and glycerophospholipids while neurons rely heavily on sphingolipids and gangliosides for modulation of membrane protein activity and signaling. Derivatives of cholesterol—steroids—and long chain fatty acids—endocannabinoids and prostaglandins—also act as signaling and regulatory factors.
Changes in lipid metabolism contribute to a variety of CNS disorders, including Neiman-Pick and Huntington Disease, and are also associated with Alzheimers, as in the association between hypercholesterolemia and the lipid carrier protein ApoE. The recent development of highly sensitive Liquid Chromatography with tandem mass spectrometry (LC-MS-MS) assays for lipids permits us to quantify a wide variety of CNS lipids for the first time. Our long-term goal is to utilize these methods to generate a better understanding of changes in lipids across the neuron and myelin compartments developmentally and in response to injury and repair. These assays may be particularly useful to screen for factors that can improve regeneration of neuron and myelin membranes. In the current study, we compared the abundance of cholesterol, free fatty

acids, galactosylceramides, sphingolipids and sphingomyelins in the spinal cord of male mice at postnatal day 21 (P21), the peak of myelination, or in adulthood (P90). Furthermore, we made direct comparisons between the abundance of lipids extracted from the spinal cord as a whole relative to isolated myelin. Findings indicate a general enrichment in myelin-associated lipids—cholesterols, galactosylceramides, and sphingomyelin—occurs in the spinal cord through development, with concurrent decreases in free fatty acids. In contrast, the relative abundance of the predominantly neuronal sphingolipids is diminished over the same period of CNS maturation.

Disclosures: E.M. Triplet: None. **H. Yoon:** None. **I. Lanza:** None. **I.A. Scarisbrick:** None.

Poster

740. Central and Peripheral Myelinating Cells II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 740.04/C19

Topic: B.11. Glial Mechanisms

Support: CIHR

Title: Schwann cells transport nucleic acid-containing cargo into axons via myelin injection bodies

Authors: *W. TEO[1], P. K. STYS[2];
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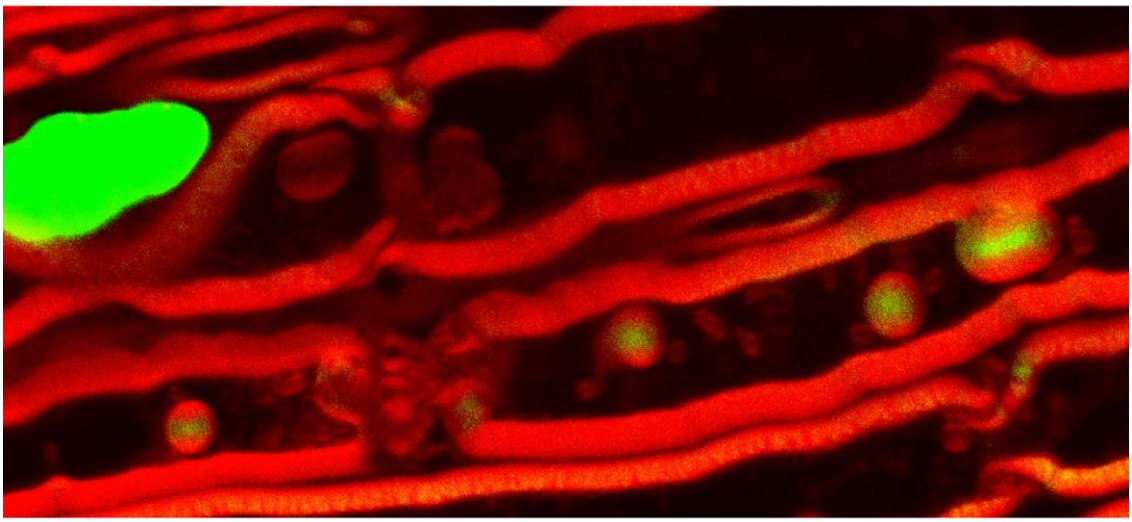
Abstract: Myelination facilitates fast action potential conduction. In addition, myelinating glia are thought toprovide trophic and metabolic support to their ensheathed axons. Thus, loss of myelination not onlyadversely affects conduction but also the survival of axons, leading to axonal degeneration andneurological disability. How glial cells support axons is only beginning to be understood. Recently weproposed a chemical communication between electrically active axons and their myelin in the CNSvia a glutamatergic "axo-myelinic synapse" (Micu et al., 2016). Here we studied myelinated spinalroot axons maintained ex vivo at 35 °C from young adult mice. Exposure to sucrose to promotefusion of vesicles and release of transmitter into the periaxonal space resulted in invagination of NileRed-labeled myelin into the axon (Figure) as discrete "myelin injection bodies (MIBs)" beginningwithin 20 min of treatment. Raising axonal Ca by release of intracellular stores with caffeine, oractivation of L-type voltage gated Ca channels with Bay K8644 (both of which we hypothesize willpromote transmitter release from axon into the periaxonal space) produced a similar effect. Theinterior of most (but not all) MIBs stained positive with the membrane-permeable nucleic acid dyeSYTO40. The precise nature of this cargo is currently under investigation.CONCLUSION:

we proposed that an important mechanism by which myelinating glia can supporttheir fibers is by deliberately orchestrated deformation of the myelin sheath and injection of MIBs intothe axon. The nature of the injected cargo is not yet known, but may include nucleic acid-containingorganelles.



Disclosures: **W. Teo:** None. **P.K. Stys:** None.

Poster

740. Central and Peripheral Myelinating Cells II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 740.05/C20

Topic: B.11. Glial Mechanisms

Title: To explore the characteristics of glial cells in pig models

Authors: ***N. YU**[1], W. ZUO[2], S. YANG[1];
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Abstract: Objective: To explore the characteristics of glial cells in pig models.
Materials and methods: Compare the different kinds of glial cells in the central and peripheral nervous systems of the large animal model——pig model(BAMA Mini pig)and small animal model——mouse model, guinea pig model and rat model.
Results:(1)Morphology: In pig model nervous system, except that the myelin ensheathing of

optic nerve or olfactory nerve is central myelin sheath, the other ten pairs of cranial nerves all have the transition area of central myelin sheath and peripheral myelin sheath, which can be called transition zone. The two ends of the transition zone are different from the complete structure of the Nodes of Ranvier, and its morphological and electrophysiological characteristics are similar to the "heminode" of the cochlear nerve through the habenular hole. In addition, the satellite cells also express the specific marker of neurons——2-phospho-D-glycerate hydrolase(NSE). The associations between Satellite cells and neurons in pig models are more similar to humans than other small animal models.(2)Nerve injury test: after short-term noise exposure of auditory nerve, it was found that no obvious damage was found in the neurons of spiral ganglion, and the satellite cells which were around the neurons were damaged and then proliferated and repaired. After compression of the trigeminal nerve, it was found that the pathological changes were mainly located in the transitional zone, but no significant abnormality was found in the rest areas.
Conclusions:(1)Except optic nerve and olfactory nerve, the other ten pairs of cranial nerve had transitional zones. The transitional zone is the transition between central myelin sheath and peripheral myelin sheath. Its structure is unstable and it is easy to appear pathological changes when it is affected by the outside world. Therefore, the neurilemmoma and neuralgia of the cranial nerve may all originate here.(2)The satellite cells which are around the ganglion neurons in the peripheral nervous system, some of which are similar to glial cells and some of which are similar to neuron cells. Therefore, these cells may not be only classified as glial cells or neuron cells. The satellite cells may differentiate earlier than glial cells in the process of stem cell differentiation. It may not only secrete neurotrophic factors, but also participate in the formation and differentiation of neurons.(3)Large animal model——pig model is more similar to human, and it is a more suitable research object than small animal model, like mouse model, guinea pig model and rat model.

Disclosures: **N. Yu:** None. **W. Zuo:** None. **S. Yang:** None.

Poster

740. Central and Peripheral Myelinating Cells II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 740.06/C21

Topic: B.11. Glial Mechanisms

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Karolinska Institutet

Wellcome Trust 100269/Z/12/Z

Title: Specific oligodendrocyte populations have differential spatial distribution and susceptibility to injury

Authors: *E. M. FLORIDDIA[1], S. ZHANG[3], D. VAN BRUGGEN[1], J. P. GONCALVES DOS SANTOS[1], M. ALTINKOK[1], E. LLORENS-BOBADILLA[2], J. FRISÉN[2], G. CASTELO-BRANCO[1];
[2]Dept. of Cell. and Mol. Biol., [1]Karolinska Institutet, Stockholm, Sweden; [3]Whitehead Inst. for Biomed. Res., Cambridge, MA

Abstract: Oligodendrocytes (OLs) are the myelinating cells of the central nervous system (CNS). While the OL is thought to be homogenous, we recently found twelve transcriptionally distinct OL states/subtypes in the juvenile and adult mouse CNS. The functional consequences of the OL transcriptional heterogeneity are unknown. Here, we unveil spatial preference and differential susceptibility to injury of distinct mature OLs (MOLs). Using RNAscope in situ hybridization (ISH), we observed that a specific subtype of MOLs, MOL2, is preferentially distributed in the white matter of the spinal cord. In contrast, MOL5/6 were found to be most abundant in the corpus callosum in the brain and in the dorsal horn of the spinal cord. Furthermore, we observed that these subtypes also segregate in the dorsal funiculi of the spinal cord, with MOL2 and MOL5/6 preferentially distributed at the level of the dorsal columns (sensory ascending tracts) and corticospinal tract (motor descending tracts), respectively. These spatial preferences could reflect diverse developmental origins of these MOL subtypes. However, fate mapping and single-cell RNASeq analysis indicated that the developmental origin of the OL progenitors does not influence their specification into distinct MOL subtypes. In the context of disease, we observed a significant loss of MOL2 but not MOL5/6 following spinal cord injury, suggesting that MOL2 are more susceptible to traumatic injury than MOL5/6. Altogether, our data suggest that the transcriptional heterogeneity of the OL lineage reflects functional MOL subtypes, most likely dictated by their final location and environment rather than their developmental origin.

Disclosures: E.M. Floriddia: None. **S. Zhang:** None. **D. van Bruggen:** None. **J.P. Goncalves dos Santos:** None. **M. Altinkok:** None. **E. Llorens-Bobadilla:** None. **J. Frisén:** None. **G. Castelo-Branco:** None.

Poster

740. Central and Peripheral Myelinating Cells II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 740.07/C22

Topic: B.11. Glial Mechanisms

Support: VA Merit Award 1I01RX012345

Title: Satellite glial cells in sensory ganglia express functional TRPA1 that is sensitized in neuropathic and inflammatory pain

Authors: *S. SHIN[1], H. YU[1], Q. HOGAN[1], B. PAN[1], I.-Z. BRANDON[1], F. WANG[3], Y. CAI[4], C. L. STUCKY[2];
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Abstract: Transient Receptor Potential Ankyrin 1 (TRPA1) is well documented as an important molecule in pain hypersensitivity following inflammation and nerve injury and in many other cellular biological processes. Here, we show that TRPA1 is expressed not only by sensory neurons of the dorsal root ganglion (DRG) but also in their adjacent satellite glial cells (SGCs), as well as non-myelinating Schwann cells. TRPA1 immunoreactivity is also detected in various cutaneous structures of sensory neuronal terminals, including small and large caliber cutaneous sensory fibers and endings. The SGC-expressed TRPA1 is functional. Like DRG neurons, dissociated SGCs exhibit a robust response to the TRPA1-selective agonist allyl isothiocyanate (AITC) by an increase of intracellular Ca2+ concentration ([Ca2+]i). These responses are abolished by the TRPA1 antagonist HC-030031 and are absent in SGCs and neurons from global *Trpa1* null mice. SGCs and neurons harvested from DRGs proximal to painful tissue inflammation induced by plantar injection of complete Freund's adjuvant show greater AITC-evoked elevation of [Ca2+]i and slower recovery compared to sham controls. Similar TRPA1 sensitization occurs in both SGCs and neurons during neuropathic pain induced by spared nerve ligation. Together, these results show that functional TRPA1 is expressed by sensory ganglia SGCs, TRPA1 function in SCGs is enhanced after both peripheral inflammation and nerve injury, and suggest that TRPA1 in SGCs may contribute to inflammatory and neuropathic pain.

Disclosures: S. Shin: None. **H. Yu:** None. **Q. Hogan:** None. **B. Pan:** None. **I. Brandon:** None.

Poster

740. Central and Peripheral Myelinating Cells II

Location: Hall A

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Program #/Poster #: 740.08/C23

Topic: B.11. Glial Mechanisms

Support: NIH Grant NS043474

Title: Targeting of Neurofascin to nodes of Ranvier is regulated by a paranodal switch

Authors: *Y. ZHANG[1], S. YUEN[1], E. PELES[2], J. L. SALZER[1];
[1]Neurosicence Inst., NYU Sch. of Med., New York, NY; [2]Deptartment of Mol. Cell Biol., Rehovot, Israel

Abstract: The paranodal junctions flank mature nodes of Ranvier and provide a barrier between ion channels at the nodes and juxtaparanodes. These junctions also promote node assembly and maintenance by mechanisms that are poorly understood. Here, we examine their role in targeting of NF186, a key adhesion molecule of PNS and CNS nodes. We previously showed NF186 is targeted via its ectodomain to forming PNS (hemi)nodes by diffusion trapping whereas it is later trafficked to mature nodes by a transport-dependent mechanism mediated by its cytoplasmic segment. To address the role of the paranodes in this trafficking switch, we compared targeting of NF186 ectodomain and cytoplasmic domain constructs in wild type vs. paranode defective, i.e. Caspr-null mice. Both pathways are affected in the paranodal mutants. In the PNS of Caspr-null mice, diffusion trapping mediated by the NF186 ectodomain aberrantly persists into adulthood whereas the cytoplasmic domain/transport-dependent trafficking is impaired. In contrast, targeting of NF186 to CNS nodes does not undergo a switch - it is predominantly targeted to both forming and mature CNS nodes via its cytoplasmic domain and requires intact paranodes. FRAP analysis indicates the paranodes provide a membrane diffusion barrier that normally precludes diffusion of NF186 to nodes. Linkage of paranodal proteins to the underlying cytoskeleton likely contributes to this diffusion barrier based on analysis of 4.1B and βII spectrin expression in Caspr-null mice. Together, these results implicate the paranodes as membrane diffusion barriers that regulate trafficking to nodes and highlight differences in the assembly of PNS and CNS nodes.

Disclosures: Y. Zhang: None. **S. Yuen:** None. **E. Peles:** None. **J.L. Salzer:** None.

Poster

740. Central and Peripheral Myelinating Cells II

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Program #/Poster #: 740.09/C24

Topic: B.11. Glial Mechanisms

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Wellcome studentship 102160/Z/13/Z
Paul G. Allen Frontiers Group Allen Distinguished Investigator Award 12076
Medical Research Council studentship
Gates Cambridge Trust scholarship
Biotechnology and Biological Sciences Research Council studentship

Title: Oligodendrocyte progenitor cell regional and temporal heterogeneity indicate diverse functional states

Authors: *Y. KAMEN, S. O. SPITZER, S. SITNIKOV, K. A. EVANS, D. KRONENBERG-VERSTEEG, H. PIVONKOVA, S. DIETMANN, O. DE FARIA, JR, S. AGATHOU, H. O. B. GAUTIER, R. T. KARADOTTIR;
Wellcome - MRC Cambridge Stem Cell Institute, Dept. of Vet. Med., Univ. of Cambridge, Cambridge, United Kingdom

Abstract: In the central nervous system, oligodendrocyte progenitor cells (OPCs) give rise to oligodendrocytes, which myelinate axons throughout life. Myelin is essential for rapid electrical conduction through axons and input synchronicity, and the importance of myelin is made clear in white matter disorders such as Multiple Sclerosis. Recent evidence also shows that the generation of new myelin is a mechanism underlying learning in adults. OPCs receive synaptic inputs from neurons, have voltage-gated ion channels, and neurotransmitter receptors, allowing them to sense neuronal activity, which is thought to regulate myelination and myelin regeneration. Functional expression of voltage-gated sodium channels (Na_V), voltage-gated potassium channels (K_V), AMPA/kainate receptors (AMPA/KAR), and NMDA receptors (NMDAR) is often described as a hallmark of OPCs. Using whole-cell patch-clamp in NG2-eYFP transgenic mice, we show that OPCs are first born without any voltage-gated ion channels or glutamate receptors, and gradually acquire them at different rates. In the second postnatal week, OPCs diverge between and within regions, with a greater proportion of OPCs responding to NMDA application in heavily myelinated regions, with larger current densities, while NMDAR disappear from unmyelinated regions first. Thus, unlike previously believed, OPCs are heterogeneous both temporally and between and within regions. In addition, by combining patch-clamp with flow cytometry and bulk RNAseq, we show that ion channel expression correlates with the proliferation or differentiation potential of OPCs, suggesting that this heterogeneity rather indicates different functional states. Finally, we find similar OPC states during remyelination following ethidium bromide-induced demyelinating lesions. A number of cues, such as cytokines, growth factors, or G protein-coupled receptors, are known to regulate ion channel expression, and may therefore regulate OPC state transitions both in healthy and lesioned tissue. Moreover, drugs acting on G protein-coupled receptors promote myelin repair in demyelinating lesion models. Thus, understanding both OPC functional states and state transitions may be fundamental to our understanding of myelination and myelin repair.

Disclosures: **Y. Kamen:** None. **S.O. Spitzer:** None. **S. Sitnikov:** None. **K.A. Evans:** None. **D. Kronenberg-Versteeg:** None. **H. Pivonkova:** None. **S. Dietmann:** None. **O. de Faria:** None. **S. Agathou:** None. **R.T. Karadottir:** None. **H.O.B. Gautier:** None.

Poster

740. Central and Peripheral Myelinating Cells II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 740.10/C25

Topic: B.11. Glial Mechanisms

Support: NIH T32 GM007183
NIH/NIHGMS R01-GM120322

Title: Structural basis for adhesion G protein-coupled receptor Gpr126 function

Authors: *K. LEON[1], R. L. CUNNINGHAM[3], J. A. RIBACK[2], E. FELDMAN[1], J. LI[1], M. ZHAO[1], T. R. SOSNICK[1], K. R. MONK[4], D. ARAC-OZKAN[1];
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Abstract: Many drugs target the extracellular regions (ECRs) of cell-surface receptors. The large and alternatively-spliced ECRs of adhesion G protein-coupled receptors (aGPCRs) have key functions in diverse biological processes including neurodevelopment, embryogenesis, and tumorigenesis. However, their structures and mechanisms of action remain unclear, hampering drug development. The aGPCR Gpr126/ADGRG6 regulates Schwann cell myelination, ear canal formation, and heart development; and *GPR126* mutations cause myelination defects in human. Here, we determined the structure of the complete Gpr126 ECR and revealed five domains including a previously-unknown proteolytic domain. Strikingly, the Gpr126 ECR adopts a closed conformation that is stabilized by an alternatively spliced linker and a conserved calcium-binding site. Alternative splicing regulates ECR conformation and receptor signaling, while mutagenesis of the newly-characterized calcium-binding site abolishes Gpr126 function *in vivo*. These results demonstrate that Gpr126 ECR utilizes a multi-faceted dynamic approach to regulate receptor function and provide novel insights into ECR-targeted drug design.

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Poster

740. Central and Peripheral Myelinating Cells II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 740.11/C26

Topic: B.11. Glial Mechanisms

Support: Swedish Research Council
ERC

Title: Dynamics of oligodendrocyte generation in multiple sclerosis

Authors: *M. YEUNG[1], M. DJELLOUL[1], E. STEINER[1], S. BERNARD[2], M. SALEHPOUR[3], G. POSSNERT[3], L. BRUNDIN[4], J. FRISÉN[1];
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Abstract: Myelin is formed by oligodendrocytes in the central nervous system and functions to maximize the efficiency and velocity of action potentials along neuronal axons. A hallmark of multiple sclerosis is the loss of oligodendrocytes and myelin, leading to conduction deficits, and resulting in severe neurological symptoms and disability. Myelin can be regenerated (remyelination), especially early in the disease process. In animal models of MS, myelin is regenerated by newly generated oligodendrocytes, and remaining mature oligodendrocytes do not seem to contribute to this process. Given the differences in the dynamics of oligodendrocyte generation and myelination between rodents and humans from previous studies, it is not clear how well experimental animal models reflect the situation in multiple sclerosis. To address this we assessed the dynamics of oligodendrocyte generation in patients with multiple sclerosis by analyzing the content of ^{14}C derived from nuclear bomb tests during the Cold War, in genomic DNA of oligodendrocytes. We found that the generation of new oligodendrocytes in normal appearing white matter was increased several-fold in a subset of patients with aggressive multiple sclerosis, revealing the ability to substantially increase the generation of oligodendrocytes that fails in most patients. Surprisingly, oligodendrocytes in shadow plaques - thinly myelinated lesions thought to represent remyelinated areas - were old in multiple sclerosis patients. This absence of new oligodendrocytes in shadow plaques suggest that remyelination is not carried out by new but by old pre-existing oligodendrocytes, or that remyelination of lesion occurs transiently or not at all in multiple sclerosis. We reveal unexpected oligodendrocyte generation dynamics in multiple sclerosis, which highlights the heterogeneity of the disease process and should guide the use of current and the development of new therapies.

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Poster

740. Central and Peripheral Myelinating Cells II

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Program #/Poster #: 740.12/C27

Topic: B.11. Glial Mechanisms

Support: NIH Grant RO1 NS-066977
NIH Grant R01 NS-057305
NIH Grant P30 NS-45713

Title: Modulation of sympathetic neuronal activity in spontaneously hypertensive rats

Authors: ***M. HABURCAK**, S. SONA, N. GERARD, J. ENES, S. J. BIRREN;
Biol., Brandeis Univ., Waltham, MA

Abstract: We present data that implicate peripheral, local satellite glial cells of the superior cervical ganglion (SCG) in the modulation of sympathetic neuronal activity and investigate this regulation under pathological conditions, namely in a hypertensive animal model. Spontaneously hypertensive rats (SHRs) display increased sympathetic drive that precedes the onset of hypertension. We evaluated morphological changes within the developing ganglion, and determined the effects of satellite glial cells on intrinsic properties and excitability of SCG neurons of normotensive rats and prehypertensive SHRs during the postnatal period. Within the SCG, satellite glia enwrap individual neuronal soma during a developmental period of neuronal hypertrophy. Glial changes in SHR ganglia included expression of the glial activation marker glial fibrillary acidic protein (GFAP) in young animals, suggesting that activated glia contribute to pathological processes in prehypertensive animals. We found that satellite glia promote cholinergic neurotransmission between cultured sympathetic neurons, further suggesting that glial interactions contribute to heightened sympathetic drive preceding hypertension. In addition, these glia release neurotrophins, providing a non-target-derived alternative, local source of neurotrophic factors in the sympathetic system. These actions of satellite glial cells open new possibilities for designing new targets for manipulating sympathetic neuronal activity in hypertension. In addition to the actions of glia, SHR neurons exhibited alterations in their excitability and intrinsic properties that were dependent upon interactions with cardiomyocytes isolated from the hearts of prehypertensive animals, demonstrating that cells from both the local ganglionic environment and distant targets contribute to the regulation of the peripheral sympathetic circuit in hypertension. Taken together, our results provide a greater understanding of the complex interplay of a variety of cell types and sympathetic neuronal activity implicated in the development of cardiac dysfunction in the hypertensive model.

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Poster

740. Central and Peripheral Myelinating Cells II

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Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 740.13/C28

Topic: B.11. Glial Mechanisms

Support: F31 NS103353-01A1

Title: Title

Authors: ***B. ZOTTER**[1], O. DAGAN[1], J. SAMANTA[2], H. BALOUI[3], J. L. SALZER[1]; [1]Neurosci. Inst. and Dept. of Neurosci. and Physiol., NYU Sch. of Med., New York, NY; [2]Sch. of Vet. Med., Univ. of Wisconsin Madison, Madison, WI; [3]Depts. of Neurosci. and Clin. Neurosci., Karolinska Institutet, Stockholm, Sweden

Abstract: Peripheral nerves contain a variety of cell types in addition to axons and Schwann cells (SCs) including perineurial glia (PG), endoneurial fibroblasts (EFs), and vascular components. Interactions among all of these cellular elements are important for proper nerve organization. During development, SCs express the morphogen Desert Hedgehog (Dhh), which is critical for PG development. Dhh expression continues in myelinating SCs throughout adulthood. The cellular targets of Dhh both during development and in the adult PNS are incompletely characterized. Here we used a genetic fate-mapping strategy to identify hedgehog-responsive cells in peripheral nerves. Binding of Dhh to its cognate target cells upregulates the transcription factor Gli1, which is therefore a sensitive reporter for hedgehog signaling; Gli1 is also a marker of neural stem cells as well as perivascular mesenchymal stem cells. Here, we demonstrate that PG, EFs, and pericytes in the PNS are Gli1 positive and co-express PDGFRα, a marker of mesenchymal stem cells. Knockout of Gli1 during development had no obvious effect on the perineurium but drove the majority of EFs to dramatically alter their phenotype and form minifascicles, perineurial-like cellular sheaths which divide the nerve into many small compartments. Gli1-positive EFs also give rise to minifascicles following nerve transection injury and are involved in the formation of a fibrotic tissue bridge between the cut ends of the nerve, highlighting their plasticity with injury. Taken together, these results indicate Gli1-positive EF have stem-like properties and suggest their fate during development and after nerve injury is under the control of SCs via Dhh-Gli1 signaling. Pharmacological manipulation of Dhh

signaling by specific targeting of Gli1 may be useful in regulating the EF phenotype during nerve repair and regeneration.

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Poster

740. Central and Peripheral Myelinating Cells II

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Topic: B.11. Glial Mechanisms

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the Dr. Miriam and Sheldon G. Adelson Medical Research Foundation
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Title: How is the regional specificity of myelination established and maintained?

Authors: *L. O. SUN[1], S. B. MULINYAWE[1], H. Y. COLLINS[1], A. IBRAHIM[1], Q. LI[1], D. J. SIMON[2], M. TESSIER-LAVIGNE[2], B. A. BARRES[2];
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Abstract: Nervous system function depends on proper myelination for insulation and critical trophic support for axons. Myelination is tightly regulated spatially and temporally, but how it is controlled molecularly remains largely unknown. Here, we identified key molecular mechanisms governing the regional and temporal specificity of central nervous system (CNS) myelination. We leveraged our whole-genome RNA sequencing datasets (Zhang et al., 2014 Journal of Neuroscience) and identified a novel oligodendrocyte(OL)-enriched transcription factor, transcription factor EB (TFEB), that is highly expressed by premyelinating OLs and is critical to mediate programmed cell death of a subset of premyelinating OLs. Genetic deletion of TFEB in OL lineage cells causes ectopic myelin formation in the cerebellar molecular layer, a non-myelinated brain region, as well as precocious myelination in many other brain areas. To determine the downstream mechanisms, we conducted unbiased RNA-Seq analysis in TFEB KO premyelinating OLs and found that TFEB induces transcriptional expression of PUMA, which encodes a pro-apoptotic factor that further activates Bax/Bak-dependent programmed cell death. Indeed, PUMA KO mice as well as Bax/Bak OL conditional KO mice completely phenocopy TFEB conditional KO animals in ectopic OL survival and aberrant myelination in vivo. Finally,

TFEB conditional KO, PUMA KO, and Bax/Bak conditional KO mice phenocopy each other in disrupted myelination timing. Our results demonstrate that OL programmed cell death mediated by the TFEB-PUMA-Bax/Bak pathway powerfully controls regional and temporal specificity of CNS myelination that allows for proper circuitry function, shedding lights on a common principle shared by neurons and glia in shaping the nervous system.

Disclosures: L.O. Sun: None. **S.B. Mulinyawe:** None. **H.Y. Collins:** None. **A. Ibrahim:** None. **Q. Li:** None. **D.J. Simon:** None. **M. Tessier-Lavigne:** None. **B.A. Barres:** None.

Poster

740. Central and Peripheral Myelinating Cells II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 740.15/C30

Topic: B.11. Glial Mechanisms

Support: NS094171
NS105638

Title: Regulation of glial size by a Golgi membrane protein eas-1/GOLT1B

Authors: *A. ZHANG, D. YAN;
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Abstract: The regulation of glial growth is a fundamental biological process necessary for the proper morphogenesis and continued function of the nervous system. Not only do glia have to grow in accordance with the developing nervous system to maintain their cellular contacts, but glia such as oligodendrocytes cells continue growing postnatally to myelinate axons, a process associated with learning. However, due to the complexity of the nervous system and the broad range of cellular contexts, the underlying molecular mechanisms regulating glial growth are poorly understood.
To investigate the mechanisms involved in regulating glial size, we used *C. elegans* amphid sheath (AMsh) glia as a model owing to their simple nervous system and genetic tractability. We show that a conserved Golgi membrane protein *eas-1/GOLT1B* negatively regulates glial growth, whose function has not been characterized in animals. Using a heat shock promoter to drive *eas-1* expression, we show that the gene is required for the continued maintenance of glial size beyond the initial morphogenesis during the embryonic development. Through a suppressor screen, we found that *eas-1* inhibits a conserved ER-resident E3 ubiquitin ligase *rnf-145/RNF145*, which in turn promotes nuclear activation of *sbp-1*, the *C. elegans* homolog of the SREBPs, which are key regulators of sterol and fatty acid homeostasis, to restrict cell growth. In accordance with the role of *sbp-1* in regulating the expression of genes that catalyze the production of long chain polyunsaturated fatty acids (LC-PUFAs), we found that dietary

supplementation of eicosapentaenoic acid (EPA) but not the saturated palmitic acid in *eas-1* mutants rescued the glial size phenotype. Furthermore, our genetic analyses show that the *rnf-145- sbp-1* pathway functions in parallel with the TOR pathway while *eas-1* functions upstream of both to regulate AMsh cell growth. Together, our findings reveal a novel and potentially conserved mechanism underlying the regulation of glial size, that may aid in our understanding of how glia regulate their size given the diversity of cellular contexts.

Disclosures: A. Zhang: None. **D. Yan:** None.

Poster

740. Central and Peripheral Myelinating Cells II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 740.16/C31

Topic: B.11. Glial Mechanisms

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ELA 2018-023I4
Hunter Hope Foundation
Krabbe Connect

Title: GALC is required by myelinating glia and macrophages to prevent psychosine-induced demyelination and galactosylceramide-induced neuronflammation

Authors: *M. FELTRI[1], N. WEINSTOCK[2], D. SHIN[2], N. SILVESTRI[3], H. XINYING[4], N. DUC[5], J. KOFLER[6], M. ESCOLAR[7], M. GELB[4], E. BONGARZONE[5], L. WRABETZ[2]; [2]Hunter James Kelly Res. Inst., [3]Neurol., [1]State Univ. of New York at Buffalo, Buffalo, NY; [4]Departments of Chem. and Biochemistry,, Univ. of Washington,, Seattle, WA; [5]Dept. of Anat. & Cell Biol. Col. of Medicine,, Univ. of Illinois at Chicago, Chicago, IL; [6]Dept. of Pathology, [7]Dept. of Pediatrics,, Univ. of Pittsburgh Sch. of Medicine,, Pittsburgh,, PA

Abstract: Lysosomal storage disorders (LSDs) are inherited metabolic diseases caused by enzyme deficiencies [1]. Therapy for LSDs relies on cross-correction of lysosomal enzymes between cells [2,3]. In globoid cell leukodystrophy (GLD), mutations in the galactosylceramidase gene (GALC) cause toxic accumulation of a minor GALC-substrate, psychosine, that may directly induce demyelination, a neuroinflammatory “globoid” cell reaction and neurodegeneration. The cellular origin of psychosine, the role of the GALC major substrate galactosylceramide and the efficiency of GALC transfer *in vivo* are poorly understood [4 5,6]. Using a novel GLD model we show that cross-correction does not occur *in vivo* in the peripheral nervous system and that GALC-deficient Schwann cells are the source of psychosine, which

causes demyelination, but not formation of globoid cells. Infiltrating neural macrophages require GALC for myelin degradation, as ablating GALC in Schwann cells and macrophages produce a GLD-like phenotype. GALC-deficient macrophages are induced to globoid cells by galactosylceramide, suggesting a role for this major GALC substrate. Finally, nerves from GLD patients treated with hematopoietic stem cell transplantation have fewer globoid cells than untreated patients, suggesting that the effect of therapy is strongly influenced by the phagocytic function of healthy macrophages. These data reveal that GLD pathogenesis may consist of two intertwined mechanisms: psychosine-induced demyelination and secondary neuroinflammation from galactosylceramide storage in macrophages.

Disclosures: **M. Feltri:** None. **N. Weinstock:** None. **D. Shin:** None. **N. Silvestri:** None. **H. Xinying:** None. **N. Duc:** None. **J. Kofler:** None. **M. Escolar:** None. **M. Gelb:** None. **E. Bongarzone:** None. **L. Wrabetz:** None.

Poster

740. Central and Peripheral Myelinating Cells II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 740.17/C32

Topic: B.11. Glial Mechanisms

Support: Wellcome Trust RG68763

Title: Developmental origin of oligodendrocytes determines their function in the adult CNS

Authors: ***S. FORSTER**[1], R. J. M. FRANKLIN[1], E. M. FLORIDDIA[3], D. VAN BRUGGEN[3], G. CASTELO-BRANCO[3], S. CHENG[3], T. BUSSEY[2], B. PHILIPPS[2], E. KIM[2], C. J. HEATH[2], W. D. RICHARDSON[4], R. B. TRIPATHI[4];
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Abstract: In the mouse embryonic forebrain, oligodendrocyte progenitor cells (OPCs) are generated in consecutive waves from distinct brain regions along a spatiotemporal gradient, with ventral OPCs emerging before dorsal OPCs. Whether this developmental diversity of oligodendrocyte lineage cells is functionally important is unknown. Using a genetic strategy to ablate dorsally-derived oligodendrocyte lineage cells (OLCs), we found that the areas in which dorsally-derived OLCs normally reside in the adult CNS are now populated and myelinated by the ectopic dispersion of OLCs of ventral origin. These ectopic OLs have a distinctive gene expression profile, as well as subtle myelin abnormalities. The failure of ectopic OLs to assume the role of the original dorsally-derived cells results in behavioural deficits in the adult animal. This study thus provides evidence for the biological significance of developmental heterogeneity

within the oligodendrocyte lineage, revealing why this heterogeneity is important for homeostatic brain function.

Disclosures: **S. Forster:** None. **R.J.M. Franklin:** None. **E.M. Floriddia:** None. **D. van Bruggen:** None. **G. Castelo-Branco:** None. **S. Cheng:** None. **T. Bussey:** None. **B. Philipps:** None. **E. Kim:** None. **C.J. Heath:** None. **W.D. Richardson:** None. **R.B. Tripathi:** None.

Poster

740. Central and Peripheral Myelinating Cells II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 740.18/C33

Topic: B.11. Glial Mechanisms

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National Key Basic Research Program of China 2015CB553500
Key Research Program of Frontier Sciences QYZDJ-SSW-SMC002
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Key Field Research and Development Program of Guangdong Province 2018B030337001
Shanghai Municipal Science and Technology Commission 17ZR1435300

Title: Essential role of NG2 glia in the regulation of brain innate immunity

Authors: *S.-Z. ZHANG, Y.-J. LIU, Q.-Q. WANG, Q.-Q. YANG, Y.-Q. YIN, R. CHEN, Q.-Q. SUN, Y.-J. LIU, Y.-D. LI, J.-C. HOU, J.-W. ZHOU;
Inst. of Neuroscience, CAS, Shanghai City, China

Abstract: Brain innate immunity is vital for maintaining normal brain functions. Immune homeostatic imbalances play pivotal roles in the pathogenesis of neurological diseases. However, the molecular and cellular mechanisms underlying the regulation of brain innate immunity are still largely unknown. Here, we show that neuron-glial antigen 2 (NG2) glia are required for the maintenance of immune homeostasis in the brain via transforming growth factor-β2 (TGF-β2)-TGF-β type II receptor (TGFBR2)- CX3C chemokine receptor 1 (CX3CR1) signaling, which suppresses the activation of microglia. We demonstrate that ablation of NG2 glia results in profound downregulation of the expression of microglia-specific signature genes. Mice with ablated NG2 glia display a remarkable inflammatory response in multiple brain regions following exposure to endotoxin lipopolisaccharides (LPS). The microglia become hyper-responsive to LPS stimulation in the absence of NG2 glia, which is accompanied by marked downregulation of expression of microglia enriched genes. Gain- or loss-of-function studies

show that NG2 glia-derived TGF-β2 and its receptor TGFBR2 in microglia are key regulators of the CX3CR1-modulated immune response. These findings suggest that NG2 glia play a critical role in modulation of neuroinflammation and define a new fundamental mechanism by which brain innate immune homeostasis is maintained.

Disclosures: **S. Zhang:** None. **Y. Liu:** None. **Q. Wang:** None. **Q. Yang:** None. **Y. Yin:** None. **R. Chen:** None. **Q. Sun:** None. **Y. Liu:** None. **Y. Li:** None. **J. Hou:** None. **J. Zhou:** None.

Poster

740. Central and Peripheral Myelinating Cells II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 740.19/C34

Topic: B.11. Glial Mechanisms

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RG-1501-02797
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Myelin Repair Foundation
Dr Miriam and Sheldon G. Adelson Medical Research Foundation

Title: Phosphorylation state of ZFP24 controls oligodendrocyte differentiation

Authors: *B. ELBAZ, A. KOLARZYK, B. POPKO;
Dept. of Neurol., Univ. of Chicago, Chicago, IL

Abstract: Myelin is a multilayer lipid membrane structure that ensheaths and insulates axons. In the central nervous system (CNS), myelin is formed by oligodendrocytes. During CNS development oligodendrocyte progenitor cells terminally differentiate into mature oligodendrocytes, produce myelin and wrap axons. The differentiation of oligodendrocytes and their expression of myelin protein gene transcripts are under tight transcriptional control. Zinc finger protein ZFP24, formerly known as ZFP191, is necessary for oligodendrocyte maturation and CNS myelination. We have demonstrated that ZFP24 binds to a consensus DNA sequence in proximity to genes important for oligodendrocyte differentiation and CNS myelination, and we have shown that this binding enhances target gene expression. We have also demonstrated that ZFP24 DNA binding is controlled by phosphorylation. Phosphorylated ZFP24, which does not bind DNA, is the predominant form in oligodendrocyte progenitor cells. As these cells mature into oligodendrocytes, the non-phosphorylated, DNA-binding form accumulates. We performed a large, unbiased screen and found that ZFP24 is phosphorylated by several isoforms of Protein

Kinase C (PKC) and Calcium and Calmodulin dependent Kinase (CAMK). We also found that ZFP24 is dephosphorylated by the calcium and calmodulin dependent phosphatase Calcineurin. Using the Cuprizone model, we found that ZFP24 is important for CNS remyelination. In addition, we found that active, non-phosphorylated, ZFP24 is capable of inducing oligodendrocyte differentiation. Therefore, our studies provide potential therapeutic targets, the modulation of which might enhance the presence of the non-phosphorylated form of ZFP24 and the promotion of oligodendrocyte maturation and CNS remyelination.

Disclosures: B. Elbaz: None. **A. Kolarzyk:** None. **B. Popko:** None.

Poster

741. Metabolism, Stress, and Brain Wellness

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 741.01/C35

Topic: C.01. Brain Wellness and Aging

Support: ALS Canada

Title: The role of oxidized SOD1 aggregates in aging

Authors: *K. SHAFIQ, T. GUAN, J. KONG;
Dept of Human Anat. of Cell Sci., Univ. of Manitoba, Winnipeg, MB, Canada

Abstract: Super oxide dismutase 1(SOD1) is one of the primary anti-oxidant enzymes in human body that converts the superoxide free radicals into oxygen and less toxic H_2O_2. Oxidative stress induced SOD1 aggregation is found to be a common pathology of age related neurodegenerative conditions like Amyotrophic lateral sclerosis, Parkinson's and Alzheimer's disease. Among the four cysteine residues, cysteine 111 group is unique to human SOD1 (hSOD1) which is located on the surface of the protein in a reduced state. In transgenic mice expressing mutant G93A-SOD1, we found that cysteine 111 is prone to oxidation and such modified SOD1 monomers irreversibly crosslink with each other and form intracellular aggregates. The aggregates appear to increase as early as the mice are 100 days old, and the mutation of cysteine111 group abolished such process. Aberrant accumulation of protein aggregates are prominent in aging and age-related neurodegenerative diseases. Based on these, we hypothesized that 1) oxidation of cysteine 111 leads to the formation of SOD1 aggregates which in turn accelerate the aging in the central nervous system; 2) selective clearance of aggregates can delay the aging process. To observe the progressive changes, we have tested G93A mice of different age groups ranging from 50 days to 150 days. Collected spinal cord samples were incubated with maleimide polyethyleneglycol (malPEG) which reacts to reduced thiol group of cysteine 111 residue. MalPEG-modifiable SOD1 represent the native SOD1 and shows a band shift of 5-10 KDa in western blot. We then investigated the serum samples using an oxi-sod1 ELISA assay. Samples

are first incubated with iodoacetate-agarose to pull down the native SOD1, then the supernatant is subjected to ELISA to measure the remaining oxidized SOD1. We found a significant increase of oxidative SOD1 in both spinal cord and serum in older age mice. Present findings indicate that SOD1 aggregates can be a potential biomarker of aging, and inhibiting SOD1 aggregate formation may offer avenues to reduce aging and age-related diseases.

Disclosures: K. Shafiq: None. **T. Guan:** None. **J. Kong:** None.

Poster

741. Metabolism, Stress, and Brain Wellness

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 741.02/C36

Topic: C.01. Brain Wellness and Aging

Support: KAKENHI 19K07987

Title: Dietary yeast restriction attenuates polyglutamine toxicity via insulin-like signaling and immune signaling in *Drosophila*

Authors: *M. SUZUKI[1,2,3], A.-M. NEUMANN[3], Y. SAITOH[3], N. FUJIKAKE[3], K. WADA[3], K. SANGO[1], Y. NAGAI[2,3];
[1]Tokyo Metropolitan Inst. of Med. Sci., Setagaya, Japan; [2]Dept Neurotherapeutics, Osaka Univ. Grad Sch. Med., Suita, Japan; [3]Dept Degenerative Neurolog. Dis., Natl. Inst. Neurosci, NCNP, Kodaira, Japan

Abstract: Aging is known to be a significant risk factor for neurodegenerative diseases, most of which share a common molecular pathogenesis involving protein misfolding and aggregation. The balance between protein and carbohydrate in diet is known to be one of the determinant for life-span in flies and mice. In *Drosophila*, dietary yeast restriction (DR) regimen produces low protein to carbohydrate ratio and delays age-associated changes and extends life-span. We explored whether DR improves misfolding protein-induced neurodegeneration. *Drosophila* models of Alzheimer's disease, polyglutamine disease or amyotrophic lateral sclerosis either expressing Aβ, MJD or TDP-43 protein, respectively, were fed a high-yeast diet (HD: 5% sucrose, 20% yeast extracts) or a low-yeast diet (LD: 5% sucrose, 5% yeast extracts). We found that LD significantly suppresses compound eye degeneration, locomotor dysfunction and shortened life-span of these model flies. Meanwhile, the diet did not affect the compound eye degeneration induced by apoptosis, suggesting that its effects are specific to misfolding protein-related neurodegeneration. DR also suppressed misfolding of these proteins as evident by reduced accumulation of MJD protein inclusions and TDP-43 protein oligomers. Next we focused on the role of insulin-like signaling, which is known to mediate the effect of DR in aging. It was showed that the beneficial effects of DR are canceled by using mutant background

of *insulin-like peptides* and *chico*, a homolog of IRS. To further explore the mechanisms we performed microarray analyses and found that immune signaling activation might be attenuated by DR. Genetic analyses demonstrated that knockdown of *Relish*, a homolog of NFκB, canceled the effect of DR both in cell-autonomous and non-cell autonomous manners. Our findings demonstrate that the DR condition suppresses neurodegeneration through affecting protein misfolding, and suggest the role of metabolic and immune signaling in the effect of the DR.

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Poster

741. Metabolism, Stress, and Brain Wellness

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 741.03/C37

Topic: C.01. Brain Wellness and Aging

Support: NIH/NINDS Pioneer Award
NIH/NINDS R01 NS076558
HHMI - Faculty Scholars Program

Title: Phosphofructokinase (PFK-1) self-interaction is necessary for its clustering near synapses

Authors: *Z. XUAN[1], D. COLÓN-RAMOS[1], S. JANG[1], I. GONZALEZ[1], M. SINGH[1], S. PRASHAD[1], B. KIM[1], R. LAGOY[2], D. ALBRECHT[2], A. HYMAN[3], A. PATEL[3], L. JAWERTH[3];
[1]Yale Univ., New Haven, CT; [2]Worcester Polytechnic Inst., Worcester, MA; [3]Max Planck Inst. of Mol. Biol. and Genet., Dresden, Germany

Abstract: Glycolysis is a fundamental and conserved pathway responsible for generating ATP and metabolites. We previously observed that glycolytic enzymes form clusters near the synapse in response to energy stress (induced by transient hypoxia). To better understand the dynamics of the clusters under transient hypoxia, we combined microfluidics with imaging and characterized the relocalization of the rate-limiting glycolytic enzyme, phosphofructokinase (PFK-1) in *C. elegans* neurons. We observed that PFK-1 dynamically forms clusters under transient hypoxia and diffuses in the cytoplasm under normoxia. We also identified that this glycolytic compartment exhibits liquid-like characteristics. PFK is active in its tetrameric state, and a PFK-1 mutant that is incapable of forming tetramers (PFK-1 mutant F674K) is also incapable of dynamic relocalization to synapses upon energy stress. We also observed that the CRY2 tagged PFK-1 is sufficient to induce non-CRY2 tagged PFK-1 clusters via self-association. In summary, our study suggests that PFK-1 self-interaction (tetramer formation) is necessary for its clustering near synapse and might be important for its function.

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Poster

741. Metabolism, Stress, and Brain Wellness

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 741.04/C38

Topic: C.01. Brain Wellness and Aging

Support: University of Southern California Provost Scholarship
P.E.O Scholar's Award

Title: Driving brain aging by disruption of muscle proteostasis: Role of ABC transporters in protein clearance and tissue aging

Authors: *M. MORI[1], M. MOUJAHIDINE[2], A. BASSETT[3], P. HAGHIGHI[2];
[1]Buck Inst. For Res. On Aging, Novato, CA; [2]Buck Inst. for Res. on Aging, Novato, CA; [3]Univ. of San Francisco, San Francisco, CA

Abstract: The decline in protein homeostasis (proteostasis) is a major hallmark of aging and is a central pathology for various diseases of age. Using genetic tools available in *Drosophila melanogaster*, we have identified a novel regulator of tissue proteostasis and demonstrate the interplay between muscle proteostasis and brain aging. We have identified a member of the ABC transporter family to be required to maintain proteostasis in various tissues including the brain. Tissue-specific knockdown of the ABC transporter is sufficient to disrupt age-dependent proteostasis in respective tissues. As the transporter is responsible for the import of amino acids and metabolites, we believe amino acid metabolism plays a key role in the maintenance of proteostasis. Furthermore, muscle-specific manipulation of the ABC transporter results in an increased inflammatory response in the brain of aged animals. Transcription levels of inflammatory stress response genes are increased with age, and disruption of muscle proteostasis further aggravates inflammation. These results indicate that brain aging can be driven by amino acid metabolism and deterioration of proteostasis in the muscle.

Disclosures: **M. Mori:** None. **M. Moujahidine:** None. **A. Bassett:** None. **P. Haghighi:** None.

Poster

741. Metabolism, Stress, and Brain Wellness

Location: Hall A

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Program #/Poster #: 741.05/C39

Topic: C.01. Brain Wellness and Aging

Support: MSIT Grant 2017M3C7A1023478
MEST Grant 2019R1A2C2009440
CRPASTD Grant PJ01324801
BK21 Grant 10Z20130012243

Title: VRK2 regulates the formation of stress granules via phosphorylation of G3BP1

Authors: *K.-W. JO, Y.-H. JEONG, K.-T. KIM;
Pohang Univ. of Sci. and Technol., Pohang, Korea, Republic of

Abstract: In mammalian cells, global translational repression occurs by the assembly of cytoplasmic messenger ribonucleoprotein (mRNP) granules called stress granules (SGs) in response to environmental stresses. The RasGAP SH3 domain binding protein 1 (G3BP1) is one of the factors of stress granule assembly and it is known to induce the formation of SGs through oligomerization. Previous reports showed that G3BP1 is phosphorylated at serine 149 (S149), which causes the interference in G3BP1 oligomerization. However, a kinase involved in the phosphorylation of G3BP1 is still yet to be revealed. Here we identified Vaccina-related kinase 2 (VRK2) directly interacts with G3BP1. Furthermore, VRK2 interacts with G3BP1 and phosphorylates at serine 149 of G3BP1, which attenuates the aggregation of SGs. Moreover the phosphorylated form of G3BP1 and VRK2 levels are consistently decreased under cell stress conditions. Notably, our work reveals a novel function of VRK2 in cellular defensive response under stress condition by regulating SG formation as an upstream kinase of G3BP1.

Disclosures: K. Jo: None. **Y. Jeong:** None. **K. Kim:** None.

Poster

741. Metabolism, Stress, and Brain Wellness

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 741.06/C40

Topic: C.01. Brain Wellness and Aging

Support: RGC Areas of Excellence Grant P-705/16

Title: Deletion of Caveolin 1 accelerates hippocampal senescence via reprogramming glucose metabolism

Authors: *M. WU, C. GAO, Q. DU, J. SHEN;
Sch. of Chinese Med., The Univ. of Hongkong, Hong Kong, Hong Kong

Abstract: Ageing is the biggest risk factor to neurodegenerations including Alzheimer's disease etc. Convergent lines of evidence suggest membrane/lipid rafts (MLR) is essential for development and stabilization of synapse and neural plasticity. Exploring the molecules in regulating MLR functions would offer the therapeutic targets against neurodegenerations. Caveolin-1 (Cav-1), a well-established mediator for lipid homeostasis, was documented as a target to alleviate the ageing associated neurodegeneration. Deletion of Cav-1 induced the alternative cellular glucose metabolism, which would help to explain the roles of such protein in ageing associated neurodegeneration. In our study, we found that compared with adult mice (4 months), Cav-1 protein displays the increasing expression in aged hippocampus (18 months). We employed Cav-1 knockout adult mice to investigate the glucose metabolic related biological phenomena in hippocampus. By detecting the markers of oxidative damage 4-HNE as well as glycolysis/TCA switch turnover the activity of pyruvate dehydrogenase, we found Cav-1 KO increased the byproduct of oxidative damage as well as the reprogrammed glucose metabolism, which mimic the phenomena in aged wild type mice. In addition, at age of 18 months, Cav-1 KO mice showed deficit cognitive functions and increased cell death in hippocampus. As one of the components of mitochondria-associated membrane (MAM), down regulation of Cav-1 detached the mitochondria and ER and thus cause the glucose metabolic reprogram by ROS burst, thereby induced the ageing associated neurodegeneration. As a conclusion, Cav-1 may be a potential target for anti-ageing and neurodegenerative therapy.

Disclosures: M. Wu: None. **C. Gao:** None. **Q. Du:** None. **J. Shen:** None.

Poster

741. Metabolism, Stress, and Brain Wellness

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 741.07/C41

Topic: C.01. Brain Wellness and Aging

Title: Study of the development and aging of the brain through metabolic pathways

Authors: *K. BAI, C. J. CORTES, A. R. LA SPADA;
Dept. of Neurology, Dept. of Cell Biology, Dept. of Neurobiology, Duke Ctr. for Neu, Duke Univ., Durham, NC

Abstract: The purpose of this study is to investigate activity of metabolic pathways in mice brain models at different stages of aging. Certain pathways, such as lysosomal biogenesis and autophagy pathways, are known to decline with age. Dysfunction of these pathways lead to neurodegeneration in the brain, which can manifest as a variety of neurodegenerative diseases, such as Alzheimer's and Parkinson's disease. qPCR analysis and immunohistochemistry were performed on brain samples from mice categorized into different age groups (6 months, 14 months, and 24 months). Markers of glycolysis, chaperones, ER stress, inflammation, and autophagy pathways were selected and studied. Preliminary results from qPCR indicate that younger age groups have significantly higher transcription levels of markers of certain cellular pathways in brain cells, suggesting a decline in transcriptional activity of protein quality control and bioenergetic pathways in the aging brain. Immunohistochemistry will be a necessary next step to further explore these findings. The ultimate goal of this study is to better our understanding of brain pathways in order to find more effective therapeutic candidates for neurodegenerative diseases.

Disclosures: K. Bai: None. **C.J. Cortes:** None. **A.R. La Spada:** None.

Poster

741. Metabolism, Stress, and Brain Wellness

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 741.08/C42

Topic: C.01. Brain Wellness and Aging

Title: Anti-obesity effects of tocotrienols and rice bran in high-fat diet-treated mice: Does obesity accelerate brain oxidation?

Authors: *K. FUKUI[1], M. SHIRAI[2], T. NINUMA[3], Y. KATO[1];
[2]Dep of Biosci. and Engin., [1]Shibaura Inst. Technol., Saitama, Japan; [3]Shibaura Insti Technol., Saitama, Japan

Abstract: The ratio of obesity is increasing in many countries and is known to increase the risk of many severe diseases. The onset and progression of these diseases are deeply correlated with oxidative damage. However, the relationship between obesity and oxidative damage has not yet elucidated. Recently, several lines of evidence have demonstrated that neurodegenerative diseases such as Alzheimer's and Parkinson's are also related to oxidative damage. On the other hands, tocotrienols (T3s) which are one kind of vitamin E, have unique functions. One beneficial effect of T3s is anti-obesity. In this study, we investigated brain antioxidant networks in high-fat (HF) diet-treated mice in the presence or absence of T3s and bran. Before start of study, we measured T3 levels in five different commercially-available non-mixed breeds of whole grain wheats, and bran. The highest T3s level was bran. Co-treatment with T3s and bran significantly inhibited bodyweight gain in HF diet-treated mice. Although, we recognized that enough volume

of T3s reached liver in T3s-treated groups, serum and cortex T3 levels and brain antioxidant enzyme activities and protein expressions did not differ among the groups. These results indicate that treatment with T3s for eight weeks had showed an anti-obesity effect in HF diet-treated mice. However, significant alterations in T3 levels were not observed in the serum and brain of mice.

Disclosures: K. Fukui: None. **M. Shirai:** None. **T. Ninuma:** None. **Y. Kato:** None.

Poster

741. Metabolism, Stress, and Brain Wellness

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 741.09/C43

Topic: C.01. Brain Wellness and Aging

Support: MH110550
MH101874

Title: CYP46A1 knock-out causes age-dependent transcriptional changes in cholesterol biosynthesis within the mouse hippocampus

Authors: *L. H. ZIOLKOWSKI, H.-J. SHU, A. BENZ, S. J. MENNERICK;
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Abstract: Brain cholesterol plays an important role in myelin composition, membrane structure and cellular physiology. Due to its inability to cross the blood-brain barrier (BBB), cholesterol is produced in the brain by local *de novo* synthesis. Subsequent removal of the labile neuronal pool of cholesterol from the brain is facilitated by cholesterol 24-hydroxylase (Ch24H), an enzyme that converts cholesterol into 24S-hydroxycholesterol (24S), which can readily pass through the BBB. 24S is an endogenous agonist of the Liver X Receptor (LXR) transcription factor, through which it regulates cholesterol homeostasis. 24S also positively modulates NMDAR function, which might also affect transcription to alter neuronal function. To investigate the transcriptional effects that result from a lack of 24S, we examined whole-body deletions of CYP46A1, the gene that encodes cholesterol 24-hydroxylase. We performed RNA-seq and qPCR on the dentate gyrus and CA1 regions of the hippocampus in knock-out mice. Interestingly, transcription was largely unaffected by CYP46A1 loss in young animals at post-natal day 45, possibly due to the high cholesterol demands in the brain after birth. Conversely, at post-natal days 100 and 365, transcription of various genes involved in cholesterol metabolism was depressed in knock-outs compared to wild-types. Gene set enrichment analysis revealed that transcription of cholesterol biosynthesis pathways were downregulated in the hippocampi of adult and aged CYP46A1 knock-out mice. LXR target genes were largely unaffected throughout all age points, with the exception of ABCA1, which was unexpectedly upregulated in CA1 at P100 and P365. Our

results confirm an earlier study that suggests that constitutive 24S loss does not alter LXR target genes in a predictable manner. Our work adds distinct developmental and sub-region effects to the transcriptional consequences of 24S deletion. It appears that excess cholesterol in the brain causes delayed downregulation of its own synthesis through an unknown mechanism, warranting further investigation.

Disclosures: L.H. Ziolkowski: None. **H. Shu:** None. **A. Benz:** None. **S.J. Mennerick:** None.

Poster

741. Metabolism, Stress, and Brain Wellness

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 741.10/C44

Topic: C.01. Brain Wellness and Aging

Support: NIH Grant AG047652

Title: Short term caloric restriction in mice attenuates age related increases in calcium buffering of basal forebrain neurons

Authors: *E. BANG, A. FINCHER, S. NADER, D. A. MURCHISON, K. S. MONTOGOMERY, W. H. GRIFFITH;
Texas A&M Hlth. Sci. Ctr., Bryan, TX

Abstract: Age is the greatest risk factor for acquiring Alzheimer's disease and related dementias and the resulting cognitive impairment is a major contributor to a decreased quality of life in the aging population. Extensive pharmaceutical efforts to address this problem have not produced effective treatments. Recent studies have shown the potential of dietary regimens to support healthy aging. The data presented here are part of a project to study the effects of caloric restriction (CR) on age-related cognitive decline, intracellular $^{Ca2+}$ homeostasis and synaptic transmission in the mouse basal forebrain (BF). Previously, we have shown that an age-related increase in intracellular $^{Ca2+}$ buffering in the rat BF is associated with altered spontaneous synaptic transmission and cognitive impairment. This change in buffering is prevented by post-adolescent life-long CR. Here, we investigate whether intermittent fasting (IF), a form of CR, alters age-related changes in BF physiology and behavior in a mouse model. We will use both young (3-7 mo) and aged (20-24 mo) mice and alternate day fasting/ad libitum feeding for 4-6 weeks as an IF protocol with age-matched ad lib. fed controls. Experiments are in progress to study cognitive abilities (Barnes Maze), intracellular calcium buffering and synaptic transmission. After IF, aged mice showed reduced body weight compared to aged controls (8% after last feeding day and 15% after last fasting day). IF aged mice were observed to binge on feeding day, and food intake per feeding day increased 68% compared to aged control. However, total food consumption was reduced by 25% in IF mice relative to aged controls. We assessed

intracellular $^{Ca2+}$ buffering in acutely dissociated neurons of the medial septum/diagonal band using a non-invasive method that leaves native buffers intact. Fura-2 was loaded into the neurons by the AM method and $^{Ca2+}$ transients were stimulated by increasing durations of picospritzer applied depolarizing solution (HEPES-buffered saline + 20 mM K^+). Relative buffering slopes for each cell were generated by plotting the calibrated amplitude of transients against the stimulus duration (x10). Smaller slopes indicate greater buffering. Slopes were: for young controls 67.4 ± 4.5 (n=44); aged controls 35.6 ± 4.2 (n=39); and for aged IF 50.6 ± 5.9 (n=38). Young and aged IF slopes were significantly greater ($p<0.05$) than aged control slopes, but were not different from each other. These data suggest that short-term IF can reverse the increased $^{Ca2+}$ buffering observed during aging in mouse BF.

Disclosures: E. Bang: None. **A. Fincher:** None. **S. Nader:** None. **D.A. Murchison:** None. **K.S. Montogomery:** None. **W.H. Griffith:** None.

Poster

741. Metabolism, Stress, and Brain Wellness

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 741.11/C45

Topic: C.01. Brain Wellness and Aging

Support: NIH Grant 5R01DK100281-03
Department of Veteran's Affairs 5I01RX000441-04 to CMK

Title: Chemogenetic activation of orexin/hypocretin neurons ameliorates aging induced changes in behavior and energy expenditure

Authors: *J. PALLAIS, Jr[1], M. STANOJLOVIC[1], V. MAVANJI[2], C. M. KOTZ[1,2];
[1]Integrative Biol. and Physiol., Univ. of Minnesota Twin Cities, Minneapolis, MN; [2]Minneapolis VA Hlth. Care Syst., Minneapolis, MN

Abstract: Aging is a complex and multifactorial process that reduces the overall quality of life, life expectancy, and ultimately leads to death. Aging is known to affect numerous physiological processes in addition to behavior. Many of the processes affected by aging are at least partially regulated by orexin neurons in the lateral hypothalamus. In this study, it was hypothesized that stimulation of orexin neurons would ameliorate the adverse effects of aging on metabolism and behavior. To test this, young and middle-aged mice were prepared with DREADDs (Designer Receptors Exclusively Activated by Designer Drugs) in orexin neurons. DREADD targeting was achieved by stereotaxic injection of AAV vectors (AAV2-hSyn-DIO-hM3D(Gq)-mCherry) into the lateral hypothalamus, which contains the orexin field, of 5 and 12 month old orexin-cre female mice. The DREADD targeting was then confirmed by immunohistochemistry (IHC) analysis of orexin A and mCherry expression. After recovery from the procedure, the animals

were subjected to several behavioral assays that include the elevated plus maze (EPM), open field test (OFT), and the novel object recognition test (NORT). These assays were used to assess the effects of aging on general locomotion, anxiety-like behavior, and working memory. To measure spontaneous physical activity (SPA) and energy expenditure (EE), a comprehensive laboratory animal monitoring system (CLAMS) was used. The results indicate that chemogenetic activation of orexin neurons ameliorates aging-induced reductions in anxiety-like behavior in middle-aged mice ($p<0.005$) as well as increases general locomotion in both young and middle-aged mice ($p<0.05$). Chemogenetic stimulation of orexin neurons increases SPA ($p<0.01$) and EE ($p<0.005$) in middle-aged mice, restoring SPA and EE to the levels observed in young animals. These data demonstrate that orexin neurons have neuromodulation potential and can be used as potential therapeutic targets for age-related impairments in cognitive and anxiety-related behavior, and energy balance.

Disclosures: **J. Pallais:** None. **M. Stanojlovic:** None. **V. Mavanji:** None. **C.M. Kotz:** None.

Poster

741. Metabolism, Stress, and Brain Wellness

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 741.12/C46

Topic: C.01. Brain Wellness and Aging

Support: R01NS094543-02
2017 - 2018 Russell and Diana Hawkins Family Foundation Discovery Fellowship

Title: The characterization of neuronal pexophagy *in vitro*, and in an *in vivo* model of brain aging

Authors: ***N. UZOR**, J. MORUNO MANCHON, D. MORALES-SCHEIHING, C. R. REYNOLDS, J. STEPHENSON, A. F. MACK, L. D. MCCULLOUGH, A. S. TSVETKOV; McGovern Med. Sch., Houston, TX

Abstract: Aging in the brain leads to the gradual impairment of pathways involved in organelle and protein turnover. Previous research shows that the turnover of organelles (like mitochondria) changes with age, but it is unclear if the turnover of peroxisomes, related structures that metabolize fatty acids, and both produce and break down reactive oxygen species, is explicitly affected.
To answer this question, we first investigated pexophagy - the selective autophagy of peroxisomes - in cultured primary neurons. We transfected a cohort of embryonic rat neurons with Keima-per, a fluorescent protein tagged to peroxisomes that changes its excitation and emission based on pH, and an empty plasmid. Analysis of Keima-per acidic fluorescence (an

indicator of peroxisomes that are degraded in acidic lysosomes) revealed that 1) neuronal pexophagy is basally active, and that 2) neuronal pexophagy occurs faster than neuronal mitophagy.
Pex5 is a protein necessary for pexophagy to occur, so, next, we investigated how neuronal aging affects Pex5 *in vivo*. Using Western blotting and qRT-PCR, we analyzed the whole mouse brain; with immunohistochemistry, we analyzed the cortex and hippocampus. We discovered that 1) global Pex5 protein levels are lower in the aging mouse brain compared to younger brains (n=5, young v. aged males $P<0.05$, young v. aged females $P<0.01$), that 2) *Pex5* gene expression is lowered in the aged mouse brain, particularly in the male mouse brain (n=5, young v. aged males $P<0.01$), and that 3) in preliminary IHC data, Pex5 protein levels are lowered in aged mouse neurons in both the cortex and hippocampus. From these results, we conclude that aging abnormally influences Pex5, a critical regulator of pexophagy. These findings identify pexophagy as a future target for improving homeostasis in neuronal aging.

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Poster

741. Metabolism, Stress, and Brain Wellness

Location: Hall A

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Program #/Poster #: 741.13/C47

Topic: C.01. Brain Wellness and Aging

Support: RO1 AG051807
PO1 AG000538
T32 AG000096
RF1 AG057558

Title: Histone methyltransferase inhibition attenuates H3K9me3 elevation and synaptic dysfunction caused by oxidative stressors

Authors: *A. IONESCU TUCKER[1], L. TONG[1], N. C. BERCHTOLD[2], K. TSEUNG[3], C. W. COTMAN[1];
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Abstract: Age is the number one risk factor for cognitive decline, and recent findings show that age-related repression of gene expression plays a role in compromising learning and memory. Our lab has previously found that a specific repressive epigenetic mark, histone 3 lysine 9 trimethylation (H3K9me3) is increased in aged mice and humans. We repressed H3K9me3's catalyzing enzyme (SUV39H1) with a selective inhibitor called ETP69, and found that it

increased hippocampal BDNF levels, hippocampal spine density and cognition in aged mice. We predicted that hippocampal H3K9me3 and coincident neuronal impairments are upregulated by age-associated stressors. Oxidative stress is a key contributor to brain aging, so we investigated if oxidative stressors, such as amyloid beta oligomers and the catalase inhibitor 3-amino-1,2,4-triazole (3AT), elevated H3K9me3 levels. We found that both amyloid beta oligomers and 3AT led to an increase in H3K9me3 without affecting cell survival in rat hippocampal neuron cultures. Amyloid beta oligomers further reduced levels of the synaptic marker PSD-95, while 3AT reduced levels of the glutamate receptor GluR1, thus impairing synaptic plasticity. Concurrent treatment with ETP69 and optimized doses of oxidative stressors attenuated synaptic impairments and H3K9me3 elevation. Our data reveal that catalase inhibition and amyloid beta oligomer treatment cause SUV39H1 dependent epigenetic changes and synaptic dysfunction which can be prevented by ETP69.

Disclosures: **A. Ionescu Tucker:** None. **L. Tong:** None. **N.C. Berchtold:** None. **K. Tseung:** None. **C.W. Cotman:** None.

Poster

741. Metabolism, Stress, and Brain Wellness

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Topic: C.01. Brain Wellness and Aging

Support: NIH Grant AG016573
NIH Grant MH109036

Title: Interacting, subject-specific, and accelerated aging-related features of the human choroid plexus

Authors: M. J. NEEL, B. A. JOHNSON, I. NGUYEN, N. L. VUKALOVICH, B. H. NGUYEN, Z. MUTTALIB, *E. S. MONUKI;
Pathology & Lab. Med., UC Irvine Sch. of Med., Irvine, CA

Abstract: The choroid plexus (ChP) contributes to central nervous system (CNS) homeostasis through its function as an immune cell gateway, production of cerebrospinal fluid (CSF), and blood-CSF barrier formation. Despite these functions, the ChP is a relatively understudied tissue. In particular, aging and disease-related features of the ChP, including fibrosis, oncocytic transformation, lipid vacuoles, and Biondi amyloid inclusions lack thorough characterization. Studying these features can help us understand ChP dysfunction in aging and disease and help validate disease models using stem cell-derived ChP cells. In our ChP studies, we came across a pediatric case with undiagnosed type I diabetes that presents all four features. This case contains clusters of Biondi inclusions throughout the ChP, a feature previously seen only in adults. To

study the Biondi inclusions further, we histologically studied human ChP autopsy samples from the pediatric case and from adult and Alzheimer's disease (AD) cases. We used a novel whole-mount thioflavin S staining protocol to visualize Biondi inclusions in three dimensions for blinded counting and categorization into distinct morphologies. We detected several distinct morphologies not previously described. Relative distributions appeared consistent across multiple regions from the same case, except for the pediatric case, but varied across different cases. Inclusions also appeared fragmented when present in oncocytic cells. Our results suggest that Biondi inclusions can occur in ages much younger than previously reported, possibly in relation to stressors such as those present in diabetes, and suggest that Biondi inclusions and their interactions with other features are more varied and complex than previously thought.

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Poster

741. Metabolism, Stress, and Brain Wellness

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

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Topic: C.01. Brain Wellness and Aging

Support: Dirección General de Asuntos del Personal Académico, Universidad Nacional Autónoma de México (IN221417)
Consejo Nacional de Ciencia y Tecnología (219703)
Postdoctoral Fellowship from Dirección General de Asuntos del Personal Académico, Universidad Nacional Autónoma de México

Title: Effect of chronic ozone exposure on object-place recognition task and dendritic spines of CA1 neurons

Authors: *P. C. BELLO-MEDINA[1], R. A. PRADO-ALCALA[2], S. L. RIVAS-ARANCIBIA[3]; [1]Dept. de Fisiologia, Facultad de Medicina-UNAM, UNAM, Mexico; [2]Inst. de Neurobiología-UNAM, Queretaro, Queretaro, Mexico; [3]Facultad De Medicina, UNAM, 04510 Mexico DF, Mexico

Abstract: Currently, the increase in the amount of atmospheric pollutants such as ozone, produces reactive oxygen species (ROS), which cause oxidative stress throughout the body, causing an increase in the number of people with respiratory and neurodegenerative diseases. The purpose of this research was to evaluate whether chronic exposure to ozone produces a deleterious effect on object-place recognition task and on density and morphology of dendritic spines in CA1 of dorsal hippocampus. Rats were exposed to ozone (0.25 ppm) or to ozone-free air for a period of 15, 30, 60, or 90 days. Once the period of exposure to ozone was over, the

animals were trained in an object-place recognition task and were sacrificed immediately afterward. The brains were stained with the Golgi-Cox technique. The chronic oxidative stress produced a deficit in learning and in the retention of the object-place recognition task. Likewise, there was a decrease in the density of dendritic spines and in mushroom spine ratio, and an increase in stubby spine ratio in the pyramidal neurons of CA1. These results suggest that environmental contaminants affect learning and memory, which could be caused by the loss of inputs in the neurons of CA1 from dorsal hippocampus. We thank to Erika Rodríguez-Martinez, Gabino Borgonio-Perez, and Andrea C. Medina for their excellent technical assistance. The present work was supported by Dirección General de Asuntos del Personal Académico, Universidad Nacional Autónoma de México (IN221417) and Consejo Nacional de Ciencia y Tecnología (219703). Paola C. Bello-Medina was a recipient of a postdoctoral Fellowship from Dirección General de Asuntos del Personal Académico, Universidad Nacional Autónoma de México.

Disclosures: P.C. Bello-Medina: None. **R.A. Prado-Alcala:** None. **S.L. Rivas-Arancibia:** None.

Poster

741. Metabolism, Stress, and Brain Wellness

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 741.16/C50

Topic: C.01. Brain Wellness and Aging

Support: R01AG042890

Title: Modulation of antioxidant response and neuroinflammation in frontal cortex of demented vs. non-demented individuals with Alzheimer's neuropathology

Authors: *A. FRACASSI[1], O. ZOLOCHEVSKA[1], S. MORENO[2], G. TAGLIALATELA[1]; [1]The Mitchell Ctr. for Neurodegenerative Diseases, Dept. of Neurol., Univ. of Texas Med. Br., Galveston, TX; [2]Science-LIME, Univ. Roma Tre, Rome, Italy

Abstract: Alzheimer's disease (AD) is characterized by progressive neurodegeneration in the cerebral cortex, histopathologically hallmarked by amyloid β (Aβ) extracellular plaques and intracellular neurofibrillary tangles, constituted by hyperphosphorylated Tau protein. Correlation between these pathological features and dementia has recently been challenged by the emergence of "Non-Demented with Alzheimer's Neuropathology" (NDAN) individuals, cognitively intact despite displaying pathological features of AD. The existence of these subjects suggests that some unknown mechanisms are triggered to resist Aβ-mediated detrimental events. Notably, Aβ accumulation affects mitochondrial redox balance, increasing oxidative stress status, which in turn is proposed as a primary culprit in AD pathogenesis. To clarify the relationship linking Aβ,

oxidative stress and cognitive impairment, we performed a comparative study on AD, NDAN and normally-aged human *post-mortem* frontal cortices. We quantitatively analyzed immunofluorescence distribution of 8-oxo-dG, as oxidative damage marker, and of SOD2, CAT, PGC1α, PPARα, as key factors in antioxidant response, as well as the expression of miRNA-485, as a PGC1α upstream regulator. Our results confirm dramatic redox imbalance, associated with impaired antioxidant defenses in AD brain. By contrast, NDAN individuals display low oxidative damage, associated with high levels of scavenging systems, possibly resulting from lack of PGC1α miRNA-485-related inhibition. Comparative analyses in neurons and astrocytes further highlighted cell-specific mechanisms to counteract redox imbalance. Furthermore, given the involvement of microglia in activating neuroinflammation and the scavenging function of activated microglia in the clearance of Aβ deposits, we addressed the expression and localization of such microglial/proinflammatory proteins (IBA1, CD68 and TREM2). Overall, our data emphasize the importance of transcriptional and post-transcriptional regulation of antioxidant response and neuroinflammation in AD. This suggests that efficient antioxidant "safety mechanism" and the modulation of neuroinflammation may prevent Aβ-mediated damage, supporting neuroprotective therapies aimed at ameliorating redox imbalance and neuroinflammation in AD patients.

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Poster

741. Metabolism, Stress, and Brain Wellness

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Topic: C.01. Brain Wellness and Aging

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Ellison Medical Foundation
Glenn Foundation for Medical Research
Mayo Clinic Children's Research Center
Alzheimer's Disease Research Center of Mayo Clinic

Title: Clearance of senescent glial cells prevents tau-dependent pathology and cognitive decline

Authors: *T. BUSSIAN[1], D. BAKER[1,2];
[1]Biochem. and Mol. Biol., [2]Pediatric and Adolescent Med., Mayo Clin., Rochester, MN

Abstract: Cellular senescence is a state of irreversible cell-cycle arrest that is induced by a variety of intracellular and extracellular stress factors. Characterized by expression of $p16^{INK4a}$, a protein that inhibits cell cycle progression, senescent cells play a prominent role in the aging

process through their distinct, inflammatory, secretory phenotype. Indicators of senescence have been found in patients suffering from a variety of neurodegenerative diseases, but whether these cells play a role in these pathologies is unknown. Here we demonstrate a causal link between the accumulation of senescent cells and tauopathy-induced cognitive decline. Using the $MAPT^{P301S}$PS19 mouse model of tau-dependent neurodegeneration, we discovered that $p16^{INK4a}$-positive astrocytes and microglia accumulate prior to neurofibrillary tangle (NFT) deposition and neurodegenerative cognitive decline. Clearance of these cells with the INK-ATTAC transgenic mouse model prevented gliosis, hyperphosphorylation of soluble and insoluble tau, and NFT formation. Importantly, senescent cell removal also prevented the loss of neurons in the hippocampus and cortex, thereby preserving cognitive function. Pharmacological treatment with a first-generation senolytic also impacted tau aggregation. Collectively, these results indicate that cellular senescence plays a role in the initiation and progression of neurodegenerative tauopathies and suggest that these cells may provide a novel therapeutic avenue for disease treatment.

Disclosures: **T. Bussian:** None. **D. Baker:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Unity Biotechnology.

Poster

741. Metabolism, Stress, and Brain Wellness

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 741.18/C52

Topic: C.01. Brain Wellness and Aging

Title: Aquaporin-4 distribution correlates to increase in phosphorylated tau accumulation in sprague dawley rats fed a high fructose diet

Authors: P. WOLLER[1], *J. K. MORRIS[2];
[1]Neurosci. Program, [2]Biol., Baldwin Wallace Univ., Berea, OH

Abstract: According to the Center for Disease Control, 10% of the U.S. population has type 2 diabetes. Type 2 diabetes is a resistance to the presence of insulin in the bloodstream and occurs in adults over 45. In a person with type II diabetes, their cells utilize glucose in response to insulin in the bloodstream. Since neurons main energy source is glucose, this can have devastating effects on neurons and may result in neurodegeneration. Consumption of fructose may lead to a greater risk of diabetes. Individuals that consume fructose, convert the fructose into lipids or free fatty acids in the liver. The brain's glymphatic system is connected to major blood vessels in the brain covered by astrocytes that form a barrier between brain tissue and the blood. The aquaporin proteins are present in the astrocytic endfeet that surround the blood vessels and allow the fluid to enter and leave the brain. Inflammation and brain injury leads to a

redistribution of the aquaporin 4 channel from the endfeet to the cell bodies. Thus, disruption of the glymphatic system might lead to the accumulation of amyloid plaques. The glymphatic system is disrupted in streptozotocin (STZ) injected animal model of type II diabetes mellitus Since the STZ-model of diabetes can be toxic to animals and cause stress, we are seeking to compare this model directly to a fructose-fed rat model. Sprague Dawley rats were either fed a control diet (n=3) or a 60% fructose diet (n=2) for 12 weeks and then perfused and tissues were collected. Floating sections were stained for cresyl violet, phosphorylated Tau, or aquaporin-4 proteins and then analyzed with non-biased stereology using the Microbrightfield system on the Olympus BH2 fluorescent microscope. The area of the hippocampus was not altered between the control, STZ injected or 60% fructose-fed rats ($p > 0.5$) while the distribution of phosphorylated tau particle density increased 2.5-fold between the control and rats fed 60% fructose diet ($p<0.5$). Additionally, we identified a significant decrease ($p<0.5$) in aquaporin-4 protein distribution on blood vessels in control (3.1 +/- 0.2 positive vessels/mm2) compared to STZ induced diabetes (2.0 +/- 0.2) or fructose-fed rats (1.45 +/- 0.2). Thus, the accumulation of phosphorylated tau may be due to the decrease in the interstitial fluid clearance that may result from the redistribution of aquaporin-4 channels from the astrocytic endfeet surrounding the blood-brain barrier to the astrocytic cell bodies.

Disclosures: P. Woller: None. **J.K. Morris:** None.

Poster

741. Metabolism, Stress, and Brain Wellness

Location: Hall A

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Program #/Poster #: 741.19/C53

Topic: C.01. Brain Wellness and Aging

Title: Association of improved metabolic state and behavior in long-lived DGAT1-deficient mice

Authors: R. D. CARTER[1], L. LINQUEST[1], B. A. GRUETER[3], ***C. A. GRUETER**[2]; [2]Anesthesiol., [1]Vanderbilt Univ. Med. Ctr., Nashville, TN; [3]Anesthesiol., Vanderbilt Univ. Sch. of Med., Nashville, TN

Abstract: Lipids are recognized as signaling molecules that have the capacity to trigger profound physiological responses in processes of the central nervous system (CNS). Imbalances in lipid signaling networks may contribute to the pathogenesis of multiple disease states including obesity- and aged- related neuropsychiatric (stress) disorders. Evidence suggests that lipids, particularly triglycerides (TG, frequently elevated in obese and aged subjects), directly affect both energy homeostatic and reward processes by modulating hypothalamic and striatal circuits, respectively. Pathways of TG metabolism can provoke a complexity of cellular responses, depending on the metabolic state of the organism. Mice lacking the triglyceride

synthesis enzyme acyl CoA:diacylglycerol acyltransferase 1 (DGAT1) are long-lived, living 25% (mean) longer than controls, and are protected from age-related increases in body fat, tissue triglycerides, and inflammation. We hypothesized that leanness, with a concomitant improvement in the metabolic state of the organism, also protects against age-related changes in cognitive function and stress behaviors. Our findings suggest that *Dgat1*-deficient mice provide a model of leanness and extended longevity which can be utilized to enhance the understanding of the interaction between the metabolic state of an organism, cognition, and behavior.

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Poster

741. Metabolism, Stress, and Brain Wellness

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 741.20/C54

Topic: C.01. Brain Wellness and Aging

Title: Nature-inspired hybrids as multi-target pharmacological agents: Antioxidant, neuroprotective and anti-inflammatory entanglement

Authors: F. FAGIANI[1], M. CATANZARO[2], M. M. SERAFINI[3], I. ROMANONI[2], F. BASAGNI[4], M. RACCHI[2], B. VIVIANI[3], R. MICHELA[4], S. GOVONI[2], *A. PITTALUGA[5], C. LANNI[2];
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Abstract: Nature offers a wide chemical diversity and provides a great source of therapeutics. By combining molecular fragments deriving from garlic and curcumin, we synthesized new nature-inspired hybrids targeting the nuclear factor (erythroid-derived 2)-like 2 (Nrf2)-pathway. Since data from literature suggest that several natural compounds exhibit antioxidant, neuroprotective and anti-inflammatory activities, we tested whether our molecules exert such effects in a view of multi-target pharmacological agents. To determine the potential interest of our hybrids as antioxidants, we investigated their protective effects against H_2O_2-induced oxidative damage and evaluated their potency in comparison to two reference molecules activating Nrf2, curcumin and dimethyl fumarate (DMF). The scavenging effect on reactive oxygen species (ROS) was evaluated by DCF-DA assay to quantify the intracellular ROS production. The expression of proteins involved in the antioxidant phase II response was examined by RT-PCR and Western Blotting (WB). To evaluate whether our molecules are capable to exert a neuroprotective action by modulating the brain-derived neurotrophic factor

(BDNF) levels, BDNF protein content was assessed by WB and its RNA expression byRT-PCR. Then, we compared the effects of our hybrids on BDNF content to curcumin, a reference molecule known to significantly increase it. Finally, to investigate the anti-inflammatory potential of our molecules, we investigated their protective effect against inflammatory response, induced by lipopolysaccharide (LPS), and compared their efficacy to curcumin. The anti-inflammatory action was determined by RT-PCR and ELISA test to assess the modulation in the expression and release of pro-inflammatory cytokines such as tumor necrosis factor-α and interleukin-8. Our results suggest that the hybrids protect against oxidative damage and affect the antioxidant response by modulating Nrf2 and its main targets. In addition, the hybrids exert antioxidant effects more actively than curcumin and DMF. Furthermore, a significant increase both in BDNF protein amount and mRNA expression was observed upon treatment with the hybrids. Moreover, the molecules significantly suppressed the LPS-induced increases in mRNA expression as well as the release of pro-inflammatory cytokines, with a higher potency compared to curcumin. Overall, our data demonstrate that our molecules exhibit antioxidant, neuroprotective and anti-inflammatory properties and provide evidence of their therapeutic potential as agents counteracting oxidative stress, neurodegeneration and inflammation by affecting the neuro-glial environment.

Disclosures: **F. Fagiani:** None. **M. Catanzaro:** None. **M.M. Serafini:** None. **I. Romanoni:** None. **F. Basagni:** None. **M. Racchi:** None. **B. Viviani:** None. **R. Michela:** None. **S. Govoni:** None. **A. Pittaluga:** None. **C. Lanni:** None.

Poster

741. Metabolism, Stress, and Brain Wellness

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 741.21/C55

Topic: C.01. Brain Wellness and Aging

Support: NIA Grant R01- AG052606
NIA Grant T32- AG052363

Title: Effects of chronic rapamycin on substantia nigra dopamine neurons in aging mouse brain

Authors: *I. PARIKH[1], M. TRZECIAK[1], M. J. BECKSTEAD[2];
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Abstract: The aged population of the world is expected to more than double by 2050. Age related differences have been described in the context of neurodegeneration and cognitive decline; however, alterations that contribute to age-related motor deficits are less well understood. Dopamine neurons of the substantia nigra are necessary for the initiation of movement and are believed to decline in function with normal aging. Here we used rapamycin, a

life-extending intervention that inhibits the mammalian target of rapamycin (mTOR), to study the role of dopaminergic signaling in aging mice. We performed an electrophysiological and morphological comparison of substantia nigra dopaminergic neurons in which mTOR signaling was decreased by treatment with rapamycin. Female and male of 22 month old age mice were treated with control diet, low rapamycin (14ppm) diet, or high rapamycin (42ppm) diet for 16 weeks. Using whole cell voltage-clamp recordings, we found that low and high rapamycin treatment increased the amplitude of the HCN channel-mediated hyperpolarization-activated cation current I(h) when compared to control group. There were no obvious effects of rapamycin on spontaneous firing or pacemaking of dopamine neurons. Since mTOR also regulates neuronal growth and dendrite formation, we also conducted a detailed morphometric analysis of dopaminergic neurons by filling cells with neurobiotin and performing confocal imaging. Neurons from rapamycin-treated mice showed an increase in both soma size and neuritic branching consistent with returning to a younger phenotype. We also correlated electrophysiological and morphological measures to previously-obtained open-field locomotion in individual mice. Our findings suggests that some of the positive effects of rapamycin on healthspan could be due to the improvement of structural and functional parameters in single dopamine neurons in the substantia nigra.

Disclosures: I. Parikh: None. **M. Trzeciak:** None. **M.J. Beckstead:** None.

Poster

741. Metabolism, Stress, and Brain Wellness

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 741.22/C56

Topic: C.01. Brain Wellness and Aging

Support: AHA17SDG33410366
HL-093554
U54GM104940

Title: Sexual disparities of mitochondria-associated proteins in rat brain micro-vessels: Using tandem-mass-tags to elucidate metabolic phenotypes

Authors: S. CIKIC[1], P. K. CHANDRA[1], I. RUTKAI[1], J. C. HARMAN[2], J. J. GUIDRY[2], P. V. G. KATAKAM[1], *D. W. BUSIJA[1];
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Abstract: Adverse changes in small cerebral blood vessels due to aging promote cognitive impairment, strokes, vascular dementia, and Alzheimer’s disease. The frequency and severity of these diseases, age of onset, and underlying mechanisms differ between men and women. The

mechanisms underlying cerebral micro-vessel (MV) diseases are not fully known but mitochondria in endothelium appear to play pivotal roles. In this study, we assessed the sex-dependent differential expression of mitochondria-related proteins in cerebral MVs, isolated from young male and female Sprague-Dawley rats. MVs with diameter < 70 μm were used to perform a 3-vs-3 quantitative-multiplexed experiment utilizing Tandem-Mass-Tags, coupled with Liquid Chromatography Mass Spectrometry (LC/MS). MVs were homogenized in a 1% SDS solution. Then MS sample prep was performed utilizing an offline fractionation procedure. MS data and bioinformatic analyses were performed using Thermo Fisher Proteome Discoverer version 2.2., and Panther Gene Ontology and Ingenuity Pathway Analysis, respectively. Simple Wes was used for validation of proteins of interest. Protein-Protein Enrichments/Interactions were analyzed to determine the top canonical and signaling cascades involved. Our dataset identified a total of 1,969 proteins, of which, 1,871 were quantified through the use of TMT labels. 64 proteins were found to be significantly ($p<0.05$) higher expressed in female samples compared with males. In general, males exhibited more mitochondria-destructive proteins. Overexpression of one of the pentraxins in male MVs might influences the translocation of proapoptotic proteins to the mitochondria. Increased expression of a monocarboxylate transporter and its chaperon protein in male MVs might be indicative of the inhibition of glycolysis, impaired oxidative phosphorylation, and/or reduced anaplerosis. Conversely, females expressed more mitochondrial membrane proteins, anti-oxidant enzyme proteins, and those involved in use of beta oxidation. Here we present the first comparison of brain MVs and characterize sexually dimorphic mitochondrial proteins. The top 5 canonical pathways that exhibit sex-based differences are mitochondrial dysfunction, oxidative phosphorylation, sirtuin signaling, TCA cycle, and EIF2 signaling. Our preliminary results suggest there are a considerable number of mitochondria-associated proteins enriched within MVs, many of which differ by sex. Overall, female rats appear to have more anti-inflammatory/pro-healing proteins associated with mitochondrial activity than their male counterparts.

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Poster

741. Metabolism, Stress, and Brain Wellness

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 741.23/C57

Topic: C.01. Brain Wellness and Aging

Title: Analysis of kynurenine pathway metabolism in C6 malignant glioma cells

Authors: *G. I. VÁZQUEZ CERVANTES[1], B. PINEDA OLVERA[2], D. F. GONZALEZ ESQUIVEL[1], V. PEREZ DE LA CRUZ[1];

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Abstract: The kynurenine pathway (KP) is the major route of tryptophan catabolism. The intermediary products of the KP have been described as relevant molecules of brain physiology playing important roles in neurodegenerative diseases, regulation of inflammation and immune response. Most recently, expression levels of indoleamine 2,3-dioxygenase (IDO), the rate limiting enzyme of the KP have been associated with the aggressiveness of some types of cancer including glioblastoma multiforme (GBM). GBM stands as the most frequent and the most aggressive of the primary brain tumors with a survival median ranging between 13 to 15 months despite of the conventional treatments. Immunosuppressive mechanisms exerted by GBM cells allow tumors to reach their growth rate and invasiveness. In this study we explored the KP metabolism in C6 cell line. $1^{x}10^{5}$ C6 cells and primary astrocytes were incubated with 100 µM tryptophan (Trp) or L-kynurenine (L-KYN) for 2h at 37 °C. After the incubation period kynurenic acid (KYNA), 3hydroxykynurenine (3-HK) and L-KYN levels were determined by HPLC. Astrocytes and C6 cells were not able to metabolize Trp. However, C6 cells metabolized 70% more L-KYN than astrocytes. KYNA levels were higher in astrocytes compared to C6 cells. 3-HK production was not detectable in astrocytes but was present in C6 cells. KAT II activity was higher in C6 cells vs. astrocytes. KMO expression was present in C6 cells but not in astrocytes, which correlated with the activity of KMO found in C6 cells. These data suggest that C6 cells show a KP metabolism different to the astrocytes primary culture, which can be related to alteration with the immune and metabolic reprogramming C6 cells.

Disclosures: G.I. Vázquez Cervantes: None. **B. Pineda olvera:** None. **D.F. Gonzalez esquivel:** None. **V. Perez De La Cruz:** None.

Poster

741. Metabolism, Stress, and Brain Wellness

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 741.24/C58

Topic: C.01. Brain Wellness and Aging

Support: Fundamental Research Grant Scheme (FRGS) of the Ministry of Education Malaysia (Grant No. FRGS/2/2013/SKK01/UKM/03/4).

Title: Effects of age on feeding response: Focus on the rostral C1 neuron and its glucoregulatory proteins

Authors: H. RAMLAN, ***H. A. DAMANHURI**;
Dept. of Biochemistry, Fac. of Med., The Natl. Univ. of Malaysia, Kuala Lumpur, Malaysia

Abstract: Older people are likely to develop the anorexia of aging. Previous research has shown rostral C1 (rC1) neurons in rostral ventrolateral medulla (RVLM) are responsible for the regulation of food intake. This study aims to determine the effect of age on the function of rostral C1 (rC1) neurons in mediating the feeding response. Male Sprague Dawley rats at 3-months (n=46) and 24-months (n=46) old were used and further divided into two subgroups; 1) treatment group with 2-deoxy-D-glucose (2DG) and 2) vehicle group. Feeding hormones such as cholecystokinin (CCK), ghrelin and leptin were analysed by enzyme-linked immunosorbent assay (ELISA). Rat brain was carefully dissected to obtain the brainstem RVLM region. Further analysis was carried out to determine the level of proteins and genes in RVLM that were associated with the feeding pathway. Protein expression of tyrosine hydroxylase (TH), phosphorylated TH at Serine40 (pSer40TH), AMP-activated protein kinase (AMPK), phosphorylated AMPK (phosphoAMPK) and neuropeptide Y Y5 receptor (NPY5R) were determined by western blot. Expression of TH, AMPK, and NPY genes were determined by real-time PCR. The localization of TH, AMPK, and NPY5R within the brainstem area were determined by the double immunofluorescence staining. This study showed that blood glucose level was elevated in young and old rats following 2DG administration. Plasma CCK-8 concentration was higher in the aged rats at basal and increased with 2DG administration in young rats, but the leptin and ghrelin showed no changes. Aging decreased AMPK-positive TH neurons. Old rats showed higher TH and lower AMPK mRNA levels. Glucoprivation decreased AMPK mRNA level in young rats and decreased TH mRNA in old rats. Aged rC1 neurons showed a higher NPY5R protein level. Following glucoprivation, rC1 neurons produced distinct molecular changes across age in which, in young rats, AMPK phosphorylation level was increased, and in old rats, TH phosphorylation level was unchanged. These findings suggest that glucose-counterregulatory responses by rC1 neurons contribute to the ability of young and old rats in coping glucoprivation. Age-induced molecular changes within rC1 neurons may attenuate the glucoprivic responses. This situation may explain the impairment of feeding response in the elderly.

Disclosures: **H. Ramlan:** None. **H.A. Damanhuri:** None.

Poster

741. Metabolism, Stress, and Brain Wellness

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 741.25/C59

Topic: C.01. Brain Wellness and Aging

Support: NIA 1R21NS108138
SLU Start-up Funds Dr. Xu

Title: Treatment with exogenous adropin peptide improves age-related cognitive decline and neuronal health

Authors: *S. A. FARR[1], F. XU[2], M. L. NIEHOFF[3], R. JAYANTH[5], B. A. MERSMAN[6], A. A. BUTLER[4];
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Abstract: There is a clear, unmet need for developing new therapies against the neurodegenerative processes causing dementia, of which AD is the most prevalent. However, few treatment options are available for treating AD and other forms of dementia. Drugs approved for AD, and many in the development pipeline, are 'disease modifiers' that target neurotransmitters. For example, cholinesterase inhibitors (AChEI: donepezil, galantamine and rivastigmine) increase acetylcholine signaling and the N-methyl-D-aspartate-receptor antagonist memantine suppresses glutamatergic (excitatory) pathways. At best, these drugs either only produce modest improvements in cognition and daily activity or temporarily slow disease progression. They do not prevent progress of neurodegeneration and atrophy. Drugs affecting multiple target pathways may have a greater chance of producing significant delays in the progression of AD. Adropin is a natural neuropeptide that is expressed throughout the brain and high levels of expression are found in the hippocampus. We previously observed that transgenic C57/BL/6J (B6) mice over expressing adropin have delayed onset of cognitive deficits and reduced inflammation at 18 months of age compared to age matched controls. Here, we examined cognitive function of 18-month old male B6 mice administered adropin (90 nmol/kg by i.p. injection at 0900) for 4 wk. After two weeks of treatment mice were tested in T-maze, novel object recognition, activity and elevated plus maze. Aged C57/BL mice treated with adropin had improved learning and memory in T-maze ($P<0.0001$ in both acquisition and 1 week retention) and NOR with 24 hour delay ($P<0.05$), both hippocampal tasks. There were no differences in activity or anxiety between the two groups. To reveal the cellular mechanisms of adropin effects on hippocampus neurons, mouse hippocampal neurons were cultured in the absence or presence of adropin. Neurons treated with adropin exhibited a more robust neural development and network formation. In addition, acute addition of adropin to cultured neurons induced an increase in neuronal firing activity and elicited a rise in intracellular calcium. The positive effects of adropin on cognition and neural morphological development and functional network activity of hippocampal neurons indicate a positive role of adropin in learning and memory. These results suggest that adropin may be a potential drug treatment for age-related dementia.

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Poster

741. Metabolism, Stress, and Brain Wellness

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 741.26/C60

Topic: C.01. Brain Wellness and Aging

Support: National Research Foundation of Korea Grant NRF-2016R1A2B4014707
National Research Foundation of Korea Grant NRF-2017M3A9G2077568

Title: Etoposide induce mitochondrial dysfunction and cellular senescence in primary cultured rat astrocytes

Authors: *M. BANG, D. KIM, E. GONZALES, K. KWON, C. SHIN;
Konkuk Univ., Seoul, Korea, Republic of

Abstract: Brain aging is an inevitable process that is characterized by structural and functional changes and is a major risk factor for neurodegenerative diseases. Most brain aging studies are focused on neurons and less on astrocytes which are the most abundant cells in the brain and known to be in charge of various functions including the maintenance of brain physical formation, ion homeostasis, and secretion of various extracellular matrix proteins. Recent studies have reported that altered mitochondrial dynamics, defective mitophagy or mitochondrial damage led to mitochondrial dysfunction, which is linked to age-related disorders. In this study, we investigated mitochondrial dysfunction phenotypes in etoposide-induced astrocyte senescence model. Senescence-associated β-galactosidase (SA-β-gal) activity was used as a cellular senescence marker. Etoposide-treated astrocytes showed cellular senescence phenotypes including increased SA-β-gal-positive cells associated with increased nuclear size and senescence-associated secretory phenotypes (SASP) such as increased IL-6 expression. Decreased expression of cell cycle markers including phospho-H3/H3 and CDK2 were also observed as well as dysregulation of cellular functions which were observed in wound-healing, neuronal protection, and phagocytosis assays. Finally, mitochondrial dysfunction was noted through the determination of mitochondrial membrane potential using tetramethylrhodamine methyl ester (TMRM) and mitochondrial oxygen consumption rate (OCR) experiments. These data suggest that etoposide can induce cellular senescence and mitochondrial dysfunction in astrocytes which may play particular roles in brain aging and neurodegenerative conditions.

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Poster

741. Metabolism, Stress, and Brain Wellness

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 741.27/C61

Topic: C.01. Brain Wellness and Aging

Support: NSF 1515587

Title: A novel dynamic network imaging analysis method reveals aging-related fragmentation of cortical networks in mouse

Authors: *D. A. LLANO[1], C. MA[3], A. TAHERI[3], U. DI FABRIZIO[3], K. STEBBINGS[2], G. YUDINTSEV[2], R. V. KENYON[3], T. Y. BERGER-WOLF[3];
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Abstract: Network analysis of large-scale neuroimaging data has proven to be a particularly challenging computational problem. In this study, we adapt a novel analytical tool, known as community dynamic inference method (CommDy), which was inspired by social network theory, for the study of brain imaging data from a mouse model of presbycusis. CommDy has been successfully used in other domains in biology; this report represents its first use in neuroscience. We used CommDy to investigate aging-related changes in network structure in the auditory cortex using flavoprotein autofluorescence imaging. Analysis of spontaneous activations in the auditory cortex of slices as well as in vivo images of the motor cortex taken from young and aged animals demonstrated that cortical networks in aged brains were highly fragmented compared to networks observed in young animals. Specifically, the degree of connectivity of each activated node in the aged brains was significantly lower than those seen in the young brain, and multivariate analyses of all derived network metrics showed distinct clusters of these metrics in young vs. aged brains. CommDy network metrics from slice data were then used to build a random-forests classifier based on NMDA-receptor blockade data, which successfully recapitulated the aging findings. CommDy therefore provides a new dynamic network analytical tool to study the brain and provides links between network-level and synaptic-level dysfunction in the aging brain.

Disclosures: **D.A. Llano:** A. Employment/Salary (full or part-time):; University of Illinois at Urbana-Champaign, Carle Hospital. **C. Ma:** A. Employment/Salary (full or part-time):; University of Illinois at Chicago and Conversant LLC. **A. Taheri:** A. Employment/Salary (full or part-time):; University of Illinois at Chicago. **U. Di Fabrizio:** A. Employment/Salary (full or part-time):; University of Illinois at Chicago, BOOM Imagestudio. **K. Stebbings:** A. Employment/Salary (full or part-time):; MD Anderson. **G. Yudintsev:** A. Employment/Salary (full or part-time):; University of Illinois at Urbana-Champaign. **R.V. Kenyon:** A.

Employment/Salary (full or part-time):; University of Illinois at Chicago. **T.Y. Berger-Wolf:** A. Employment/Salary (full or part-time):; University of Illinois at Chicago.

Poster

741. Metabolism, Stress, and Brain Wellness

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 741.28/C62

Topic: C.01. Brain Wellness and Aging

Support: NIA Grant 1R15AG050292

Title: Assessment of central AMYR blockade in the regulation of peripheral versus central metabolism mechanisms in APP/PS1 mice

Authors: *R. R. CORRIGAN[1], J. GRIZZANTI[1], G. CASADESUS[2];
[1]Sch. of Biomed. Sci., [2]Biol. Sci., Kent State Univ., Kent, OH

Abstract: Metabolic dysregulation as in METS/T2D is a major risk factor for Alzheimer's disease development. Recent evidence highlights the potential therapeutic benefits of non-aggregating recombinant forms of the pancreatic hormone amylin in AD. However, whether these effects are mediated peripherally through the improvement of metabolic tone or centrally through direct amylin receptor (AMYR) activation is not known. Furthermore, conflicting evidence exists as to the benefits of AMYR agonism versus antagonism. To test this, APP/PS1 and wild-type littermate mice were chronically treated with amylin in the periphery under central inhibition of the amylin receptor using the AC187 antagonist delivered ICV. Here we show confirmatory data on the benefits of amylin on cognition and amyloid-beta pathology. Importantly, we also show that central delivery of AC187 impairs function and increases pathology; effects mitigated by peripheral administration of amylin. This is despite the ability of AC187 to regulate glucose tolerance; an aspect also normalized by peripheral delivery of amylin. Together our data demonstrate a potentially indirect mechanism, beyond AMYR activation, associated with therapeutic benefits of this drug while also identifying a potentially detrimental role of AMYR blockade in CNS function.

Disclosures: R.R. Corrigan: None. **J. Grizzanti:** None. **G. Casadesus:** None.

Poster

741. Metabolism, Stress, and Brain Wellness

Location: Hall A

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Program #/Poster #: 741.29/C63

Topic: C.01. Brain Wellness and Aging

Support: NIA-R15-AG0502920-01A1

Title: The influence of sex and metabolism on the development of Alzheimer's disease

Authors: *J. GRIZZANTI[1], R. R. CORRIGAN[1], S. SERVIZI[1], G. CASADESUS SMITH[2]; [1]Sch. of Biomed. Sci., [2]Biol. Sci., Kent State Univ., Kent, OH

Abstract: One of the most prominent risk factors for the development of AD is metabolic disease, particularly type II diabetes (T2D). However, to date, how T2D leads to the AD development is unclear. In addition, sex-differences in the development of both T2D and AD make the evaluation of these underlying mechanisms more difficult. As such, we aimed to discern the temporal development of AD under diet-induced METS/T2D in both sexes and in WT and the APP/PS1 AD mouse model. Our data demonstrate a male specific vulnerability to metabolic disease in both WT and AD genotypes that mimics that observed in humans and an acceleration of the AD phenotype in females. Full transcriptome sequencing was performed on 3, 6, and 9-month-old male and female WT and APP/PS1 mice and revealed interesting differences that may reflect the basis for the sexual dimorphism in metabolic disease and AD in addition to temporal changes in the expression of genes associated with AD development. These data will be validated to provide potential novel therapeutic targets.

Disclosures: J. Grizzanti: None. **R.R. Corrigan:** None. **S. Servizi:** None. **G. Casadesus Smith:** None.

Poster

742. Alpha-Synuclein Models and Mechanisms II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 742.01/C64

Topic: C.03. Parkinson’s Disease

Support: China Science Fund
Centre National de la Recherche Scientifiique

University of Bordeaux

Title: Characterization of Lewy bodies-induced neurodegeneration and synucleopathy in wild-type mice

Authors: *E. BEZARD[1], L. ZHANG[2], X. YU[2], X. SUN[2], W. ZHAO[2], M. WANG[2], X. LI[2], Y. ZHANG[2], T. ZHU[2], L. ZHOU[2], G. RAN[2], L. BREGER[1], S. DOVERO[1], M. PERSILLET[1], G. PORRAS[1], P.-O. FERNAGUT[1], B. DEHAY[1], C. QIN[2];
[1]Inst. of Neurodegenerative Dis., Bordeaux, France; [2]Inst. of Lab. Animal Sci., Beijing, China

Abstract: Neurodegenerative diseases, such as Parkinson's disease, Multiple System Atrophy or Dementia with Lewy Bodies (LB) are characterized by accumulation of misfolded α-synuclein proteins. Cell to cell spreading of misfolded proteins may be considered as a hallmark in Prion-like diseases. Using disease-specific aggregates, extracted from patient's post-mortem brains, the PRIPRO project aimed at elucidating the cellular commonalities and specificities, as well as temporo-spatial development of each pathology. The first part of this project was dedicated to the evaluation of the toxicity of LB extracts collected from different patients (patient-specific) or different brain regions (brain structure-specific), injected stereotactically into the substantia nigra of wild-type mice. The second part of the PRIPRO project aimed at assessing the infectious nature of these pathological inclusions, using parabiotic pairing of wild-type mice. In both experiments, animals were sacrificed 4 months after stereotaxic surgery. Their brains were fixed and processed for immune-histological analysis. Similarities and differences between the pathologic triggers are evaluated in relation to: (i) the extent of the induced lesion in the nigrostriatal pathway, and (ii) the extent of synucleinopathy, focusing notably on phosphorylated-α-synuclein at Ser129. Our results suggest that Lewy Bodies collected from different brain areas do not yield the same extent of neurodegeneration, thus calling for a thorough differential characterization of the specific synuclein species present in post-mortem extracts collected from different patients and different brain regions.

Disclosures: **E. Bezard:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Motac Holding, Treefrog Therapeutics. F. Consulting Fees (e.g., advisory boards); Motac neuroscience. **L. Zhang:** None. **X. Yu:** None. **X. Sun:** None. **W. Zhao:** None. **M. Wang:** None. **X. Li:** None. **Y. Zhang:** None. **T. Zhu:** None. **L. Zhou:** None. **G. Ran:** None. **L. Breger:** None. **S. Dovero:** None. **M. Persillet:** None. **G. Porras:** None. **P. Fernagut:** None. **B. Dehay:** None. **C. Qin:** None.

Poster

742. Alpha-Synuclein Models and Mechanisms II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 742.02/C65

Topic: C.03. Parkinson's Disease

Support: LABEX BRAIN

Title: Sleep/wake activity in the Lewy bodies mouse model of Parkinson's disease

Authors: *G. PORRAS[1], **M. PERSILLET**[2], F. DECOEUR[3], B. DEHAY[2], A. NADJAR[3], E. BEZARD[2];
[1]Motac, Manchester, United Kingdom; [2]Inst. of Neurodegenerative Dis., Bordeaux, France; [3]Univ. of Bordeaux, Bordeaux, France

Abstract: Parkinson's disease (PD) is characterized by the loss of dopaminergic (DA) neurons of the substantia nigra pars compacta (SNc) and the presence of cytoplasmic inclusions named Lewy Bodies (LB) containing notably misfolded alpha-synuclein (α-syn). Although primarily a movement disorder, PD patients exhibit a myriad of non-motor symptoms. Sleep/wake alterations, such as rapid-eye movement (REM) sleep behavioral disorder (RBD), REM loss or increased day time sleepiness, may occur in the prodromal phase of PD. They are even considered as predictors of PD. While neurotoxin-based experimental models recapitulate both motor and non-motor symptoms, their poor face validity with regard to the neurodegenerative process make them unsuitable for investigating the likelihood of a relationship between progression of neurodegeneration, progression of the α-syn pathology and occurrence of sleep/wake issues. We here take advantage of the recently developed LB mouse model of parkinsonian degeneration to investigate the potential occurrence of sleep/wake deficits as the pathology develops. Wild-type mice were injected with LB, containing pathological α-syn, extracted from the brain of PD patients leading to a progressive loss of DA neurons (LB mice). Control mice were injected with a fraction devoid of aggregated α-syn, extracted from the same patients (NoLB mice). Mice were implanted with a device recording both cortical neuronal activity (ElectroEncephaloGraphy, EEG) and neck muscles contractions (ElectroMyoGraphy, EMG) enabling the discrimination of sleep/wake cycle stages: wake, non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep. Recording sessions were performed once a month for 48h over a 4-month period. Alteration of the sleep/wake cycles are detailed in both LB and NoLB mice with an emphasis put upon the changes in power band frequencies. Understanding if sleep disorders may serve experimentally as a surrogate marker of neurodegeneration or pathology progression could provide a way of early detection and lead to new therapeutic strategies to slow down its progression.

Disclosures: **G. Porras:** A. Employment/Salary (full or part-time):; Motac neuroscience. **M. Persillet:** None. **F. Decoeur:** None. **B. Dehay:** None. **A. Nadjar:** None. **E. Bezard:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Motac Holding. F. Consulting Fees (e.g., advisory boards); Motac neuroscience.

Poster

742. Alpha-Synuclein Models and Mechanisms II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 742.03/C66

Topic: C.03. Parkinson's Disease

Support: Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No. 116060 (IMPRiND)

Title: High content screening of synucleinopathy in primary cortical neurons: Dissecting out the interplay between the basic synuclein pools

Authors: *W. MEISSNER, F. DE GIORGI, E. BEZARD, F. ICHAS;
Inst. of Neurodegenerative Dis., Bordeaux, France

Abstract: We set up a robust 96-well High Content Screening assay of synucleinopathy in primary cultures of cortical neurons. The initiation and spread of synucleinopathy in primary cultures of cortical neurons can be achieved by treating the latter with preformed fibrillar assemblies of recombinant synuclein (PFFs) and appreciated by immunofluorescence (IF) imaging. However, several barriers have slowed the adoption of this type of assay for screening purposes: (i) the ease and reliability of the isolation and culture protocols capable to insure long term survival (>21 DIV) of primary cortical neurons in a 96 well culture format, (ii) the batch-to-batch variability of artificial recombinant PFFs in terms of bioactivity, (iii) the relative lack of characterization of the anti-synuclein antibodies for a specific use in non-denaturing conditions such as IF imaging, and (iv) the absence of dedicated image analysis routines best serving the characterization of synucleinopathy in 2D neuronal cultures. We worked at raising specifically these 4 barriers by designing novel standard operating procedures and came up with a standardized assay system exploiting automation. The base High Content Screening assay was developped for WT mouse cortical neurons cultured in 96 well plates and challenged with specific human recombinant synuclein PFFs batches. In a first phase, the extent of synucleinopathy was quantified by imaging phosphorylated synuclein at S129. This assay was characterized by a Z' factor >0.5, and was thus successfully generalized to the other key basic synuclein pools (unstructured and alpha-helical monomeric, alpha-helical multimeric, and beta-strand oligomeric & fibrillar), as well as the study of the uptake and fate kinetics of the added PFFs. The assay was also successfully transposed to primary cortical cultures of transgenic mice and to primary cortical cultures transduced using AAV infections. In conclusion, these different assays can be routinely used to characterize the bioactivity of test-compounds.

Disclosures: W. Meissner: None. **F. De Giorgi:** None. **E. Bezard:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding

diversified mutual funds); Motac Holding, Treefrog Therapeutics. F. Consulting Fees (e.g., advisory boards); Motac neuroscience. **F. Ichas:** None.

Poster

742. Alpha-Synuclein Models and Mechanisms II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 742.04/C67

Topic: C.03. Parkinson's Disease

Support: MJFF 2013-8499

Title: GCI-induced neurodegeneration and synucleinopathy in non-human primates

Authors: M. TEIL[1], S. DOVERO[1], M.-L. AROTCARENA[1], M. BOURDENX[1], S. CAMUS[1], G. PORRAS[1], M.-L. THIOLAT[1], N. KRUSE[2], B. MOLLENHAUER[2], I. TRIGO DAMAS[3], C. ESTRADA[4], N. GARCIA CARRILLO[5], M. TRINIDAD HERRERO EZQUERRO[4], P. DERKINDEREN[6], M. VILA[7], J. OBESO[3], *B. DEHAY[1], E. BEZARD[1];
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Abstract: Aggregation of alpha-synuclein has been implicated in several neurodegenerative diseases, termed synucleinopathies, which include Parkinson's Disease (PD), Dementia with Lewy Bodies (DLB) and Multiple System Atrophy (MSA). These synucleinopathies are characterized by the deposit of alpha-synuclein aggregates in intracellular inclusions in neurons and/or glial cells. Unlike in PD and DLB, where these aggregates are located predominantly in neurons, MSA is associated with cytoplasmic inclusions of alpha-synuclein in oligodendrocytes. These glial cytoplasmic inclusions (GCIs) are the pathological hallmarks of MSA and are associated with neuroinflammation, demyelination and, ultimately, neurodegeneration. This study aimed at determining the potential to induce MSA pathology in non-human primates. To this end, we inoculated MSA-derived GCI fractions into the striatum of baboon monkeys that were terminated 2 years later. Extensive histochemical and biochemical analyses were performed on the whole brain and biological fluids to evaluate pathological markers known to be affected in MSA. We characterized the pattern of dopaminergic loss in the striatum and in the substantia nigra, the regional distribution of α-synuclein immunoreactivity in several brain structures (i.e.

within hippocampus, striatum, substantia nigra, and cortex), as well as its pathological state (i.e. S129 phosphorylation) and occurrence of intracellular inclusion formation, neuroinflammation and demyelination. Overall, we observed region-specific alterations in several brain areas related to MSA pathology. In conclusion, this study provides a potential new non-human primate model for MSA research.

Disclosures: **M. Teil:** None. **S. Dovero:** None. **M. Arotcarena:** None. **M. Bourdenx:** None. **S. Camus:** None. **G. Porras:** None. **M. Thiolat:** None. **N. Kruse:** None. **B. Mollenhauer:** None. **I. Trigo Damas:** None. **C. Estrada:** None. **N. Garcia Carrillo:** None. **M. Trinidad Herrero Ezquerro:** None. **P. Derkinderen:** None. **M. Vila:** None. **J. Obeso:** None. **B. Dehay:** None. **E. Bezard:** None.

Poster

742. Alpha-Synuclein Models and Mechanisms II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 742.05/C68

Topic: C.03. Parkinson's Disease

Support: University of Bordeaux
Centre National de la Recherche Scientifique
LABEX BRAIN

Title: Potential for weighting fibroblasts as a diagnostic tool in Parkinson's disease

Authors: G. PREVOT[1], *S. DOVERO[2], E. BEZARD[2], L. COGNET[4], B. DEHAY[3], P. BON[5]; [1]Inst. of Neurdegenerative Dis. UMR5293, Bordeaux, France; [2]Inst. of Neurodegenerative Dis., Bordeaux, France; [3]Inst. of Neurodegenerative Dis., Bordeaux Cedex, France; [4]CNRS - Univ. of Bordeaux, Bordeaux - Talence, France; [5]Optic Inst., Talence, France

Abstract: The search for diagnostic and/or progression surrogate biomarkers is of paramount importance. Skin fibroblasts retain specific environmental and aging history of patient making them a suitable model, reflecting the disease status and progression. Previous studies have studied alterations in growth, morphology and mitochondrial function in Parkinson's disease skin fibroblast. Here we measured the dry of fibroblasts from several pathologies using state-of-the-art phase microscopy.To determine the dry mass of fibroblasts obtained from apparently healthy individuals and patients, fibroblasts were obtained from biopsy of patients suffering from Parkinson's disease (genetic or sporadic cases), Huntington's disease, epilepsy, Rett syndrome, cystic fibrosis or familial adenomatous polyposis and cultured. A label-free technique, the quantitative phase microscopy using Quadriwave Lateral Shearing Interferometry, was used to allow a high-sensitivity observation of living fibroblasts and to determine their dry mass[2]. We detected changes in morphology and in dry mass according to disease-related fibroblasts.

Strikingly, we observed that Parkinson's disease fibroblasts mass was statistically very different from control fibroblasts mass.These data suggest that the variations in dry mass of skin fibroblasts may reflect molecular changes associated to a given pathological status.

Disclosures: **G. Prevot:** None. **E. Bezard:** None. **L. Cognet:** None. **B. Dehay:** None. **S. Dovero:** None. **P. Bon:** None.

Poster

742. Alpha-Synuclein Models and Mechanisms II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 742.06/C69

Topic: C.03. Parkinson's Disease

Support: United States of America Department of Defense Congressionally Directed Medical Research Programs Early Investigator Award (W81XWH1810233:PD170100)

Title: Genetic signature of early synucleinopathy in nigrostriatal dopamine neurons

Authors: *J. R. PATTERSON[1], C. J. KEMP[1], J. W. HOWE[1], M. F. DUFFY[1], A. C. STOLL[1], K. M. MILLER[1], J. S. BECK[1], S. E. COUNTS[1], K. C. LUK[2], C. E. SORTWELL[1]; [1]Michigan State Univ., Grand Rapids, MI; [2]Univ. of Pennsylvania, Philadelphia, PA

Abstract: Early phases of synucleinopathies, such as Parkinson's disease (PD), have been difficult to study as animal models often fail to recapitulate the protracted progression from inclusion formation and accumulation to neurodegeneration. The alpha-synuclein (a-syn) preformed fibril (PFF) synucleinopathy model in rats, however, exhibits distinct and predictable stages throughout the progression of the synucleinopathy. With the current parameters used in the PFF model, the number of phosphorylated a-syn (pSyn) inclusion-containing neurons in the substantia nigra pars compacta (SNpc) peaks between 1 and 2 months after injection. During this time, dopamine transporter (DAT) binding decreases in the axon terminal region of the nigrostriatal dopamine neurons (striatum) long before approximately 50% of TH-immunoreactive (TH-ir) SNpc neurons are lost by 6 months. In the present study, we leverage the pretoxic synucleinopathy stage to identify the genetic signature associated with early synucleinopathy in the SNpc.
Three-month-old male and female Fischer 344 rats received unilateral, intrastriatal injections of 16 total μg of sonicated mouse α-syn PFFs or an equal volume of vehicle (phosphate buffered saline). At 1 and 2 months post-injection, animals were perfused with saline, brains removed and flash frozen. Frozen sections (20 μm thick) from the SNpc were collected and rapidly immunolabeled for either TH or pSyn. Laser capture microdissection (LCM) was used to collect TH-ir neurons from vehicle-injected rats or pSyn-ir neurons from PFF-injected rats. Genomic

DNA was removed, total RNA isolated, and ribosomal RNA removed prior to pre-amplification and library preparation performed for RNA sequencing (RNASeq).
RNASeq results are pending and will be presented at the meeting. The goal of the sequencing is to identify novel genes and pathways associated with early synucleinopathy, preceding neurodegeneration, that may identify targets for genetic or pharmaceutical intervention to prevent or slow neurodegeneration.
Research was supported by United States of America Department of Defense Congressionally Directed Medical Research Programs Early Investigator Award (W81XWH1810233:PD170100)

Disclosures: J.R. Patterson: None. **C.J. Kemp:** None. **J.W. Howe:** None. **M.F. Duffy:** None. **A.C. Stoll:** None. **K.M. Miller:** None. **J.S. Beck:** None. **S.E. Counts:** None. **K.C. Luk:** None. **C.E. Sortwell:** None.

Poster

742. Alpha-Synuclein Models and Mechanisms II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 742.07/C70

Topic: C.03. Parkinson's Disease

Support: NIH Grant NS099416 (CES)

Title: Longitudinal PET imaging reveals early and progressive deficits in striatal dopaminergic transmission induced by synucleinopathy

Authors: *C. E. SORTWELL[1], J. R. PATTERSON[1], C. J. KEMP[1], K. M. MILLER[1], A. C. STOLL[1], K. C. LUK[2], V. SOSSI[3];
[1]MIchigan State Univ., Grand Rapids, MI; [2]Univ. of Pennsylvania, Philaldelphia, PA; [3]Univ. of British Columbia, Vancouver, BC, Canada

Abstract: We have previously optimized and characterized the magnitude of phosphorylated a-syn (pSyn) accumulation and nigrostriatal degeneration following intrastriatal injection of a-syn preformed fibrils (PFFs) into rats using immunohistochemical methods. Peak pSyn accumulation in the ipsilateral substantia nigra pars compacta (SNpc) occurs within 2 months with no associated loss of tyrosine hydroxylase immunoreactive (THir) SNpc neurons at this time point. Within 4 months post injection significant loss of ipsilateral THir SNpc neurons occurs (~35%) that progresses to ~50% degeneration by 6 months. In the present study we sought to examine the impact of a-syn PFF injections on dopamine transporter (DAT) binding and dopamine (DA) synthesis in the striatum using positron emission tomography (PET). Male Fischer 344 rats were injected unilaterally to the striatum with either a-syn PFFs or an equal volume of saline/site as a control condition. PET scans with both [18F] fluoro-3,4-dihydroxyphenyl-Lalanine (FDOPA: DA synthesis, storage and turnover) and 11C-methylphenidate (^{11}C-MP for DAT: DAT density)

were conducted at 2, 4 and 6 months post surgery. ^{11}C-MP PET revealed significant decreases in DAT binding in the ipsilateral striatum at 2, 4 and 6 months compared to controls. Within PFF injected rats, DAT binding reduction in the ipsilateral striatum progressed significantly over the course of 6 months. FDOPA imaging revealed progressive deficits in DA synthesis/storage in the ipsilateral striatum. DA distribution volume (EVDR - reflects DA release) was significantly reduced (suggesting an increase in DA turnover) at 2, 4 and 6 months compared to controls with reductions progressing over time. The largest magnitude of decrease was observed for DAT binding, followed by EDVR and DA synthesis/storage (~ 35%, 62% and 84% of controls at 6 months).These results provide the first *in vivo* evidence that a-syn inclusion-bearing nigrostriatal neurons undergo early axonopathy and degenerative changes in dopamine transmission prior to overt degeneration. The magnitude of FDOPA and ^{11}C-MP reductions resulting from PFF-induced synucleinopathy recapitulates the progression observed in early Parkinson's disease subjects. In addition, the relative reduction in DAT binding, DA effective distribution volume and DA synthesis and storage follows the same rank order as observed in humans, with DA synthesis being relatively preserved. This external PET validation of the progression of a-syn PFF induced nigrostriatal degeneration will facilitate preclinical assessment of novel disease-modifying therapies.

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Poster

742. Alpha-Synuclein Models and Mechanisms II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 742.08/C71

Topic: C.03. Parkinson's Disease

Support: NS099416

Title: Intrastriatal injection of alpha-synuclein preformed fibrils in rats results in motor and non-motor impairments

Authors: *S. M. FLEMING[1], J. R. PATTERSON[2], C. J. KEMP[2], K. M. MILLER[2], A. C. STOLL[2], M. F. DUFFY[2], D. E. HERMAN[1], K. C. LUK[3], C. E. SORTWELL[2];
[1]Pharmaceut. Sci., Northeast Ohio Med. Univ., Rootstown, OH; [2]Translational Sci. and Mol. Med., Michigan State Univ., Grand Rapids, MI; [3]Dept of Pathology and Lab. Med., Univ. Pennsylvania, Philadelphia, PA

Abstract: The ideal animal model of Parkinson's disease (PD) should exhibit alpha-synuclein (a-syn) pathology, protracted degeneration of the nigrostriatal system and detectable sensorimotor impairments that result in a reproducible time course and magnitude. We have

previously optimized and characterized the magnitude of phosphorylated a-syn (pSyn) accumulation and nigrostriatal degeneration following intrastriatal injection of a-syn preformed fibrils (PFFs) into rats using immunohistochemical methods. Peak pSyn accumulation in the ipsilateral substantia nigra pars compacta (SNpc) occurs within 2 months with no associated loss of tyrosine hydroxylase immunoreactive (THir) SNpc neurons at this time point. Within 4 months post injection, significant loss of ipsilateral THir SNpc neurons occurs (~35%). By 6 months PFF-induced degeneration progresses to ~50% and is accompanied by modest deficits in contralateral forelimb use. In the present study we sought to examine the effect of increased striatal distribution and injection quantity of a-syn PFFs on sensorimotor and non-motor function related to PD. Male Fischer 344 rats were injected unilaterally in the striatum with a total of 24μg a-syn PFFs into 3 sites or an equal volume of saline as a control condition. Sensorimotor function was assessed using a battery of behavioral tests sensitive to varying degrees of SNpc neurodegeneration. Non-motor testing included assays for olfaction, emotional reactivity, and cognitive function. At 6 months post injection, PFF rats displayed significant movement and somatosensory asymmetries compared to control rats. Time to initiate a forelimb step and time to contact an adhesive stimulus on the forepaw were significantly longer for the contralateral limb compared to the ipsilateral limb. Further, hindlimb stepping in the cylinder was significantly reduced in PFF-injected rats compared to controls. Cognitive function was also affected in the PFF rats, with investigation time significantly decreased in an object recognition test. Levodopa reversibility and stereological analysis of SNpc degeneration are ongoing. Establishment of a-syn PFF surgical parameters resulting in motor and non-motor deficits will facilitate preclinical assessment of novel disease-modifying therapies.

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Poster

742. Alpha-Synuclein Models and Mechanisms II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 742.09/C72

Topic: C.03. Parkinson’s Disease

Support: Industrial Postdoc, Innovation Fund Denmark

Title: A model system in primary neurons used to identify new targets modulating seed-induced alpha-synuclein pathology using siRNA-based screening

Authors: *M. AMBJORN, N. DAMSGAARD, M. LUBAS, K. FOG;
Proteinopathy, Neurosci., H Lundbeck A/S, Valby, Denmark

Abstract: Synucleinopathies incl. Dementia with Lewy bodies and Parkinson's disease are characterized by the presence of inclusions rich in phosphorylated α-synuclein and ubiquitin (Goedert M. et al., JPD, 7 (2017) S51–S69 and Sampathu D.M. et al., Am J Pathol. 2003 Jul;163(1):91-100). Evidence suggest that pathological α-synuclein species may be released from neurons to seed aggregation in adjacent cells thereby propagating disease progression (Goedert M et al, 2017). To find new targets modulating disease progression it is important to build assays recapitulating relevant aspects of human PD pathology while retaining suitability for gene loss-of function screening. We show here that exogenous α-synuclein pre-formed fibrils (PFFs) made from recombinant human α-synuclein can "seed" primary cortical neurons from hSNCA Tg mice (F28), resulting in accumulation of endogenous detergent-insoluble α-synuclein, which is phosphorylated and partly ubiquitylated, as seen during PD. Using Accell siRNAs from Dharmacon that are passively taken up by the neurons due to a special modification, we can efficiently silence genes in the mouse neurons. By targeting hSNCA as a "proof of principle", we show that the PFF-induced α-synuclein pathology can be significantly reduced using this technique, suggesting that the assay has the potential to be used for new target identification screening. It is currently not clear which function ubiquitin add to pathological α-synuclein. One likely possibility is that it targets the pathological α-synuclein for degradation, suggesting that increasing its ubiquitylation by de-ubiquitylase (DUB) inhibition could be a feasible strategy for reducing the pool of pathological α-synuclein. Along this line, it has previously been shown that USP8 inhibition can decrease the pool of soluble α-synuclein (Alexopoulou Z. et al., PNAS, 2016 Aug 9;113(32)). We are currently using our model system to silence each of the ~100 DUBs present in the mouse genome and evaluate their loss-of function effect on pathological α-synuclein accumulation following seeding and to understand how the DUBs modulate a-synuclein ubiquitylation.

Disclosures: **M. Ambjorn:** A. Employment/Salary (full or part-time):; H. Lundbeck A/S. **N. Damsgaard:** A. Employment/Salary (full or part-time):; H. Lundbeck A/S. **M. Lubas:** A. Employment/Salary (full or part-time):; H. Lundbeck A/S. **K. Fog:** A. Employment/Salary (full or part-time):; H. Lundbeck A/S.

Poster

742. Alpha-Synuclein Models and Mechanisms II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 742.10/C73

Topic: C.03. Parkinson's Disease

Support: Michael J Fox Foundation
NCATS intramural research program
R21NS081182
R01NS097903

R37NS033123
U01NS103883

Title: Discovery of candidate therapeutics for Parkinson's disease by quantitative high throughput screening (qHTS) for compounds targeting α-synuclein expression

Authors: D. P. HUYNH[1], M. GANDELMAN[1], S. PAUL[1], W. DANSITHONG[1], E. AOYAMA[1], M. HENDERSON[2], S. KALES[2], A. ZAKHAROV[2], A. JADHAV[2], G. BANTUKALLU[2], A. SIMEONOV[2], S. PULST[1], ***D. R. SCOLES**[1];
[1]Dept. of Neurol., Univ. of Utah, SALT LAKE CITY, UT; [2]Natl. Ctr. for Advancing Translational Sci. (NCATS), Rockville, MD

Abstract: Objectives: To identify compounds lowering α -synuclein expression toward a therapy for Parkinson's disease. **Background:** Toxic gain of α-synuclein function is an underlying feature of Parkinson's disease (PD). We hypothesize that lowering SNCA expression will be therapeutic for PD. **Methods:** We used genome editing to place luciferase in frame after the *SNCA* gene in HEK-293, reporting SNCA expression under native expression control. We used this cell line assay to perform a quantitative high throughput screen (qHTS) to identify compounds that lower SNCA expression. Compounds were screened using a multiplexed cell viability assay to ensure target reduction in the absence of cytotoxicity. Compounds were counterscreened using a CMV-luciferase HEK-293 cell line and luciferase directly. Candidate compounds were tested for lowering SNCA expression in HEK-293 cells and PD patient derived skin cell fibroblasts using ELISA assays, western blotting, and quantitative PCR. The best lead compounds were evaluated for protecting PD fibroblasts against rotenone toxicity, and for lowering SNCA expression in PD patient induced pluripotent stem cell (iPSC) derived neurons. **Results:** Compounds from six libraries totaling 149,947 were screened at 4-11 doses each, with 24 hrs treatment. Z'-factors for all screens (by library) were >0.6. Four active lead compounds that lowered SNCA-luciferase expression with IC50 < 0.1 μM by ELISA were also protective in a rotenone toxicity assay. Of these, we placed our focus on one compound, a known inhibitor of AKT, that lowered SNCA in cultured iPSC neurons by nearly 50% following treatment with 0.1 μM for 48 hrs. **Conclusions:** This study identified an AKT inhibitor that potently lowered SNCA expression in all assays including PD relevant neurons. Further evaluation will include testing for modification of PD phenotypes in a mouse model of PD, and medicinal chemistry toward the development of a new therapeutic for PD. **Support:** Supported by a grant from the Michael J Fox Foundation and the NCATS intramural research program. This work was also supported in part by National Institutes of Health (NIH) / National Institute of Neurological Disorders and Stroke (NINDS) grants R21NS081182, R01NS097903, R37NS033123, and U01NS103883.

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Poster

742. Alpha-Synuclein Models and Mechanisms II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 742.11/C74

Topic: C.03. Parkinson's Disease

Support: PDF/APDA Summer Research Grant

Title: Insight into Parkinson's disease from yeasts: Combined impact of covalent modifications and familial mutations on α-synuclein

Authors: *Y. P. GANEV, R. THOMAS, A. ROMAN, C. MWALE, P. JONES, A. BALARAM, E. TCATURIAN, S. DEBBURMAN;
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Abstract: Parkinson's disease (PD) is a neurodegenerative disorder linked to the loss of dopaminergic neurons in the midbrain. A key pathological marker of PD is the presence of Lewy bodies, which are composed of misfolded α-synuclein protein. α-Synuclein is a highly post-translationally modified protein, in healthy and diseased states. While phosphorylation and nitration of α-synuclein are well-studied as contributors to PD pathology, less is known about SUMOylation, acetylation, and glycation. Also, the combined effects of these modifications remain largely unclear, on both wildtype α-synuclein (linked with sporadic PD) and the six mutant forms (A30P, E46K, H50Q, G51D, A53T, A53E) linked with early-onset familial PD. We first evaluated the effects of blocking SUMOylation on α-synuclein in the well-established budding yeast model for PD and found that α-synuclein becomes more toxic and aggregated, losing its membrane localization. Second, we found that SUMOylation and phosphorylation counteract each other in toxicity and localization. Third, we expanded our investigation to two newly reported modifications - acetylation and glycation. We found that acetylation is protective and glycation is harmful. When we combined acetylation or glycation manipulations with SUMOylation and phosphorylation alterations on the α-synuclein level, we found that the effects of these modifications are not additive - the impacts of acetylation and glycation depends on phosphorylation status. Finally, we investigated the effects of the familial mutants in tandem with altered SUMOylation or glycation. We report two familial mutant-specific effects: G51D is surprisingly sensitive and toxic to hypo-SUMOlyation, while A53E is highly toxic to hypo-glycation. These studies show the relevance of covalent modifications in sporadic and familial PD, and their in-tandem effects that underlie toxicity mechanisms.

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Poster

742. Alpha-Synuclein Models and Mechanisms II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 742.12/C75

Topic: C.03. Parkinson's Disease

Support: Lady Tata research fellowship

Title: Studying the effect of co-expression of α-synuclein and leucine rich repeat kinase 2 in modelling Parkinson's disease in *drosophila melanogaster*

Authors: *D. R. JHONSA[1], I. PADDIBHATLA[3], M. SARAF[2];
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Abstract: Familial cases of Parkinson's disease (PD) is attributed to mutations in a number of genes of which α-synuclein (SNCA) and leucine rich repeat kinase 2 (LRRK2) are being studied extensively. Using *Drosophila* model organism these genes reported to exhibit selective loss of dopaminergic neurons and locomotor dysfunction. Point mutations in both the genes resulting in formation of aberrant proteins, changes in the level of expression of wild type genes are documented affect a number of cellular processes such as synaptic vesicle trafficking, lysosomal autophagic pathway, microtubule based transport, neurotransmitter release, inflammation and mitochondrial integrity. Therefore, study of the impact of the combined expression of SNCA and LRRK2 on neurons and glial cells using *Drosophila melanogaster* as the model system can be studied to mimic PD. Hence, we are using *Drosophila* model with GAL4/UAS expression system to express α- synuclein, leucine rich repeat kinase 2 and also their mutated forms (leucine rich repeat kinase 2 LRRK2, G2019S) in the neurons and the glia cells. We have assessed neurodegenerative phenotype by performing climbing assays and immunostaining dopaminergic neurons to observe neurodegeneration. Our data shows that expression of SNCA, LRRK2 and LRRK2 G2019S individually in a pan neuronal manner and specifically in dopaminergic neurons exhibits a premature decrease in climbing ability as compared to control flies. The study of the effect of expression of SNCA, LRRK2 and LRRK2 G2019S in glia as well as the generation of recombinant flies co-expressing SNCA and LRRK2 is on-going. By comparing the effect of individual and combined expression of SNCA and LRRK2 in all the neurons, glia and dopaminergic neurons we will be able to demonstrate whether the co-expression of SNCA and LRRK2 is able to mimic the pathophysiology of PD more effectively as compared to expression of the individual genes. This study can provide further insights into the pathophysiology of PD. The data obtained from this research investigation can contribute in the search for new therapeutic targets.

Disclosures: D.R. Jhonsa: None. **I. Paddibhatla:** None. **M. Saraf:** None.

Poster

742. Alpha-Synuclein Models and Mechanisms II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 742.13/C76

Topic: C.03. Parkinson's Disease

Title: Exploring anxiety-like behaviors and neurochemical changes in the line 15 alpha synuclein overexpressing Parkinson's disease model

Authors: *H. B. JANSSENS[1], L. YU[1], J. ROESER[1], A. RASSOULPOUR[1], T. CREMERS[2]; [1]Charles River Labs., South San Francisco, CA; [2]Dept. of Sci. and Engin., Univ. of Groningen, Groningen, Netherlands

Abstract: Anxiety and depression have been reported to preclude motoric symptoms in Parkinson's (PD) patients years prior to PD onset, suggesting a lengthy prodromal period with compensatory neural mechanisms. Therefore, we set out to assess anxiety-like behavior and examine the levels of aSYN and neurotransmitters [dopamine (DA), serotonin (5-HT), gamma-amino butyric acid (GABA), glutamate, acetylcholine (ACh) and tryptophan] in brain regions associated with anxiety of male B6 WT and hemizygous (TG) mice of Line 15, Tg(Thy1-SNCA)15Mjff/J (JAX) at ages 12 and 18 months.

To this end, anxiety-like behavior was assessed with the open field (OF), light-dark box (LDB), and elevated plus maze (EPM) paradigms in 12 and 18 month old male C57Bl/6 WT and Line 15 TG mice. *In vivo* microdialysis was carried out following the behavioral battery. Levels of aSYN in dialysate samples were analyzed via MSD® assays, and neurotransmitters were measured via LC MS/MS.

Motoric deficits were not observed in TG versus WT mice but a general decrease in mobility with age was noted. Interestingly, we found a lack of anxiety-like behavior in TG mice compared to WT in the EPM, OF, and LDB test. In fact, a significant increase in open arm entries were observed in Tg animals compared to age matched WT animals in the EPM. In the same animals basal aSYN levels were found to vary across brain regions at 12 months of age and were significantly higher than aSYN levels at 18 months of age. This pattern was also observed with the neurotransmitters DA, ACh and GABA, all of which were higher in younger TG animals as compared to older animals. No significant changes in 5-HT, tryptophan or glutamate were observed.

Overall, these results show that an animal model of PD that has elevated aSYN levels does not mirror the observed anxiogenic phenotype observed in patients. Interestingly, we do observe age related elevations of aSYN that may be driving elevations in DA, ACh and GABA. These neurochemical changes may also underlie the observed anxiolytic phenotype in the EPM, and other yet to be examined behaviors.

Disclosures: **H.B. Janssens:** None. **L. Yu:** None. **J. Roeser:** None. **A. Rassoulpour:** None. **T. Cremers:** None.

Poster

742. Alpha-Synuclein Models and Mechanisms II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 742.14/C77

Topic: C.03. Parkinson's Disease

Support: Branfman Family Foundation

Title: Effects of the A53E substitution on alpha synuclein aggregation and neurotoxicity in Parkinson's disease

Authors: ***J. HENSEL**[1,2], P. C. MONTENEGRO[1,2], C. CHANDRASEKARAN[1,2], D. YSSELSTEIN[1,2], S. AGIM[3,2], N. DUTHEIL[4], B. DEHAY[4], E. BEZARD[5], J. R. CANNON[3,2], J.-C. ROCHET[1,2];
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Abstract: Parkinson's disease (PD) is a neurodegenerative disorder characterized by a loss of dopaminergic (DA) neurons from the substantia nigra pars compacta (SN) in the midbrain. A pathological hallmark of PD is the presence of cytosolic inclusions, called Lewy bodies, in surviving neurons. Lewy bodies are enriched with the presynaptic protein alpha-synuclein (aSyn). Although evidence suggests that aggregated forms of aSyn are involved in dopaminergic neuronal death, the mechanism by which aSyn forms neurotoxic aggregates in PD is not understood. Data obtained by our group and others suggest that a disruption of interactions between aSyn and phospholipid membranes leads to a shift to an 'exposed' conformation that favors aggregation of the protein at membrane surfaces. Results of biochemical and biophysical analysis have shown that the familial A53E aSyn mutant has an increased propensity to adopt an exposed membrane-bound conformation and undergo membrane-induced aggregation compared to WT aSyn. Recombinant adeno-associated viruses encoding WT aSyn, A53T, and A53E were injected into rat SN to evaluate PD behavioral and pathological endpoints. Expression of all three aSyn variants was found to cause a significant loss of TH^+ neurons and striatal terminals, as well as the formation of aSyn aggregates that stained positive for pSer129 and polyubiquitin in the SN. Current studies are focused on further characterizing aSyn aggregation in this *in vivo* model, including the spread of PD pathology to glial cells and additional brain regions. The results from these studies provide valuable insights into the molecular basis for the neurotoxicity of WT and mutant aSyn and shed light on a potential role for membrane-induced aSyn aggregation in PD

pathogenesis *in vivo,* thus setting the stage for developing therapies to prevent aSyn aggregation and slow neurodegeneration in PD.

Disclosures: J. Hensel: None. **P.C. Montenegro:** None. **C. Chandrasekaran:** None. **D. Ysselstein:** None. **S. Agim:** None. **N. Dutheil:** None. **B. Dehay:** None. **E. Bezard:** None. **J.R. Cannon:** None. **J. Rochet:** None.

Poster

742. Alpha-Synuclein Models and Mechanisms II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 742.15/C78

Topic: C.03. Parkinson's Disease

Title: The Michael J. Fox Foundation's efforts to understand the relationship between GBA1 and alpha-synuclein through the development and characterization of preclinical models

Authors: *B. CASEY[1], N. POLINSKI[1], T. N. MARTINEZ[1], S. W. CLARK[2], S. M. SMITH[3], R. C. SWITZER III[4], S. O. AHMAD[5], S. RAMBOZ[6], M. SASNER[7], M. T. HERBERTH[8], L. MENALLED[1], M. A. BAPTISTA[1], K. D. DAVE[1], M. FRASIER[1];
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Abstract: Heterozygous mutations in the GBA1 gene, which encodes lysosomal glucocerebrosidase (GCase), are the most common genetic risk factor for Parkinson's disease (PD). In addition, decreased GCase activity has been reported in both genetic and sporadic cases of PD. Experimental evidence suggests a correlation between decreased GCase activity and accumulation of alpha-synuclein (aSyn). Thus, understanding the potential synergistic effect of increased aSyn and decreased GCase activity is important for understanding how alterations in GCase activity may contribute to or exacerbate PD-related pathology. To enable a better understanding of the relationship between aSyn and GCase activity, The Michael J. Fox Foundation (MJFF) has developed and characterized two mouse models allowing investigation of aSyn pathology in the context of reduced GCase activity. The first model analyzes the neurodegeneration/pathology induced through constitutive overexpression of wild type human alpha-synuclein directed by the murine Thy-1 promoter (hemizygous transgenic) in the context of the GCase activity-reducing D409V mutant form of GBA (homozygous knockin). The second model analyzes the level of nigrostriatal degeneration and synuclein pathology in the GBA D409V knockin model versus wildtype mice following stereotaxic injection of aSyn preformed fibrils into the striatum. Here, we outline and discuss the results of these model characterization efforts. Together, these models provide important platforms for understanding the mechanisms

underlying GCase and aSyn dynamics, and for evaluating therapeutics targeting this pathway/relationship.

Disclosures: B. Casey: None. **N. Polinski:** None. **T.N. Martinez:** None. **S.W. Clark:** None. **S.M. Smith:** None. **R.C. Switzer III:** None. **S.O. Ahmad:** None. **S. Ramboz:** None. **M. Sasner:** None. **M.T. Herberth:** None. **L. Menalled:** None. **M.A. Baptista:** None. **K.D. Dave:** None. **M. Frasier:** None.

Poster

742. Alpha-Synuclein Models and Mechanisms II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 742.16/C79

Topic: C.03. Parkinson's Disease

Support: Michael J. Fox Foundation

Title: Utilizing an alpha-synuclein binding aptamer to prevent protein aggregation in an alpha-synuclein overexpressing cellular model of Parkinson's disease

Authors: K. VENTURA[1], S. BOISJOLI[2], J. CALLAHAN[2], V. HUNT[2], E. MCCONNELL[2], M. DEROSA[2], ***M. R. HOLAHAN**[1];
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Abstract: In Parkinson's disease, one hypothesis states that as misfolded native or mutant alpha-synuclein protein dimers become oligomers, they form insoluble aggregates that can trigger inflammatory, apoptotic, and other toxic signals that culminate in the death of neurons. Our goal is to examine whether a DNA aptamer targeted to bind to alpha-synuclein monomers will inhibit protein aggregation and reduce pathological outcomes such as inflammation, apoptosis and neuronal death. Aptamers are single-stranded functional nucleic acids, which form unique, 3-dimensional secondary structures that facilitate their binding with high affinity and selectivity to a cognate target. Aptamers for alpha-synuclein monomer and oligomer have been previously reported but were not selected specifically to inhibit fibril formation and have not been shown to inhibit aggregation *in vitro* or *in vivo*. We recently designed an aptamer (asyn-1) that inhibits alpha-synuclein aggregation and inhibit the formation of fibrils *in vitro*. Our recent work focused on 1) the identification of DNA aptamers that bound selectively to alpha-synuclein monomer to prevent alpha-synuclein aggregation and fibrilization and 2) the pharmacokinetic profile and biodistribution of systemic administration of the aptamer. To provide a more complete understanding of the dosing effects required for the aptamer to produce changes in alpha-synuclein biology, the effects of our asyn-1 aptamer were investigated in a transfected α-synuclein expressing SHSY-5Y cell line. We have confirmed that we are able to transfect the SHSY-5Y cells, observe phosphorylated alpha synuclein by immunostaining, and observe the

uptake of the a-syn-1 aptamer after administration either as a pretreatment, treatment at the time of transfection, or as a treatment following transfection of the virus. We are now in a position to determine whether: 1) we see reduced levels of α-synuclein protein following treatment with asyn-1; 2) asyn-1 prevents fibril formation over the long term; 3) there are any negative consequences of preventing aggregation by the aptamer such as soluble, toxic fragments that would infect other neurons. Results from these studies will be presented.

Disclosures: K. Ventura: None. **S. Boisjoli:** None. **J. Callahan:** None. **V. Hunt:** None. **E. McConnell:** None. **M. DeRosa:** None. **M.R. Holahan:** None.

Poster

742. Alpha-Synuclein Models and Mechanisms II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 742.17/C80

Topic: C.03. Parkinson's Disease

Title: Behavioral assessment of the 61SNCA mouse model of Parkinson's disease employing the NeuroCube system of movement analysis

Authors: A. EDWARDS, K. COX, K. CIRILLO, ***W. J. XU**, J. A. AVILA, S. RAMBOZ; Psychogenics Inc., Paramus, NJ

Abstract: Parkinson's disease (PD) is a neurodegenerative disorder characterized by dopaminergic neuronal loss in the substantia nigra with accumulation of α synuclein containing Lewy bodies. A number of rodent models of PD have been created to recapitulate different aspects of the disease, among these the Line 61 animal, overexpressing the human wild-type alpha-synuclein driven by the murine Thy-1 promoter, in particular has been used extensively to model α synuclein pathology [Rockenstein et al, 2002]. While previous literature has characterized the male Line 61 mice and described a gradual disease progression, female counterparts of this model have been less well studied due to the linkage of the mutation to the X chromosome. In the present study, we performed a number of behavioral assessments in the female Line 61 including wire hang and tapered beam. We also employed a proprietary NeuroCube® assessment to evaluate quantifiable, subtle changes in patterned movement in these animals. This system records and calculates several aspects of ambulation and compares them to detect emerging movement impairments that may otherwise go unnoticed. Results suggest that a mild motor phenotype is present in the female Line 61 compared to both male Line 61 as well as WT counterparts. Implications of these findings as well as use of the NeuroCube® assessment as a tool in the evaluation of rodent models of disease are discussed.

Disclosures: A. Edwards: None. **K. Cox:** None. **K. Cirillo:** None. **W.J. Xu:** None. **J.A. Avila:** None. **S. Ramboz:** None.

Poster

743. Parkinson's Disease: Therapeutics

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 743.01/C81

Topic: C.03. Parkinson's Disease

Title: Early transcranial direct current stimulation ameliorates motor and cognitive dysfunctions in Parkinson's disease model of rats

Authors: *Y.-T. HUANG[1], X.-J. FENG[3], C.-W. KUO[1,4], T.-H. HSIEH[1,2,5];
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Abstract: Background: Parkinson's disease (PD) is a neurodegenerative disorder characterized by the motor and cognitive dysfunctions associated with pathological losses of the dopaminergic neurons (DA) in the substantia nigra. Non-invasive brain stimulation approach such as transcranial direct current stimulation (tDCS), has been developed for modulating cortical excitability which is considered having therapeutic potential in PD. However, the therapeutic value of such approach for PD is still unclear. Consequently, we adopted the PD rat model for elucidating the possible therapeutic effects in PD. **Methods:** A hemiparkinsonian rat model, induced by unilateral injection of 6-hydroxydopamine (6-OHDA) into the medial forebrain bundle (MFB), was applied to identify the therapeutic effects of tDCS in motor and cognitive behaviors following long-term tDCS treatment (300μ anodal tDCS, 20 min each day for 5 consecutive days per week) under awake conditions for 4 weeks. After tDCS intervention, the detailed functional behavioral tests including gait, akinesia, anxiety, depression, apomorphine-induced rotational analysis as well as DA degeneration level were assessed up to 4 weeks. **Results:** After tDCS intervention, we found that four-week tDCS intervention ameliorated motor and cognitive deficits in gait pattern, akinesia, anxiety, apomorphine-induced rotation, and depression behavior. Immunohistochemically, tyrosine hydroxylase (TH) analysis demonstrated that the dopamine neurons were significantly preserved. **Conclusions:** These results suggest that early and daily tDCS could reduce the aggravation of PD symptoms and exert the neuroprotective effect in a PD rat model. Furthermore, our result may enhance the potential use of tDCS and serve as a translational platform bridging human and animal studies in the development of therapeutic tDCS application for PD or other neurological disorders.
Keywords: transcranial direct current stimulation, Parkinson's disease, 6-hydroxydopamine, cognitive function, motor function

Disclosures: Y. Huang: None. **X. Feng:** None. **C. Kuo:** None. **T. Hsieh:** None.

Poster

743. Parkinson's Disease: Therapeutics

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 743.02/C82

Topic: C.03. Parkinson's Disease

Title: The effects of probiotics on improving motor and cognitive functions in a mouse Parkinson's model

Authors: *K.-H. HSIEH[1], C.-W. KUO[1,4], T.-H. HSIEH[1,5,2], H.-Y. CHEN[3,6];
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Abstract: Background: Parkinson's disease (PD) is the second most common age-related neurodegenerative disease. The pathologic hallmark of PD is the loss of nigrostriatal dopaminergic neurons, leading to functional motor and non-motor disabilities. Earlier studies have been reported that gastrointestinal symptoms occur not only in advanced PD but also in the early stage of PD. In this study, we investigated whether long-term probiotics may have the neuroprotective effects in dopaminergic nigrostriatal neurons and further alleviate the impairment of gait pattern, locomotor activity, balance and novel recognition memory in a chronic progressive PD model-the MitoPark mouse.
Method: Using a MitoPark mouse model, we utilized detailed gait analysis, beam walking, rotarod, novel object recognition and immunohistochemistry to test whether daily and long-term probiotics treatment improves motor and cognitive deficits.
Results: In results, under probiotics intervention over 16 weeks in MitoPark mice, we found that the probiotics treatment for 8-16 weeks significantly reduced motor and non-motor deficits in gait, balance and memory function. Immunohistochemically, tyrosine hydroxylase (TH)-positive neurons in the substantia nigra were significantly preserved in the probiotics treatment group at the end of probiotics treatment.
Conclusion: These results suggest that early and daily probiotics treatment exerts neuroprotection and reduces the aggravation of PD symptoms in MitoPark PD mouse model. Also, our data further highlight the potential therapeutic effects of probiotics and confirm the existence of a long-term effect of daily applications of probiotics that might be useful for further potential application of human PD subjects.
Keyword: Parkinson's disease, probiotics, MitoPark, gait, motor function

Disclosures: K. Hsieh: None. **C. Kuo:** None. **T. Hsieh:** None. **H. Chen:** None.

Poster

743. Parkinson's Disease: Therapeutics

Location: Hall A

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Program #/Poster #: 743.03/C83

Topic: C.03. Parkinson’s Disease

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NYSCF
Swedish Parkinson Foundation
Strategic Research Area at Lund University Multipark

Title: Human embryonic stem cell-derived dopaminergic transplants integrate into basal ganglia circuitry in a preclinical model of Parkinson's disease

Authors: *A. F. ADLER, T. CARDOSO, S. NOLBRANT, B. MATTSSON, D. B. HOBAN, U. JARL, J. N. WAHLESTEDT, S. GREALISH, A. BJÖRKLUND, M. PARMAR;
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Abstract: Human embryonic stem cell (hESC)-derived ventral midbrain-patterned progenitors grafted into the dopamine-depleted adult rat brain survive long-term, mature into dopamine neurons, integrate synaptically with host neurons, and extend dopaminergic axons to fill functionally-appropriate target structures and reverse motor deficits. In the clinical setting, midbrain-patterned cells are grafted heterotopically into the striatum, rather than homotopically into the substantia nigra. To determine the factors dictating the appropriateness of graft integration into the host basal ganglia, we have compared the axonal outgrowth from and synaptic inputs to midbrain- and forebrain-patterned cells placed either in the striatum or the substantia nigra of dopamine-depleted host rats. We found that graft-derived axonal outgrowth to dopamine target regions depended on midbrain patterning of the transplanted cells, whereas the anatomical location of host cells making monosynaptic contact with graft neurons depended on the location of the transplant. Moreover, there was a significant anatomical and phenotypic overlap with regions known to regulate the function of intact midbrain dopamine neurons. These results suggested that grafts placed in the clinical location - heterotopically in the striatum - may nevertheless receive input from the brain regions in the host that project to the endogenous midbrain dopamine neurons in the substantia nigra. Conventional retrograde tracing performed concurrent to graft-initiated rabies tracing confirmed that grafts placed in the striatum in fact received synaptic input from individual neurons that maintained simultaneous collateral projections to the substantia nigra. In summary, our data shows that functionally-appropriate

subtypes of host neurons provide monosynaptic input to grafts, regardless of clinically-analogous heterotopic graft placement into the striatum.

Disclosures: **A.F. Adler:** None. **T. Cardoso:** None. **S. Nolbrant:** None. **B. Mattsson:** None. **D.B. Hoban:** None. **U. Jarl:** None. **J.N. Wahlestedt:** None. **S. Grealish:** None. **A. Björklund:** None. **M. Parmar:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Parmar Cells AB, U.S. patent application 15/093,927, EP17181588.

Poster

743. Parkinson's Disease: Therapeutics

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 743.04/C84

Topic: C.03. Parkinson's Disease

Support: Clene Nanomedicine sponsored this research

Title: Gold nanocatalysis as a novel therapeutic for neuroprotection in Parkinson's disease

Authors: *K. S. HO[1,2,3], M. T. HOTCHKIN[1,2], M. G. MORTENSON[1];
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Abstract: CNM-Au8 is a suspension of clean-surfaced, faceted nanocrystalline gold with unique nanocatalytic properties. CNM-Au8 efficiently converts the bioenergetic coenzyme nicotinamide adenine dinucleotide (NADH) to its oxidized form NAD+, resulting in elevated intracellular ATP levels, while independently lowering oxidative stress through superoxide dismutase-like catalytic activity. Multiple molecular lines of evidence point to bioenergetic failure as a significant contributor to dopaminergic neuronal death in Parkinson's Disease (PD). We therefore investigated the preclinical efficacy of CNM-Au8 to address manifestations of bioenergetic failure in *in vitro* and *in vivo* models of PD.
In rat dopaminergic neural-glial co-cultures, treatment with CNM-Au8 significantly increased total intracellular levels of NAD+. When co-cultured dopaminergic neurons were subjected to the neurotoxins MPP+ or 6-OHDA, CNM-Au8 treatment significantly preserved the neurite network and enhanced the survival of dopaminergic (DA) neurons ($p < 0.05$*). Importantly, CNM-Au8-treated DA neurons challenged with 6-OHDA resulted in the reduction of alpha-synuclein aggregates in a dose-dependent manner ($p < 0.05$*). In addition, CNM-Au8 prevented the accumulation of reactive oxygen species and prevented depletion of mitochondria observed with the application of MPP+ ($p < 0.05$*). *one-way ANOVA, CNM-Au8 vs. vehicle.
To determine the efficacy of CNM-Au8 *in vivo*, rats (N=12 per group) were administered CNM-Au8 or vehicle by gavage after unilateral lesion of the right striatum using stereotactic injection

of 6-OHDA. Animals were dosed daily with CNM-Au8 or vehicle starting on Day 1 or Day 14 post-injection. Both early (Day 1+) and late (Day 14+) treatment with CNM-Au8 showed contralateral paw placement improvement vs. vehicle control at Week 6 ($p=0.07$ and $p=0.006$ respectively, unpaired t-tests) in the vertical cylinder paw placement test. Early treatment with CNM-Au8 also reduced the number of apomorphine-induced rotations of lesioned rats at Week 6 by 42% compared to vehicle ($p=0.06$, unpaired t-test). Significantly, CNM-Au8 treatment outperformed L-Dopa/Carbidopa treatment in reduction of induced rotations in this assay.
In summary, CNM-Au8 demonstrated neuroprotective activity in *in vitro* assays and *in vivo* functional behavioral tests in the unilateral lesion model of PD. These data suggest that CNM-Au8, acting through an entirely novel catalytic mechanism resulting in an enhanced bioenergetic state, represents a promising new therapeutic strategy for PD.

Disclosures: **K.S. Ho:** A. Employment/Salary (full or part-time):; Clene Nanomedicine, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Clene Nanomedicine, Inc. **M.T. Hotchkin:** A. Employment/Salary (full or part-time):; Clene Nanomedicine, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Clene Nanomedicine, Inc. **M.G. Mortenson:** A. Employment/Salary (full or part-time):; Clene Nanomedicine, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Clene Nanomedicine, Inc..

Poster

743. Parkinson's Disease: Therapeutics

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 743.05/C85

Topic: C.03. Parkinson’s Disease

Support: Pearl J. Aldridge Endowment Fund

Title: STN DBS reduces Lewy body-like alpha-synuclein inclusion formation triggered by intrastriatal fibril injection

Authors: ***K. M. MILLER**[1], C. J. KEMP[1], J. R. PATTERSON[1], A. C. STOLL[1], K. STEECE-COLLIER[1], K. C. LUK[2], M. R. KUBIK[1], C. E. SORTWELL[1];
[1]Translational Sci. and Mol. Med., Michigan State Univ., Grand Rapids, MI; [2]Dept of Pathology and Lab. Med., Univ. Pennsylvania, Philadelphia, PA

Abstract: Whether deep brain stimulation (DBS) of the subthalamic nucleus (STN) is disease-modifying for Parkinson’s disease (PD) remains unclear. A hallmark of PD pathology is the progressive accumulation of alpha-synuclein (alpha-syn) inclusions (i.e.: Lewy bodies). To date,

only a single report has examined whether Lewy body pathology is impacted in PD subjects by DBS (PMID: 27911008). While no effect was observed, this study was limited by the 14-year disease duration prior to DBS, long after the establishment of Lewy body pathology. No preclinical study has examined whether STN DBS can prevent the formation of alpha-syn aggregates. The distinct alpha-syn aggregation phase in the alpha-syn pre-formed fibril (PFF) model can be leveraged to examine the impact of STN DBS on accumulation of Lewy body-like pathology. Our preliminary findings suggest that STN DBS in rats reduced the formation of alpha-syn aggregates by ≈30% ($p \leq 0.022$). In the present study we test the reproducibility of this finding. Thirty adult male rats received intrastriatal injections of alpha-syn preformed fibrils (PFFs) and were implanted with electrodes in the STN during the same surgical session. Three days later, animals were randomly assigned to receive either stimulation or no stimulation for a period of 30 days. Stereological assessment of nigral neurons possessing phosphorylated alpha-syn (pSyn), phosphorylated alpha-syn truncated adamant and reactive (pSyn*), and fibrillar alpha-syn (F2) inclusions served as the primary outcome measures. Quantification of tyrosine hydroxylase immunoreactive (THir) nigral neurons and examination of BDNF-trkB signaling (ELISA) are also being conducted. In a second cohort of animals we will evaluate whether neuroinflammation is impacted by STN DBS. Stereological assessment of ionized calcium-binding adapter molecule 1 (Iba1)-ir and major histocompatibility complex II (MHCII)-ir microglia will be the primary outcome measures. Collectively, our preliminary findings suggest that STN DBS may be disease-modifying by decreasing alpha-syn pathology.

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Poster

743. Parkinson's Disease: Therapeutics

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 743.06/C86

Topic: C.03. Parkinson’s Disease

Support: Korea Healthcare Technology R&D Project grant HI15C1928
National Research Foundation of Korea grant NRF-2017R1A2B4002675

Title: Astrocyte elevated gene-1 as an endogenous anti-apoptotic factor in nigral dopaminergic neurons *in vivo*

Authors: *E. LEEM[1], T. Y. KIM[1], U. J. JUNG[2], S. R. KIM[1,3];
[1]Sch. of Life Sciences, BK21 plus KNU Creative BioResearch Group, Kyungpook Natl. Univ., Daegu, Korea, Republic of; [2]Dept. of Food Sci. and Nutrition, Pukyong Natl. Univ., Busan, Korea, Republic of; [3]Brain Sci. and Engin. Institute, Kyungpook Natl. Univ., Daegu, Korea, Republic of

Abstract: We recently reported the protective role of astrocyte elevated gene-1 (AEG-1) in nigral dopaminergic (DA) neurons *in vivo*. Similar to decrease in the level of AEG-1 in the postmortem substantia nigra (SN) tissues from patients with Parkinson's disease (PD), the reduction of AEG-1 in nigral DA neurons was also observed in the 6-hydroxydopamine (6-OHDA)-treated mouse model of PD. In addition, AEG-1 upregulation using adeno-associated virus serotype 1 (AAV1) attenuated the 6-OHDA-triggered apoptotic death of nigral DA neurons in the SN of mouse brain. Furthermore, although the post-administration of AAV-AEG-1 alone after disruption of nigrostriatal DA system showed no neurorestorative effect, we observed that the maintenance of neuronal AEG-1 using AAV1 contributed to the intensification of neurorestoration such as behavioral recovery by post-treatment with a constitutively active form of ras homolog enriched in brain [Rheb(S16H)], which could induce axonal regeneration from damaged DA neurons in the 6-OHDA-treated animal model of PD. Collectively, these results demonstrated that the sustained level of AEG-1 as an important anti-apoptotic factor could potentiate the therapeutic effects of treatments, such as Rheb(S16H) administration, on the degeneration of the DA pathway that characterizes PD.

Disclosures: E. Leem: None. **T.Y. Kim:** None. **U.J. Jung:** None. **S.R. Kim:** None.

Poster

743. Parkinson's Disease: Therapeutics

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 743.07/DP04/C87

ControlExtraData.DynamicPosterDisplay:
Dynamic Poster
Topic: C.03. Parkinson's Disease

Title: Intracellular delivery of parkin protects dopaminergic neurons in brain-damaged animals

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Abstract: Therapeuticmolecule systemic delivery technology (TSDT), a platform for the discovery/development of new medicinal drugs, is enabled with a new generation of hydrophobic cell-penetrating peptide (CPP), namely advanced macromolecule transduction domain (aMTD). The goal of this study is to develop aMTD-fused Parkin recombinant protein as a Parkinson's disease (PD)-modifying therapeutic agent. Parkin fused to aMTD524 shows the highest solubility, yield, homogeneity and cell-permeability of the fusion protein which is called improved cell-permeable (iCP) Parkin. As an E3 ubiquitin ligase, iCP-Parkin does not require phosphorylation of Ser-78 by PINK1, but is constitutively active regardless of conformational change of its structure. In addition, iCP-Parkin is able to be distributed into deep brain by

penetrating blood-brain barrier (BBB). iCP-Parkin has therapeutic effects in various PD animal models by utilizing its capabilities of BBB penetration and cytoprotective activity. In 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced PD mice, iCP-Parkin recovers motor function in swim (83%), wire (86%) and rota-rod (93%) tests, and thereby increase expression (74%) of tyrosine hydroxylase (TH) in dopaminergic (DA) neurons. iCP-Parkin also restores movement in pole test (80%) and TH expression (74%) in 6-hydroxydopamine (6-OHDA)-induced PD mice. Lastly, in α-Synuclein-induced PD mice, iCP-Parkin recovers the behavior defect significantly in the rota-rod test (92%) and TH expression (63%), plasma dopamine (50%), and also removes aggregated α-Synuclein (75%). Based on the data, iCP-Parkin may have a great therapeutic potential as a PD-modifying agent.

Disclosures: **E. Chung:** None. **W. Nah:** None. **Y. Jung:** None. **J. Park:** None. **S. Shin:** None. **J. Lee:** None. **D. Min:** None. **M. Kwon:** None. **Y. Choi:** None. **D. Jo:** None.

Poster

743. Parkinson's Disease: Therapeutics

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 743.08/C88

Topic: C.03. Parkinson’s Disease

Support: Science Foundation Ireland (SFI) and co-funded under the European Regional Development Fund, Grant 13/RC/2073

Title: Effect of chronic stimulation on the electrode tissue interface and electric field distribution of chronically implanted deep brain stimulation electrodes in the rat

Authors: *J. EVERS[1], K. SRIDHAR[1], J. LIEGEY[1], J. BRADY[2], H. JAHNS[2], M. M. LOWERY[3];
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Abstract: Changes at the electrode-tissue interface in response to implantation of chronic deep brain stimulation (DBS) electrodes including alterations in impedance, neuroinflammation and gliosis are well-established. However, the influence of stimulation on these processes has not been fully described. The aim of this study was to examine the effect of stimulation on the electrode-tissue interface of chronically implanted DBS electrodes in the rat subthalamic nucleus (STN), and to estimate the distribution of the resulting electric field in a finite element model. Bipolar concentric electrodes were implanted in the STN of 15 male Wistar rats (430g). 8 rats received DBS (130 Hz, 100 µA, 60 µs, 7 hrs/day) and 7 received no stimulation for 8 wks. Impedance spectroscopy (20 Hz - 300 kHz) was performed ≥3 times/wk. Brains were fixed by cardiac perfusion with 10% neutral buffered formalin. Astrocytes (GFAP), neurofilament and microglia (Iba-1) were labelled in 5µm sections by immunohistochemistry. Experiments were

approved (AREC 17-22) and licenced (HPRA AE18982-P122) in Ireland. The experimental impedance and histopathology data were incorporated in a3D heterogeneous finite element model based on the Waxholm Rat Atlas and the electrical field distribution around the electrode was estimated. Baseline impedance at 1 kHz was 24.5 kΩ ± 2.9 kΩ(SEM). Comparing complete 8 wk data sets (N=11) impedance at 1 kHz was significantly lower in the stimulation group than in the non-stimulation group (two-way repeated-measures ANOVA: Time and Interaction P&lt0.001, Stimulation P=0.02). An increase in astrocytes and microglia with activation was observed around tracts of stimulated electrodes compared to unstimulated electrodes. In the finite element model, the shape and magnitude of the electric field distribution for voltage-controlled stimulation were highly dependent on the electrical properties of the encapsulation tissue and electrode-tissue interface while the electrical field distribution in current-controlled stimulation was independent of these variables. In conclusion, differences in the impedance and histopathological properties of the electrode-tissue interface were observed between chronically stimulated and non- stimulated electrodes. These influenced the electrical field and thus the efficacy in activation of neural structures around the electrode in voltage-controlled stimulation.

Disclosures: **J. Evers:** None. **K. Sridhar:** None. **J. Liegey:** None. **J. Brady:** None. **H. Jahns:** None. **M.M. Lowery:** 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.; This project is supported by Science Foundation Ireland (SFI) and the European Regional Development Fund (Grant Number 13/RC/2073) and the European Research Council (Grant Number ERC-2014-CoG-646923)..

Poster

743. Parkinson's Disease: Therapeutics

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 743.09/C89

Topic: C.03. Parkinson’s Disease

Support: ANR grant ANR-15-CE37-0005-02
ANR grant Euridol ANR-17-EURE-0022
CNRS UPR3212 and UMR5293
Université de Strasbourg UPR3212
Université de Bordeaux UMR5293
FRM FDT20170437322
NeuroTime Erasmus Mundus Joint Doctorate

Title: The lesion of the tail of the ventral tegmental area can compensate motor and non motor symptoms in a rat model of Parkinson’s disease

Authors: *M. BARROT[1], F. FAIVRE[1], S. DOVERO[2], S. BIDO[2], A. JOSHI[1], E. BEZARD[2], M.-J. SÁNCHEZ-CATALÁN[3];
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Abstract: The death of the dopamine neurons of the nigrostriatal pathway contributes to Parkinson's disease. Both motor and non-motor symptoms, such as depression and pain, are present in this neurodegenerative disease. The tail of the ventral tegmental area or tVTA, also known as the rostromedial tegmental nucleus or RMTg, is a brain structure between mesencephalon and pons, that is mostly GABAergic and that exerts an inhibitory influence on dopamine neurons from the substantia nigra *pars compacta* (SNc). The tVTA can thus control the activity of dopamine systems and influence the functions of these systems. In this study, we assessed the consequence of removing tVTA control of dopamine systems in a model of Parkinson's disease. Behaviorally, these consequences were tested on both motor and non-motor symptoms. Male Sprague-Dawley rats with a partial and bilateral 6-hydroxydopamine (6-OHDA) lesion of the SNc had lower performance in the rotarod. We observed that this deficit was no more present after an excitotoxic co-lesion of the tVTA. Doing a larger behavioral characterization of the model, we also observed some non-motor symptoms following SNc lesion, such as lower body weight, lower mechanical and thermal nociceptive thresholds, and a decrease in sucrose preference in a 2-bottle choice paradigm. The co-lesion of the tVTA, using ibotenic acid, allowed antagonizing the body weight loss, as well as the changes in mechanical nociceptive thresholds and in anhedonia-like behavior. Together, these data further support the control exerted by the tVTA on dopamine system, and show that acting on this control may modulate the motor and non-motor symptoms secondary to a partial lesion of the substantia nigra.

Disclosures: M. Barrot: None. **F. Faivre:** None. **A. Joshi:** None. **M. Sánchez-Catalán:** None. **E. Bezard:** None. **S. Dovero:** None. **S. Bido:** None.

Poster

743. Parkinson's Disease: Therapeutics

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 743.10/C90

Topic: C.03. Parkinson's Disease

Support: RK Mellon Fellowship
NIH R01NS101016
NIH R01NS104835

Title: Driving neurons in a cell-type specific manner using electrical stimulation

Authors: *T. A. SPIX, B. R. ISETT, Y. GOKSEN, A. H. GITTIS;
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Abstract: Deep brain stimulation (DBS) is a highly effective treatment for parkinsonian motor symptoms, but its therapeutic effects decay rapidly if stimulation is discontinued. Recently, we showed that long-lasting motor rescue can be induced by optogenetic interventions that transiently dissociate the activity of two neuronal subpopulations within the external globus pallidus (GPe). Optogenetic interventions that elevated the firing rates of parvalbumin-expressing GPe neurons (PV-GPe) over those of lim-homeobox 6-expressing GPe neurons (Lhx6-GPe) produced long-lasting recovery of movement that persisted for hours beyond stimulation. To determine whether electrical stimulation can be tuned to achieve similar cell-type specific responses, we used acute brain slices to measure the physiological responses of PV-GPe and Lhx6-GPe neurons to electrical stimulation of the subthalamic nucleus (STN), the primary target for DBS. Synaptic recordings revealed that Lhx6-GPe and PV-GPe neurons receive excitatory and inhibitory synaptic inputs during stimulation, but while excitatory inputs were balanced onto both cell types, inhibitory inputs were larger onto Lhx6-GPe neurons. We hypothesized that this synaptic imbalance could be leveraged to convert non-specific electrical stimulation into a cell-type specific form of neuromodulation. Using a sparse matrix optimization strategy, we found that short, high-frequency bursts (<250ms, 100hz) were effective at elevating the firing rates of PV-GPe neurons while concurrently suppressing the firing rates of Lhx6-GPe neurons. With successive trials of short-duration, high-frequency stimulation, we further confirmed that PV neurons could be preferentially excited while Lhx6 neurons were preferentially inhibited in both dopamine-intact and dopamine-depleted animals. [MOU1] These results demonstrate that by tuning electrical stimulation parameters in the STN, it is possible to evoke cell-type-specific responses in the GPe that have previously been shown to be sufficient to induce long-lasting motor rescue. These results lay the groundwork for future translational studies of cell-type-specific neuromodulation in Parkinson's disease.

Disclosures: T.A. Spix: None. **B.R. Isett:** None. **Y. Goksen:** None. **A.H. Gittis:** None.

Poster

743. Parkinson's Disease: Therapeutics

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 743.11/C91

Topic: C.03. Parkinson's Disease

Support: NIH R01 NS091236
R37 NS040894

Title: Functional magnetic resonance imaging of optogenetic deep brain stimulation of the subthalamic nucleus in the hemi-parkinsonian rat

Authors: *Y. LI[1], S.-H. LEE[4], C. YU[1], T.-W. W. WANG[4], Y.-Y. I. SHIH[4], W. M. GRILL[1,2,3,5]; [1]Dept. of Biomed. Engin., [2]Dept. of Electrical and Computer Engin., [3]Dept. of Neurobio., Duke Univ., Durham, NC; [4]Ctr. for Animal MRI, Univ. of North Carolina At Chapel Hill, Chapel Hill, NC; [5]Dept. of Neurosurg., Duke Univ. Sch. of Med., Durham, NC

Abstract: Deep brain stimulation (DBS) is an established therapy for the motor symptoms of Parkinson's disease (PD). Nevertheless, the underlying circuit mechanisms of DBS are still unclear, and this impedes the continued improvement of DBS therapy. To fill this gap, we scanned whole brain activity during different frequencies of DBS by combining function magnetic resonance imaging (fMRI) and optogenetic DBS. fMRI enables unbiased identification of brain regions and pathways that are responsible to the effects of DBS. Optogenetics further dissects the neural circuit by targeting specific cell types or pathways. We hypothesize that different brain regions are activated dependent on the DBS frequency, which is closely related to the therapeutic effects.

We scanned four female unilateral-6-OHDA-lesioned rats during optical-stimulation of the ipsilateral subthalamic nucleus (STN). We used an ultrafast opsin (AAV5-CaMKII-Chronos-GFP) to capture the frequency-dependent effects of therapeutic DBS. The 6-OHDA lesion and the expression of virus were validated by methamphetamine-induced circling behavior (before opto-DBS: 4.75 ± 1.29 cycles/min, during 130 Hz opto-DBS: 1.62 ± 0.44 cycles/min, n = 4) and histological examination. We obtained BOLD fMRI data using whole-brain isotropic EPI sequence in 9.4T Bruker MRI scanner (TR = 2000 ms, TE = 14 ms, matrix = 72 x 72 x 32, voxel size = 0.4 x 0.4 x 0.4 mm^3). Six repetitions of the optical-stimulation train including 10 s of stimulation and 20 s rest period block following an initial 10 s baseline period were applied on STN at different frequencies (5 Hz, 20 Hz, 75 Hz, 100 Hz, and 130 Hz; pulse width 1ms). We applied core preprocessing steps including slice timing correction, motion correction, reorientation of the brain into an in-house EPI brain template using AFNI software package. The stimulation-related activation map was estimated using a general linear model (GLM) framework.

The activation maps exhibited frequency-dependent changes in BOLD signals in ipsilateral GPe, SNr, and PTg (Pedunculotegmental nucleus) and peak changes of positive BOLD response during DBS above 100Hz ($\alpha > 0.05$ with FWE error correction, p-value < 0.05, voxel size > 40) while primary somatosensory(S1) and caudate putamen (CPu) showed negative BOLD changes during low frequency stimulation (5 and 20Hz). Our result suggests that the frequency-dependent effects of STN DBS are mediated by changes in the SNr and its downstream nuclei.

Disclosures: **Y. Li:** None. **S. Lee:** None. **C. Yu:** None. **T.W. Wang:** None. **Y.I. Shih:** None. **W.M. Grill:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Deep Brain Innovations LLC, NDI Healthcare Fund. F. Consulting Fees (e.g., advisory boards); Cala Health, Inc.

Poster

743. Parkinson's Disease: Therapeutics

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 743.12/C92

Topic: C.03. Parkinson's Disease

Support: Swiss National Science Foundation grant

Title: The use of a macroporous biomaterial scaffold for differentiation and transplantation of dopaminergic neurons in treatment of Parkinson's disease

Authors: *A. FILIPPOVA[1], K.-H. KRAUSE[2], T. BRASCHLER[2];
[1]Pathology and Immunol., [2]Univ. of Geneva, Geneva, Switzerland

Abstract: Parkinson's disease (PD) affects an estimated 6 million people worldwide. Cell therapy aimed at replacing degenerating dopaminergic neurons with dopamine-producing cell grafts has been advancing and gaining popularity in recent decades. Transplantation of fetal mesencephalic tissue into the striatum of diseased patients has shown impovement of motor function. Recent research has focused on the transplantation of human pluripotent stem cell (hPSC)-derived grafts, as amplifyable, more ethically sound cell sources. For transplantation purposes, hPSCs are typically differentiated into neural precursor cells (NPCs) and transplanted as single cell suspention. The efficacy of the graft is then dependent on the neuronal maturation in vivo and the outcome may vary depending on the patients innate microenvoronment. Transplantation of mature dopaminergic neurons could help evaluate the functionality of the final graft and decrease the variability. However, it has so far been hindered by the fragility of neurons and neurites and their intolerance to the harsh handling procedures.
This project aims at evaluating a porous biomaterial scaffold as structural support for NPCs during maturation and transplantation. Such scaffold would allow pre-transplantation characterization of the final graft and preservation of integrity of mature neurons during surgery. We developed an adhesive surface, permitting neurites to attach and spread during differentiation. After differentiation of hPSC-derived NPCs on the scaffold, we observed an increased expression of dopamine neuron-specific markers (MSX1, LMX1A, PAX8, TH, EN1, MAP2). After passing the scaffold through an injection needle, we observed enhanced neuronal survival, decreased cell loss and preservation of neurite architecture, compared to trypsinized neurons, pre-differentiated on 2D culture plates.
Unlike the rapidly biodegradable encapsulating materials, studied for such application previously, the scaffold used here was shown to biodegrade within twelve months in vivo. Thus, upon in vivo injection we expect the scaffold to structurally support the architecture of the grafted neurons within this time. Unlike encapsulating materials, a macroporous biomaterial would allow pefusion of the scaffolds with innate neurotrophic factors and facilitate interaction

with the endogenous neuronal neural network. The in vivo experiments on the latter hypothèses are currently ongoing.
In conclusion, we anticipate that using a macroporous biomaterial would help further impove the efficacy and decrease the variability of the currently developing cell replacement techniques.

Disclosures: A. Filippova: None. **K. Krause:** None. **T. Braschler:** None.

Poster

743. Parkinson's Disease: Therapeutics

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 743.13/D1

Topic: C.03. Parkinson's Disease

Title: Targeting the microbiome in the MPTP-lesioned mouse model of Parkinson's disease: Live biotherapeutic products (LBPs) demonstrate disease-modifying effects

Authors: S. CHETAL[1], P. RAVENSCROFT[2], A. ETTORRE[1], J. B. KOPRICH[2], ***M. P. HILL**[2], J. M. BROTCHIE[2], I. E. MULDER[1];
[1]4D Pharma Res. Ltd., Aberdeen, United Kingdom; [2]Atuka Inc., Toronto, ON, Canada

Abstract: The gut microbiome plays a vital role in host health and microbiome therapeutics have shown benefits in diseases ranging from IBD to oncology. There has been an interest in the role of the (microbiota)-gut-brain axis in Parkinson's disease (PD), supported by findings such as an altered gut microbiota composition, presence of α-synuclein in the gut, and gastrointestinal co-morbidities in PD patients. These findings have led us to investigate the development of novel, microbiome-based treatments as an appealing therapeutic strategy. 4D pharma is a clinical-stage microbiome company. Its proprietary MicroRx® discovery platform identified two live biotherapeutic products (LBPs), *Parabacteroides distasonis* MRx0005 and *Megasphaera massiliensis* MRx0029, for the treatment of PD. The ability of these two LBPs to protect against nigrostriatal dopaminergic deficits was assessed in the MPTP-lesioned mouse model of PD. Six groups (Groups 1 - 6) of animals were employed. Animals in Groups 1 and 2 were administered vehicle (PBS, *PO, QD*), while animals in Groups 3 and 4 were administered the LBPs (*PO, QD*) for 35 days (Day -14 - Day 21). Animals were administered vehicle (Group 1, 0.9% saline, *IP*) or MPTP (Groups 2 - 6, 20 mg/kg, *IP, BID*) for 5 days (Day 1 - Day 5). On Days 1 - 5, animals in Groups 5 and 6 were administered vehicle or a reference treatment, 7-nitroindazole (7-NI, 50 mg/kg, *IP*, *BID*). Animals were killed on Day 22. Striatal dopamine transporter (DAT) levels were quantified by autoradiography. Striatal dopamine (DA) and its metabolites (HVA and DOPAC) levels were quantified by LC/MS. Tyrosine hydroxylase positive (TH^+) cell number in the substantia nigra (SN) was quantified by immunohistochemistry and stereology. MPTP administration produced deficits in dopaminergic function such that in vehicle/MPTP administered mice, compared to vehicle/vehicle, the number of TH^+ SN dopaminergic neurons

was reduced by 46%, striatal DA was reduced by 77%, striatal DA turnover was increased by 154% and striatal DAT was reduced by 83% (all P<0.001). 7-NI protected against MPTP-induced losses in striatal dopamine (75% increase *cf.* vehicle/MPTP; P<0.001), striatal DAT (111% increase *cf.* vehicle/MPTP; P<0.001) and TH^+ nigral cell number (56% increase cf. vehicle/MPTP; P<0.001). MRx0029 protected against MPTP-induced loss in nigral TH^+ cell numbers (65% increase *cf.* vehicle/ MPTP; P<0.01), while MRx0005 protected against the loss of striatal DA and DOPAC to a similar degree as 7-NI. In conclusion, the LBPs MRx0029 and MRx0005 had a disease-modifying effect in the MPTP model. Further investigation is needed to fully elucidate their potential in the treatment of PD.

Disclosures: **S. Chetal:** A. Employment/Salary (full or part-time):; 4D Pharma Research Ltd.. **P. Ravenscroft:** None. **A. Ettorre:** A. Employment/Salary (full or part-time):; 4D Pharma Research Ltd.. **J.B. Koprich:** None. **M.P. Hill:** None. **J.M. Brotchie:** None. **I.E. Mulder:** A. Employment/Salary (full or part-time):; 4D Pharma Research Ltd..

Poster

743. Parkinson's Disease: Therapeutics

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 743.14/D2

Topic: C.03. Parkinson’s Disease

Support: FAPESP -Brazil - 2016/07168-2
FAPESP - Brazil - 2017/14020-4
AHA Grant 17sdg33410777

Title: Does high frequency stimulation affect astrocytes in a model of Parkinson's disease?

Authors: *A. CAMPOS[1], D. S. KIKUCHI[2], A. F. N. PASCHOA[1], M. A. KUROKI[1], B. LASSÈGUE[2], E. T. FONOFF[3], K. K. GRIENDLING[2], C. HAMANI[4], M. S. HERNANDES[2], R. L. PAGANO[1];
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Abstract: Introduction: Despite its broad therapeutic application in the management of debilitating neurological symptoms, the underlying mechanisms of high-frequency stimulation (HFS), as used in deep brain stimulation (DBS), remain largely unknown. Recent reports suggest, reactive astrocytes, which can oscillate between pro-inflammatory (A1 subtype) or neuroprotective/anti-inflammatory (A2 subtype) phenotypes, may play a role in the development and progression of neurological diseases. Given the clinical importance of HFS, we investigated the effects of DBS/HFS on astrocyte subtype in an animal model of Parkinson’s disease and

cultured astrocytes. **Methods:** Male Wistar rats were injected with 6-hydroxydopamine (6-OHDA) or saline in the left striatum. Animals were implanted or not with stainless steel electrodes in the left subthalamic nucleus (STN). Seven days after the surgery, animals were evaluated using the apomorphine-induced rotation and the bar tests. On the 8th day, animals were divided into four groups: saline, 6-OHDA, 6-OHDA + DBS OFF and 6-OHDA + DBS ON. DBS ON animals were stimulated 2 hours a day for 5 days (130 Hz, 60 µs, 0.1 mA). After the last stimulation, animals were submitted to the bar test again. On the 12th day following 6-OHDA injection, GFAP immunostaining and cytokine expression (IL-1β, IL-6, IL-10 and IFN-γ) were evaluated in the globus pallidus (GP). For *in vitro* experiments, cultured astrocytes were stimulated with HFS for 6 h, and exposed to TNFα during the last hour (for IL-6 and MCP1 expression) or the last 15 min (for NFκ-B activation by IkB-α degradation and p65 nuclear translocation) of stimulation. *In vitro* conditions were as follows: no TNFα, TNFα + HFS OFF and TNFα + HFS ON. **Results:** The DBS-treated animals presented less immobility in the bar test, suggesting an improvement of motor deficit. Six-OHDA-induced increase in GFAP was modestly but significantly reduced by DBS in GP. DBS decreased IL-1β, IL-10 and IFN-γ expression in the GP. In our *in vitro* model, MCP1 expression and NFκB activation were decreased by HFS in astrocytes. **Conclusion:** Both 6-OHDA and TNFα administration induces inflammation characterized by an increase of cytokines. Here we suggest that DBS/HFS decreases 6-OHDA/TNFα - induced astrocyte classical A1 activation. This would reduce M1 microglia attraction by inhibiting MCP1 and attenuate the INF-γ/IL-10 imbalance. These findings contribute to our understanding of the role of astrocyte signaling in HFS. They suggest that DBS can reduce neuroinflammation and thereby improve neurodegenerative disorders.

Disclosures: A. Campos: None. **D.S. Kikuchi:** None. **A.F.N. Paschoa:** None. **M.A. Kuroki:** None. **B. Lassègue:** None. **E.T. Fonoff:** None. **K.K. Griendling:** None. **C. Hamani:** None. **M.S. Hernandes:** None. **R.L. Pagano:** None.

Poster

743. Parkinson's Disease: Therapeutics

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 743.15/D3

Topic: C.03. Parkinson’s Disease

Support: NIH Grant DA011261
NIH Grant NS088554

Title: Inhibition of phosphodiesterase 10A upregulates gene expression in the striatum

Authors: F. PADOVAN-NETO, G. KUREK, R. BONATE, S. PATTERSON, F. ALTWAL, A. WEST, *H. STEINER;
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Abstract: The effects of dopamine (DA) in striatal projection neurons are mediated by cyclic nucleotides (e.g., cAMP). Phosphodiesterases (PDEs) catalyze cyclic nucleotides and thus potently control cyclic nucleotide signaling. Cyclic nucleotide levels are dysregulated in animal models of Parkinson's disease (PD), especially during L-DOPA-induced dyskinesias (LIDs). Recent studies show that inhibitors of PDE10A, a phosphodiesterase highly expressed in the striatum, can attenuate LIDs in animal models, suggesting the utility of PDE inhibitors for modifying abnormal cyclic nucleotide signaling and reducing dyskinesias in PD. We used a PD model, rats with unilateral 6-OHDA lesions treated with L-DOPA (5 mg/kg + benserazide, 12.5 mg/kg; 3 weeks), to investigate the impact of the selective PDE10A inhibitor TP-10 (3.2 mg/kg, which attenuates LIDs) on cyclic nucleotide signaling, as indicated by cAMP-dependent gene regulation in the striatum. Effects on the expression of PDE10A itself and the "activity" markers dynorphin (DYN, direct pathway) and enkephalin (ENK, indirect pathway) were assessed by in situ hybridization histochemistry. These treatments had a minor impact on PDE10A expression: The 6-OHDA lesion modestly decreased PDE10A mRNA levels throughout the striatum, an effect that was attenuated by L-DOPA and somewhat enhanced by L-DOPA+TP-10 treatment. As shown before, DA depletion alone decreased DYN expression and increased ENK expression, while L-DOPA considerably increased DYN expression and slightly further enhanced ENK expression. The L-DOPA+TP-10 combination modestly further increased DYN and ENK expression in the DA-depleted striatum, but dramatically elevated DYN and ENK expression in the intact striatum. This increase was most robust in the sensorimotor striatum and was directly related to the level of PDE10A expression in different striatal regions, suggesting local drug action. L-DOPA-induced alterations in cyclic nucleotide signaling and gene regulation in striatal neurons are implicated in LIDs. Our results show that the PDE10A inhibitor TP-10, in a dose that attenuates LIDs, increases gene expression in both striatal output pathways. These molecular changes may contribute to the beneficial effects of PDE10A inhibitors in the treatment of LIDs.

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Poster

743. Parkinson's Disease: Therapeutics

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 743.16/D4

Topic: C.03. Parkinson's Disease

Title: Therapeutic effects of cortical electrical stimulation on Parkinsonian rats

Authors: *K. CHI-WEI[1], C.-Y. PAN[1], Y.-Z. HUANG[2], T.-H. HSIEH[3];
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Physical Therapy and Grad. Inst. of Rehabil. Science, Col. of Med., Chang Gung Univ., Taoyuan, Taiwan

Abstract: Background: Parkinson's disease (PD) is one of the prevalent neurodegenerative disorder. The pathologic hallmark of the disease results from degeneration of the dopaminergic neurons (DA) in the substantia nigra (SN), several motor disturbances. Cortical electrical stimulation (CES) has been developed for modulating cortical excitability via plasticity-like mechanism and is considered having therapeutic potentials in PD. However, the therapeutic value of such approach for PD is still unclear. Accordingly, we adopted the PD rat model for elucidating the possible therapeutic effects of CES. **Methods:** A hemiparkinsonian rat model, induced by unilateral injection of 6-hydroxydopamine (6-OHDA) into the medial forebrain bundle (MFB), was applied to investigate the therapeutic roles of CES in motor functions following long-term CES treatment for 4 weeks. After CES intervention, the detailed functional behavioral tests including gait, bar test, open field, and apomorphine-induced rotational analysis as well as DA degeneration level were assessed up to 4 weeks. **Results:** After CES treatment, we found that 4 weeks of CES intervention ameliorates the motor deficits in gait pattern, akinesia, locomotor activity, and apomorphine-induced rotation. Immunohistochemistry, tyrosine hydroxylase (TH) staining analysis demonstrated that the dopamine neurons were significantly preserved. **Conclusions:** This study documents the efficacy of CES in preventing motor and dopaminergic system abnormalities in rat model of PD. This long-term CES treatment model may serve as a bridge between animal and PD human studies. Future preclinical studies are still needed to further identify the underlying mechanisms, leading to improve CES protocols and therapies in human.
Keywords: cortical electrical stimulation, Parkinson's disease, 6-hydroxydopamine, motor function, gait, locomotor function

Disclosures: K. Chi-Wei: None. **C. Pan:** None. **Y. Huang:** None. **T. Hsieh:** None.

Poster

743. Parkinson's Disease: Therapeutics

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 743.17/D5

Topic: C.03. Parkinson's Disease

Title: Characterization of 4L/PS-NA mice for different biomarkers to model Gaucher disease

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Abstract: Introduction: Gaucher disease is the most common lysosomal storage disease. The neuronal disease variant is characterized by protein accumulations in the brain and associated neurological manifestations. It is autosomal recessively inherited and modeled by 4L/PS-NA mice that express low levels of prosaposin and saposins, as well as a functionally impaired β-glucosidase (GCase) with a homozygous point mutation at V394L.
To use this model for compound tests against Gaucher disease a detailed characterization of these mice is needed. Thus, we analyzed the 4L/PS-NA mice for GCase activity, glucosylsphingosine (GlcSph) and glucosylceramide (GlcCer) levels as well as Neurofilament light chain (NF-L) levels and neuroinflammation over age.
Method: The GCase activity was analyzed using a commercially available GCase activity assay. GlcSph and GlcCer were extracted from brain homogenates by liquid-liquid extraction and the levels of GlcSph and GlcCer in the extracts were measured by ultrahigh-performance liquid chromatography coupled to tandem mass spectrometry. To explore Neurofilament light chain levels, the NF-Light® ELISA by UmanDiagnostics was used. For measurement of neuroinflammatory processes, in particular activated microglia and astrocytosis, immunofluorescent labeling on brain sections was performed.
Results: Analyses of enzyme activity show reduced GCase levels in 4L/PS-NA and also control mice compared to C57Bl/6 mice due to the mutation in GBA. The additional reduction of prosaposin and saposins leads to progressively increasing substrate concentrations in 4L/PS-NA mouse brains compared to control animals. Furthermore, 4L/PS-NA mice show strongly increased NF-L and neuroinflammation levels.
Conclusion/ Summary: 4L/PS-NA mice mimic the most prominent features of Gaucher disease suggesting that they are a good model to study the chronic neuronopathic type 3 Gaucher disease in humans.

Disclosures: **B. Hutter-Paier:** A. Employment/Salary (full or part-time):; QPS Austria GmbH. **S. Flunkert:** A. Employment/Salary (full or part-time):; QPS Austria GmbH. **S. Schmidt:** A. Employment/Salary (full or part-time):; Pronexus Analytical AB. **T. Loeffler:** A. Employment/Salary (full or part-time):; QPS Austria GmbH. **V. Niederkofler:** A. Employment/Salary (full or part-time):; QPS Austria GmbH. **J. Neddens:** A. Employment/Salary (full or part-time):; QPS Austria GmbH. **M. Posch:** A. Employment/Salary (full or part-time):; QPS Austria GmbH. **E. Auer:** A. Employment/Salary (full or part-time):; QPS Austria GmbH. **J. Kehr:** A. Employment/Salary (full or part-time):; Pronexus Analytical AB.

Poster

743. Parkinson's Disease: Therapeutics

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 743.18/D6

Topic: C.03. Parkinson’s Disease

Support: NINDS Grant NS088554 (ARW/KYT)
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Title: Using multimodal serotonergic drugs as adjunct treatments for Parkinsons's disease

Authors: *F. ALTWAL, A. RITGER, N. FALCAO VOELKNER, J. DHARGALKAR, R. MALIK, V. OLIVERA, A. WEST;
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Abstract: Parkinson's disease (PD) is a devastating neurodegenerative disorder affecting over one million Americans. The gold standard treatment for PD is levodopa (L-DOPA), which is effective for increasing dopamine (DA) tone and improving motor dysfunction, but unfortunately produces debilitating motor side-effects termed L-DOPA-induced dyskinesias (LIDs). Recent studies in dyskinetic parkinsonian models have implicated serotonergic raphe-striatal terminals in the uptake and conversion of L-DOPA to DA, as well as the non-physiological release of DA and serotonin (5-HT) which may underlie the pathophysiological mechanisms of LIDs. Indeed, the utility of co-treatments with either selective 5-HT reuptake inhibitors (SSRIs) which block the 5-HT transporter (SERT), or selective 5-$HT_{1A/B}$ receptor (5-$HT_{1A/Br}$) ligands which stimulate 5-HT autoreceptors to potentially suppress DA release from 5-HT terminals, has been assessed in pre-clinical models and clinical trials. Many of the drugs tested were found to reduce LIDs, but unfortunately also reduced the prokinetic effects of L-DOPA. The goal of the current study was to identify a multimodal 5-HT drug which can act to attenuate the expression and severity of LIDs, without interfering with the antiparkinsonian efficacy of L-DOPA.
Vilazodone is of interest in this regard as it is known to exhibit a potent SSRI-like action, along with 5-HT_{1Ar} partial agonism property. Unilateral 6-OHDA-lesioned rats modeling PD were treated with either vehicle and L-DOPA (5.0 mg/kg), vilazodone (10.0 mg/kg) and L-DOPA, or escitalopram (12.5 mg/kg) and L-DOPA. Rats were treated for 5 consecutive days/week, for 2 weeks. On the second day of each week, stepping tests were performed prior to drug administration, and 60 minutes post L-DOPA treatment, to assess forelimb akinesia. Behavioral assessment of LIDs was performed (30-180 min) at the end of each week. Vilazodone pretreatment (30 min) significantly reduced LIDs in 6-OHDA lesioned rats, but had no effects on forelimb akinesia or L-DOPA-induced prokinetic effects. Escitalopram pretreatment also induced a significant reduction in total LIDs score but interfered with the therapeutic efficacy of L-DOPA. Electrophysiological studies were conducted to assess the impact of these treatments on corticostriatal transmission and striatal neuronal activity. The current results indicate that together with L-DOPA, multimodal 5-HT drugs such as vilazodone may be an efficacious co-therapies for reducing side-effects such as hyperkinesia (LIDs) in PD patients, potentially allowing for more flexibility in L-DOPA dose ranges and protracted chronic treatment.

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Poster

743. Parkinson's Disease: Therapeutics

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 743.19/D7

Topic: C.03. Parkinson's Disease

Support: MUSC Barmore Foundation
LivaNova PLC

Title: Anti-inflammatory properties of vagus nerve stimulation provide therapeutic potential for a Parkinson's disease model

Authors: *A. Q. FARRAND[1], L. APONTE-COFRESI[1], R. VERNER[2], R. M. MCGUIRE[2], H. A. BOGER[1];
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Abstract: Vagus nerve stimulation (VNS) is known to have anti-inflammatory properties such as reduced pro-inflammatory cytokine production and reduced activation of glia and macrophages both in the periphery and in the central nervous system, thus providing a wide range of potential clinical indications for VNS. Chronic neuroinflammation is one of the mechanisms that contributes to cell damage in neurodegenerative diseases such as Alzheimer's and Parkinson's diseases. Recent studies from our lab have shown that in a double lesion (DSP-4/6-OHDA) rat model of Parkinson's disease two daily sessions of VNS for a 10-day period are sufficient to reduce neuroinflammation in the substantia nigra and locus coeruleus, thereby leading to improved neuronal health and reduced motor deficits. However, the ideal stimulation paradigm for this Parkinson's disease model remains to be determined. Therefore, the current work employs several sets of VNS parameters in this DSP-4/6-OHDA Parkinson's disease model to better characterize the relevant waveform features for this therapy. These parameters were chosen based on the hypothesis that pulse frequency and patterning can differentially regulate afferent and efferent vagal circuits. Our results indicate that higher stimulation frequencies provide greater benefits for motor function and neuronal health as measured by tyrosine hydroxylase expression in the substantia nigra and locus coeruleus, as well as reduced intrasomal α-synuclein accumulation in neurons of the substantia nigra. Studies are ongoing in the lab to assess neuroinflammation in these brain regions and levels of pro-inflammatory cytokines, acetylcholine, and norepinephrine in serum and in the central nervous system. These changes will indicate which pathways are activated by specific sets of VNS parameters, therefore helping to characterize each stimulation paradigm and determine which paradigm provides the greatest therapeutic potential for Parkinson's disease.

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Poster

743. Parkinson's Disease: Therapeutics

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Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 743.20/D8

Topic: C.03. Parkinson's Disease

Support: NIH Grant TL1TR002533
NIH Grant F31 AT010095

Title: Microbiota-targeted therapies delay age-dependent Parkinson's disease progression

Authors: *S. M. GARCIA, W. ZHOU, D. INGUITO, C. R. FREED;
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Abstract: Current therapies for Parkinson's disease (PD) temporarily improve motor function but cannot impact disease progression. We have shown that oral butyrate treatments attenuate alpha-synuclein (aSyn) pathology in the brain and improve motor and cognitive deficits in an age-dependent transgenic (Tg) mouse model of PD. However, there are obstacles associated with oral butyrate treatments such as high volume dosing and drug cost. **Objective:** To bypass these obstacles, we have designed microbiota-targeted dietary inventions to increase endogenous butyrate production in the gut. Because butyrate has multiple neuroprotective and homeostatic functions in the brain and gut, our goal was to delay CNS and ENS pathological hallmarks of PD in mice. **Methods:** To determine if our microbiota-targeted interventions delay age-dependent CNS pathological hallmarks, 12-month Thy1-Y39C *SNCA* Tg mice were separated into treatment groups (n=6) based on rotarod performance and were treated with either sodium chloride (control), oral sodium butyrate (positive control), 10% prebiotic diet, or 10% synbiotic diet for 3-months. Disease progression was determined by behavioral and aSyn neuropathology outcomes. Rotarod and Morris water maze scores assessed motor and spatial learning abilities. To assess if our microbiota-targeted interventions improve pre-motor constipation and associated ENS aSyn aggregation, 1-month PAC-A53T *SNCA* Tg mice (n=18-20) were fed a 3% oat hull control diet, control diet + oral sodium butyrate, control + probiotic diet, 20% prebiotic diet, 10% prebiotic diet, or 10% synbiotic diet for 11-months. Whole gut transit time (WGTT), fecal output/ 1-hour, fecal water content, and rotarod performance was evaluated every 3-months until 12-months. Fecal and colonic samples were collected before and after treatment to assess microbial composition for both studies. **Results:** 15-month Thy1-Y39C *SNCA* Tg mice treated with sodium butyrate, 10% prebiotic, and 10% synbiotic all show improved motor function compared to controls, but only the synbiotic treatment could reduce brain aSyn oligomerization as well as sodium butyrate. PAC-A53T *SNCA* Tg mice treated with 10% prebiotic and 10%

synbiotic diets have shorter WGTTs and increased fecal water content compared to controls as early as 3-months of age. **Conclusions:** Microbiota-targeted therapies that upregulate butyrate production in the gut improve pre-motor ENS deficits and delay disease progression in advanced stages of PD in Tg mice. Possible modes inducing the therapeutic effects observed may be due to increased circulating butyrate or modified gut-brain axis signaling.

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Poster

743. Parkinson's Disease: Therapeutics

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Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 743.21/D9

Topic: C.03. Parkinson's Disease

Support: NIH AG040261

Title: Calorie restriction: Efficacy of a lifestyle strategy to mitigate aging-related Parkinsonism when initiated in the latter half of the lifespan and nigrostriatal mechanisms

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Abstract: Up to 50% of the elderly may suffer from locomotor impairments similar to those in Parkinson's disease. These impairments greatly compromise the ability to perform daily life activities, and portend to loss of independent living, frailty, and mortality. Engagement of lifestyle strategies in middle or advanced middle age could prove beneficial to reduce risk of aging-related parkinsonism. We previously reported that initiation of caloric restriction (CR) in middle-aged rats can reduce aging-related parkinsonism without a commensurate increase in striatal dopamine (DA) content or tyrosine hydroxylase expression. Here, we evaluated if CR could prevent aging-related motor decline when initiated well into the latter half of the rat lifespan, and well after motor decline occurs, to answer to whether there is an aging-related limit of CR efficacy. 18-month old male Brown-Norway/Fischer rats maintained on a lifelong *ad libitum* (AL) diet were grouped into CR and AL groups. CR was gradually introduced to 30% by 3 weeks after study initiation and maintained for 6 months with open-field locomotor assessments of movement frequency and speed conducted every 6 weeks. A significant and sustained decline in movement frequency was observed in the AL group from 12 weeks after initiation of the study. To the contrary, CR prevented this aging-related decline, with increased movement frequency in the CR group compared to the AL group at 12 and 24 weeks and speed at 18 weeks after CR initiation. We also observed that rats with lower baseline locomotor activity

responded better to CR intervention with less decline from baseline. This preservation of motor function was associated with an increase in dopamine D1 receptor expression in the substantia nigra, but not striatum. Striatal DA content and tyrosine hydroxylase expression were also unaffected by CR. In summary, CR may be an effective lifestyle strategy to reduce aging-related parkinsonism, even when initiated well into the latter half of the lifespan and after motor decline begins in the lifespan. These results also add to the body of work that increases in striatal DA biosynthesis may not be necessary for preservation of motor function. Targeting nigral DA neurotransmission may represent an avenue to mitigate motor impairment in individuals wherein CR or other lifestyle interventions would be contraindicated.

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Poster

743. Parkinson's Disease: Therapeutics

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Program #/Poster #: 743.22/D10

Topic: C.03. Parkinson’s Disease

Support: Arizona Biomedical Research Commission (ABRC)

Title: Changes in dendritic mushroom spine density and an inflammatory marker in the striatum underlie long-term suppression of L-DOPA-induced dyskinesia by low-dose ketamine

Authors: T. FALK[1], M. J. BARTLETT[2], J. STANCATI[3], A. E. POTTENGER[4], D. C. FARRELL[4], M. L. HEIEN[5], K. STEECE-COLLIER[3], *H. W. MORRISON[4], S. J. SHERMAN[6]; [1]Dept. Of Neurol., [2]Dept. of Pharmacol., Univ. of Arizona Col. of Med., Tucson, AZ; [3]Michigan State Univ., Grand Rapids, MI; [5]Chem. and Biochem., [4]Univ. of Arizona, Tucson, AZ; [6]The Univ. of Arizona, Tucson, AZ

Abstract: Sub-anesthetic ketamine infusions are an effective therapy for the treatment of depression and pain states. We have demonstrated a therapeutic effect of sub-anesthetic ketamine in Parkinson’s disease (PD) patient case studies with L-DOPA-induced dyskinesia (LID; Sherman et al. 2016). In a preclinical model, we have reported that established LID, measured by abnormal involuntary movements (AIMs) in this model, are reduced by a 10-hr low-dose ketamine infusion paradigm (Bartlett et al. 2016), and showed since that ketamine can suppress development of LID as well, mediated by activation of mTOR, a known regulator of neuroplasticity. To further elucidate the underlying mechanism male Sprague-Dawley rats were unilaterally injected with 6-hydroxydopamine to create a PD model. In a first cohort (n = 10/group), PD rats were primed with daily injections of L-DOPA for 14 days, and treated on days 0 and 7 with either vehicle, ketamine, or ketamine plus the tropomyosin receptor kinase B

(TrkB) antagonist, ANA-12, to block signaling via brain-derived neurotrophic factor (BDNF). On day 14, ketamine treated rats showed a 50% reduction in their AIMs scores compared to vehicle ($p < 0.01$; one-way ANOVAs, Tukey *post-hoc* tests). However, this sustained effect of ketamine was blocked in rats co-treated with ANA-12 ($p < 0.05$). Dendritic spines in the striatum were then analyzed after a Golgi stain. Ketamine prevented the two-fold increase in multi-synaptic mushroom spines on the lesioned side seen in vehicle-injected rats ($p < 0.0001$). In the ketamine plus ANA-12 group ketamine's effect on mushroom spines was blocked ($p < 0.0001$). To test possible involvement of microglia in spine removal, we repeated the suppression of development of LID in a second cohort (n = 6-10). We again observed that LID AIMs were reduced at day 14 with ketamine treatment ($p < 0.05$ vs. vehicle), and investigated inflammatory markers and microglial morphology. Striatal concentrations of the pro-inflammatory IL6 were not altered by the PD-lesion, but ketamine had a significant effect to increase IL6 concentrations (2way ANOVA: lesion: $F(1,16) = 3.44$, $p = 0.08$, treatment: $F(1,16) = 10.38$, $p = 0.005$). Microglia were de-ramified in the striatum and substantia nigra of the lesioned hemisphere, but morphology was not changed with ketamine treatment at this time point, 7 days after the last ketamine treatment. In conclusion, the sustained anti-dyskinetic effect of ketamine is inhibited by blocking BDNF-signaling and involves changes in striatal spine density and a change in an inflammatory cytokine. This data provides further preclinical evidence to support repurposing of ketamine to treat PD patients suffering from LID.

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Poster

743. Parkinson's Disease: Therapeutics

Location: Hall A

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Program #/Poster #: 743.23/D11

Topic: C.03. Parkinson's Disease

Support: Department of Defense grant W81XWH-17-1-0062
Dorothy/Daniel Gerwin Parkinson's Research Fund
Neuroscience Institute and Division of Rehabilitation Sciences, College of Health Professions, University of Tennessee Health Science Center

Title: DNA double-strand-breaks as a potential therapeutic target in Parkinson's disease

Authors: *M. KHAN[1], J. XIAO[1], N. THADATHIL[2], R. HORI[3], J. MOHAMED[4], M. MCDONALD[5];
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Abstract: Parkinson's disease (PD) is a progressive neurodegenerative disease affecting approximately 1 million people in the United States, and there is no curative treatment for this disease. PD is characterized by severe loss of dopaminergic neurons in the substantia nigra and dopamine depletion in striatum resulting in a debilitating motor function. While the molecular mechanisms that regulate the progression of the PD are not fully elucidated, there is evidence to suggest that accumulation of DNA damage, particularly DNA double-strand breaks (DSBs), contribute to the progression of the dopaminergic neurodegeneration. The present study was undertaken to examine whether DSBs accumulation contributes to the nigrostriatal neurodegeneration in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) mouse model of PD. To test our hypothesis that DSBs accumulation has a pathogenic role in PD, we have treated primary mesencephalic neuron/glia cultures with 1-methyl-4-phenylpyridinium (MPP^+) (10 μM) for 48 h. We observed increased and sustained DSBs as assessed by γ-H2A.X (Ser139) and 53BP1 immunoreactivity, and degeneration of tyrosine hydroxylase-positive neurons when compare to control neuron/glia cultures. Next, we demonstrate that wild-type mice treated with MPTP display increased expression of γ-H2A.X (Ser139) and 53BP1 along with increased NLRP3-inflammasome as measured by immunohistochemistry and Western blot. Tyrosine hydroxylase labelling showed that DSBs and inflammatory markers were associated with significant increases in dopaminergic neuronal loss in MPTP-treated mice. Interestingly, increased dopaminergic neuronal loss was markedly reduced by treatment with a specific and selective NLRP3 inhibitor. In conclusion, our results provide the evidence that accumulation of DSBs in the brain causes increased neuroinflammation and contributes to dopaminergic neurodegeneration in Parkinsonian mice. Thus, targeting the DSBs-associated neuronal death pathway might offer a novel approach to prevent or slow down PD progression.

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Poster

743. Parkinson's Disease: Therapeutics

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Program #/Poster #: 743.24/D12

Topic: C.03. Parkinson's Disease

Support: R101 NS 091238-01A1

Title: Evaluation of neuroprotective PACAP glycopeptides as systemically delivered CNS active drugs to treat Parkinson's disease

Authors: *K. BERNARD[1], M. J. BARTLETT[2,3], C. LIU[4], G. MOLNAR[2], C. R. APOSTOL[4], R. BUTLER[2], L. SZABO[4], S. J. SHERMAN[3], L. MADHAVAN[3,1], J. M. STREICHER[2], R. POLT[4], M. L. HEIEN[4], T. FALK[3,2,1];
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Abstract: Pituitary adenylate cyclase activating polypeptide (PACAP) is an endogenous neuropeptide that agonizes PAC1, VPAC1, and VPAC2 receptors. PACAP is neuroprotective after injection into the striatum in a model of Parkinson's disease (PD), and it inhibits neuronal apoptosis, suggesting that it could be a drug candidate to treat PD. However, native PACAP exhibits poor pharmacokinetics, is rapidly degraded and has low bioavailability. Glycosylation of peptides was shown to improve peptide stability, enhance (or retain) the original biological activities, and modulate the ability of the peptides to cross the blood-brain barrier (BBB). We have designed and synthesized several PACAP glycopeptides with various serine glycosides at the C-terminus as well as added amino acid substitutions to enhance stability. These glycopeptides were tested for their ability to stimulate cAMP production *in vitro* using individual CHO cell lines expressing PAC1, VPAC1, and VPAC2. The $PACAP_{1-27}$ glycosides (lactoside among others) maintained receptor agonism with modest selectivity between the PAC1 and VPAC1/2 isoforms. These results were confirmed using a high throughput calcium imaging assay (FLIPR), which showed that $PACAP_{1-27}$ and the serine glucoside ($PACAP_{1-27}$S-Glc) showed equivalent activation of the PAC1 receptor. *In vitro* half-lives in 25% serum matrix: native PACAP=13.9 min, $PACAP_{1-27}$S-Glc=28.6 min, while $PACAP_{1-27}$S-Lac stays above 50% of initial concentration over 60 min. *In vitro* half-life of native PACAP in water: 2.8 min; shorter than all glycosylated derivatives in a CSF matrix. All glycosylated peptides studied were stable over 60 min in a CSF or 180 min in water. *In vivo* CSF data using 'shotgun microdialysis' coupled with $LC\text{-}MS^3$ (n=1, 15 mg/kg, *i.v.*) shows $PACAP_{1-27}$S-Lac is able to penetrate the BBB. Native PACAP at 15 mg/kg showed ~7 μM estimated CSF concentration, $PACAP_{1-27}$S-Lac showed ~24 μM estimated CSF concentration, while serum concentration of glycosylated peptides reached 20~120 μM at 5 mg/kg. To test for *in vivo* activity of the lead glycopeptide, we began a study using a mild progressive unilateral 6-hydroxydopamine (6-OHDA) rat PD model (n=16/group). In the treatment group rats were injected (*i.p.*) with 15 mg/kg of $PACAP_{1-27}$S-Lac both 6-hrs prior and 48-hrs post 6-OHDA injection. At 2 weeks post-6-OHDA a trend of reduced amphetamine-induced rotations is seen (2-tail t-test, $p = 0.09$). The study is ongoing, and after conclusion of behavioral analysis, unbiased stereology of dopaminergic neurons in the substantia nigra will be conducted (n=8/group), and striatal dopamine content will be measured (n=8/group) to evaluate the extent of any neuroprotection.

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Poster

743. Parkinson's Disease: Therapeutics

Location: Hall A

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Program #/Poster #: 743.25/D13

Topic: C.03. Parkinson's Disease

Support: Jerry T. and Glenda G. Jackson Fellowship for Parkinson's Disease Research to The University of Arizona

Title: Neuroprotective effects of VEGF-B overexpression in PINK1 gene knockout rats

Authors: *M. J. BARTLETT[1,2], S. I. SMIDT[1], S. CRISTIANI[1], M. J. CORENBLUM[1,3], D. C. FARRELL[5], K. P. DOYLE[1,4], M. L. HEIEN[5], L. MADHAVAN[1,3], S. J. SHERMAN[1], T. FALK[1,2];
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Abstract: Currently there are no therapies to slow the dopaminergic cell loss occurring in the substantia nigra pars compacta (SN) of Parkinson's disease (PD) patients. Previously, we identified vascular endothelial growth factor B (VEGF-B) as a potential therapeutic candidate due to its upregulation in the dopaminergic cells of a rat midbrain culture when challenged by rotenone. We have also published on VEGF-B's neuroprotective effects both *in vitro* and *in vivo*. Exogenous VEGF-B is neuroprotective against rotenone in the same rat midbrain culture system as above. It is also neuroprotective in a progressive unilateral 6-hydroxydopamine (6-OHDA) rat model of PD when injected in the striatum prior to the toxin. We now add information from a genetic PD model, PTEN-induced putative kinase 1 (PINK1) knockout (KO) rats. This study adds a new cohort and expands on previously reported pilot data showing that unilateral injections of an adeno-associated virus expressing human VEGF-B (AAV2/1-hVEGF-B) into the SN and striatum of 5 month old PINK1 (KO) rats reduced motor impairment in the tapered balance beam (TBB) task. In this PD model, cumulative footslips were reduced during monthly TBB sessions post-injection (months 6-12) in the contralateral hindlimb of the PINK1 KO rats compared to PINK1 KO rats treated with VEGF-B (One-way ANOVAs; *$p<0.05$; n=9-13). After completing behavioral testing, at 12 months of age, brain tissue was harvested or perfused for either dopamine (DA) content and mechanistic studies or unbiased stereology, respectively. Through the addition of more animals, we have further demonstrated that VEGF-B-over-expression increases DA content in the striatum, analyzed via HPLC-EC, by 30% in the injected hemisphere compared to the non-injected hemisphere (One-way ANOVAs; *$p<0.05$; n=4-7). To determine if VEGF-B's effects on motor function and striatal DA content is neuroprotective or due to a functional improvement in the surviving DA neurons we are currently analyzing, via

unbiased stereology, DA neurons in the SN after co-staining for tyrosine hydroxylase and the neuronal marker, NeuN. In an effort to further characterize the potential mechanisms of VEGF-B's therapeutic effects, we have completed a new pilot analysis showing a trend of elevated phosphorylation levels of striatal mTOR (mean ratio ipsilateral/contralateral of P-mTOR/mTOR ± SEM) in the injected hemisphere, as measured with a multiplex ELISA (Kruskall-Wallis rank test, Dunn *post-hoc* test; $^{\#}p=0.09$; n=3-5). We are also adding to the prior pilot study that showed striatal upregulation of pigment epithelium-derived factor, a known inhibitor of apoptosis (ELISA), after VEGF-B over-expression.

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Poster

744. Neuroinflammation: HIV and Infections

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 744.01/D14

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: Grants from Japan Ministry of Health, Labour and Welfare

Title: Differences of cognition and brain white matter between cART-treated HIV-infected patients with low and high CD4 nadir

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Abstract: The introduction of combination antiretroviral therapy (cART) lead to improve immune recovery in patients with HIV. Despite viral suppression with cART, the frequency of HIV-associated neurocognitive disorders (HAND) remains high. On the biological background of HAND, there is an impaired brain white matter integrity in the patients. Diffusion tensor imaging (DTI) is a noninvasive imaging modality that can assess white matter microstructure, and tract-based spatial statistics (TBSS) can analyze the whole-brain white matter tract. On the other hand, low CD4 T-cell counts has been associated with HAND. In the present study, using DTI and TBSS, we examined the differences of cognitive dysfunction and white matter impairment between 3 groups: fifteen HIV-infected patients with low CD4 nadir (cell count <150), 16 HIV-infected patients with high CD4 nadir (cell count ≥150), and 33 age- and handedness- matched healthy controls. In addition, we examined the correlation between the white matter impairment and cognitive dysfunction in the HIV-infected patients with low CD4 nadir. All HIV-infected patients had achieved viral suppression after cART. The participants

underwent the neuropsychological tests including seven cognitive domains and DTI scan on 1.5T MRI in the National Hospital Organization Osaka National Hospital. We assessed group differences of fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) from DTI data. The patients with low CD4 nadir had significantly lower performance of executive functions, motor skills, processing speed, and sensory-perceptual domains compared to other two groups. TBSS on the patients with low CD4 nadir showed the significant increased MD, AD, and RD in the widespread areas involving the bilateral cerebral hemispheric, cerebellar, and brain stem white matter compared to other two groups, while no differences were detected in FA. There were no significant differences of FA, MD, AD, and RD in the brain between the patients with high CD4 nadir and controls. In the patients with low CD4 nadir, there was a significant negative correlation between sensory-perceptual function scores and AD and RD in the right inferior longitudinal fasciculus. In conclusion, there were differences of cognition and white matter between cART-treated HIV-infected patients with low and high CD4 nadir. MD, AD, and RD of DTI were sensitive to detect the white matter impairment in HAND.

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Poster

744. Neuroinflammation: HIV and Infections

Location: Hall A

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Program #/Poster #: 744.02/D15

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

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Title: Combined antiretroviral therapy induces hyperactivity of medial prefrontal cortex pyramidal neurons mediated by over-activation of voltage-gated Ca^{2+} channels

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Abstract: Combined antiretroviral therapy (cART) suppresses HIV replication, improves immune function, and prolongs life of HIV^+ individuals. Despite cART, the prevalence of HIV-associated neurocognitive disorders (HAND) occurs in ~50% of HIV^+ patients. Previous studies indicate that many antiretroviral medicines (ARVs) induce neurotoxicity in the peripheral and central nervous system; but the mechanism by which cART (or individual ARVs) induces

neurotoxicity is unknown. It is also unknown if such side effects of cART exacerbate HIV-induced neurotoxicity in the medial prefrontal cortex (mPFC), which could contribute to the underlying mechanism of HAND. Our previous study shows that lamivudine (a.k.a. 3TC, a nucleoside reverse transcriptase inhibitor, NRTI) *in vitro* induces a significant increase in firing and voltage-gated Ca^{2+} channel (VGCC) activity among mPFC pyramidal neurons. It is unknown whether such dysregulation could be induced by chronic cART. Here we assessed acute (*in vitro*) and chronic (*in vivo*) effects of Triumeq on the activity of mPFC neurons in rat brain slices using whole-cell patch-clamp recording. Triumeq is a first-line cART regimen for treating HIV/AIDS, which is formulated by three ARVs: abacavir (ABC, a NRTI), dolutegravir (DTG, an integrase inhibitor), and 3TC (a NRTI). We found that, at a concentration similar to which detected in the cerebrospinal fluid (CSF) of HIV^+ patients on this cART, acute Triumeq *in vitro* did not affect firing; but at 10x or 100x (fold) concentrations, it significantly increased firing of mPFC neurons. Chronic treatment of Triumeq *in vivo* (s.c., with equivalent dosages of humans) for 4 weeks (but not 2 weeks, wk) also significantly increased firing; and that was associated with enhanced Ca^{2+} influx *via* VGCCs. Further assessment using individual ARVs showed that 4wk treatments of ABC, DTG, or 3TC *in vivo* did not affect firing of these neurons. These results demonstrate that chronic Triumeq treatment induces hyperactivity of mPFC neurons by enhancing Ca^{2+} influx *via* over-activated VGCCs; and combined chronic treatment of ARVs *in vivo* could enhance the side effects of them. Collectively, these novel findings suggest that the side effects of chronic cART may exacerbate HIV-induced neurotoxicity in the mPFC.

Disclosures: L. Chen: None. **L. Al-Harthi:** None. **X. Hu:** None.

Poster

744. Neuroinflammation: HIV and Infections

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Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: NIH NINDS R01 NS103934-01

Title: Genetically diverse mouse strains exhibit variable central nervous system lesions in response to viral infection

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Abstract: Neurological diseases such as epilepsy, Parkinson's disease, multiple sclerosis, and amyotrophic lateral sclerosis may be partly driven by a preceding viral infection for some

patients. Interestingly, the severity and prevalence of neurological diseases and symptomologies vary greatly across individuals, even in response to the same virus. Theiler's murine encephalomyelitis virus (TMEV) provides a valuable model to understand how a single viral agent can elicit variable neurological outcomes. In mice, TMEV infection causes diverse neurological conditions, depending on the strain of the infected mouse. This suggests that the genetic background of the host influences the type and severity of the neurological disease. Although TMEV responses have been well studied in inbred mouse strains such as C57BL6 and SJL, these models fail to capture the diversity of human infection outcomes. However, the genetically heterogeneous Collaborative Cross (CC) mouse resource is designed to represent the genetic diversity observed in the human population. To further our understanding of how individual genetic backgrounds impact neurological damage in response to viral infection, we histologically characterized the central nervous system tissues of TMEV-infected mice from different CC strains. Here, we demonstrate that the CC strains exhibit variable central nervous system (CNS) lesions in response to TMEV infection, depending on the mouse strain. This suggests that the genetic diversity intrinsic to the CC strains contributes to histological differences in lesion extent and location in the CNS after viral infection, which can represent virally influenced neurological diseases in humans.

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Poster

744. Neuroinflammation: HIV and Infections

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Program #/Poster #: 744.04/D17

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: NIH RO1MH109382

Title: Mechanisms regulating amyloid precursor protein secretases in HIV-induced neurotoxicity

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Abstract: Aging is increasingly appreciated as a contributor to HIV-associated neurocognitive disorders (HAND) since antiretroviral therapy has increased the life expectancy of patients. Extracellular plaques composed of amyloid-beta (Aβ) are observed in aging-related neurodegenerative disorders, including HAND. Aβ is produced by cleavage of amyloid precursor protein (APP) by the secretase BACE1. However, this is precluded by cleavage of APP by the non-amyloidogenic secretase ADAM10. Increased BACE1 protein levels have been observed in

models of HAND. Additionally, excitotoxicity has been shown to decrease levels of ADAM10 in neurons. This would suggest there is a shift in APP secretases that could contribute to HIV-mediated neurotoxicity. In Alzheimer's Disease, BACE1 upregulation is mediated by the unfolded protein response kinase PERK. For the non-amyloidogenic pathway, sirtuin-1 (SIRT1), which is implicated in aging, has been shown to regulate ADAM10 levels. This suggests that APP processing is potentially dysregulated by changes in the protein levels of APP secretases BACE1 and ADAM10 in response to these mechanisms. To characterize APP processing in the context of an HIV insult, monocyte-derived macrophages were infected with HIV and supernatants were collected. Primary rat cortical neurons were then treated with HIV-infected macrophage supernatants (HIV/MDMs) or NMDA with or without 1 hour PERK inhibitor pre-treatment. Additionally, HIV/MDM or NMDA were co-treated with PERK activator (PA). Western blotting and MAP2 staining were performed to determine protein levels and neurotoxicity levels, respectively. NMDA treatment led to an increase in BACE1 levels, which seemed to be exacerbated when co-treating with NMDA and PA. Both HIV/MDMs and NMDA treatments led to a decrease in ADAM10 levels when compared with untreated cultures. Similarly to BACE1, HIV/MDM and NMDA-mediated decreases of ADAM10 were exacerbated by PA treatment. HIV/MDMs also decreased levels of SIRT1, pointing to a possible mechanism of ADAM10 regulation. In assessing the role of PERK in toxicity, HIV/MDM and NMDA-mediated toxicity seemed to be slightly attenuated by PERK inhibition and exacerbated by PERK activation. These results would suggest that there is reduction in non-amyloidogenic processing of APP that may be contributing to HIV-related neurotoxicity which is worsened by activation of the PERK pathway. Future studies will delve into this process by examining the specific mechanism of ADAM10 down-regulation, the role of ADAM10 in mediating toxicity, and by assessing products of APP cleavage in our model such as Aβ and soluble APP-α.

Disclosures: C. Lopez-Lloreda: None. **C. Akay-Espinoza:** None. **K.L. Jordan-Sciutto:** None.

Poster

744. Neuroinflammation: HIV and Infections

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Support: National Institute for Translational Neuroscience
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Financiadora de Estudos e Projetos

Coordenação de Aperfeiçoamento de Pessoal de Nível Superior

Title: Zika virus replicates in adult human brain tissue and impairs synaptic plasticity and memory in adult mice

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Abstract: Neurological complications have been reported in adult patients infected by Zika virus (ZIKV). We aimed to determine if ZIKV replicates in human and mice adult brain tissue and its possible effects on cognition. Ex-vivo human adult cortical tissue were infected with 10^7 plaque-forming units (PFU) of a ZIKV strain isolated from a Brazilian patient, or the corresponding volume of virus-free C6/36 cells conditioned medium (mock). ZIKV mRNA in tissue and infectious particles released to medium increased in a time-dependent manner, demonstrating that ZIKV successfully replicates in adult human mature neural tissue. To study the consequences of ZIKV infection in the adult brain, we performed intracerebroventricular injections of ZIKV (10^5 PFU) in adult male Swiss mice. Brain infusion of ZIKV reduced body weight without increasing mortality when compared to mock-infused mice. Increasing viral RNA levels were found in ZIKV- infected mice brain, peaking at 6 days post-infection (dpi). Viral mRNA was higher in the hippocampus and frontal cortex when compared to others brain regions. We found increased Iba-1 (microglial) positive cells and decreased synaptic puncta levels and plasticity in the hippocampus of infected-mice. Brain TNF-α and complement system proteins, C3 and C1q, mRNA levels were markedly increased at 6 dpi. Moreover, we found increased levels of CD4+, CD8+ and macrophages cells in ZIKV-infected mice brain. Iba-1/synaptophysin colocalization was higher in infected mice, suggesting microglial synaptic engulfing. Using the novel object recognition task, memory impairment was detected as early as 1 dpi, persisting for up to 30 dpi. Remarkably, blockade of TNF-α, C3 or C1q signaling, or even microglial activation prevented synapse and memory impairment in ZIKV- infected mice. TNF-α signaling blockage reduced microgliosis but microglial activation blockage did not decrease ZIKV-induced TNF-α mRNA upregulation. Results suggest that ZIKV induces synapse dysfunction and memory impairment via a TNF-α/microglia/complement axis. Our findings establish a mechanism by which ZIKV affects the adult brain and point out to the need of evaluating memory/cognitive deficits as a potential comorbidity in ZIKV-infected adults. All procedures were approved by local ethical committee (Brazilian Ministry of Health #0069.0.197.000-05, Federal University of Rio de Janeiro #043/2016 and #126/18).

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Poster

744. Neuroinflammation: HIV and Infections

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Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: NIH NIDA R21DA047936
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Title: Prevention of HIV-1 Tat and cocaine neurotoxicity by inhibiting DEAD Box RNA Helicase 3

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Abstract: HIV-1 Associated Neurocognitive Disorder (HAND) is a clinically devastating yet common complication of HIV infection. The persistence of the virus in the central nervous system leads to viral protein release, most famously Tat, from the infected cells, which causes cumulative neuronal toxicity. Substance abuse in HIV infected patients greatly exacerbates the severity of such neuronal damage. Unfortunately, there is no viable or approved therapy for HAND despite the projected increase in the prevalence of HAND due to a rapidly aging HIV-positive population.
To find potential targets for anti-HAND therapy, our team has developed an AI-based literature mining algorithm. Through evaluation and prioritization of the highest scoring genes that are computationally associated with HAND, we uncovered Dead Box RNA Helicase 3 (DDX3). Moreover, a small molecule inhibitor of DDX3 helicase activity, RK-33, is readily available as an anti-cancer agent that selectively kills tumors without any observed systemic toxicity in the tested animal models.
We show that RK-33 rescues rat and mouse cortical cultures from the combined neurotoxicity of HIV Tat protein and cocaine. The results of RNA-seq and transcriptome analysis of the treated cultures reveal that the majority of Tat-activated transcripts are microglia specific genes, and that

RK-33 blocks their activations. These genes include major microglial markers and regulators of microglia activation, such as CSF1R and CSF3R. Treatment with RK-33 inhibits Tat and cocaine-dependent increase in the number and size of the microglia cells in cortical cultures. The elevated production of IL-1alpha and beta, IL-6 and TNF-alpha proinflammatory cytokines is also inhibited by RK-33 treatment. However, a further analysis of Tat and cocaine-dependent transcriptome suggests that RK-33 also affects astrocytes where it inhibits Tat-dependent activation of NF-kappa B signaling pathway. This necessitates a deeper look into complex interplay of microglia and astrocytes.
Taken together, these findings suggest that DDX3 is important to glial activation triggered by the combined insults of Tat and cocaine, and that pharmacological inhibition of DDX3 may have the potential to treat not only HAND, but also other neurodegenerative diseases with pathological activation of glial cells.

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Poster

744. Neuroinflammation: HIV and Infections

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BONFOR

Title: Clinicoserological spectrum and potential viral factors in biofluids of a consecutive series of patients with limbic encephalitis

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Abstract: Limbic encephalitis (LE) is increasingly recognized as a pathogenetic factor of temporal lobe epilepsy (TLE). Auto-antibodies (ABs) targeting neuronal surface structures, GAD65 as well as onconeuronal ABs play a role in LE. However, by far not all LE patients have

ABs in sera or cerebrospinal fluid (CSF) samples. Based on human herpesvirus 6 (HHV-6) DNA detection in brain tissue from patients with TLE, an association of persistent viral infection with TLE has been discussed. Furthermore, individual studies reported increased HHV-6 DNA in patients with clinical signs of previous inflammatory brain reaction including febrile seizures or meningoencephalitis as predisposing factors for TLE. The interval between new onset of seizures in adult patients and the diagnosis of LE varies considerably. We have carried out a systematic analysis on the distinct auto-AB status in sera / CSF samples of patients with short-term (n=175 individuals; seizure onset ≤ 24 months) versus long-term (n=70 individuals; seizure onset ≥ 96 months) intervals between the first onset of seizures and the clinical diagnosis of LE. Informed written consent was present from all patients. The detection rate of auto-ABs differed significantly between both groups (n=22 in short-term versus n=5 in long-term interval patients); GAD65 and LGI1 were significantly more frequently detected (α=0.01) in the short-term than in the long-term interval group. We will also report on potential differences between both groups of patients under study including semiological, imaging, further serological as well as neuropsychiatric factors and the detection of viral nucleic acids including HHV-6 and neurotrophic RNA-viruses. In summary, data of a very large consecutive cohort of biofluids in LE patients stratified according to the time interval to diagnosis will be presented and may provide new insights for therapy stratification.

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Poster

744. Neuroinflammation: HIV and Infections

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Support: Burroughs Wellcome
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Title: Estrogen receptor signaling in macrophages suppresses HIV-associated neurotoxic activity

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Abstract: Macrophages and microglia (M/M) play pivotal roles in the pathogenesis of HIV-associated neurocognitive disorders. The ensuing inflammatory M/M activation causes neuronal damage. Studies utilizing exogenous anti-inflammatory and antioxidants to mitigate disease progression have been unsuccessful; however, targeting endogenous pathways, such as estrogen signaling may be advantageous. 17β-estradiol, the most active form of estrogen, activates estrogen receptor GPER and has been reported to inhibit HIV infection in primary macrophages and peripheral blood mononuclear cells and protect neurons against HIV proteins, gp120 and tat. The literature has also suggested that Secoisolariciresinol diglucoside (SDG), a flaxseed lignin, may interact with estrogen receptors. In previous data, we have found that SDG may suppress macrophage induced neurotoxicity and viral replication during neurotoxicity. Therefore, we hypothesize that high 17β-estradiol and SDG may be neuroprotective during HIV infection and other inflammatory stimuli in an estrogen receptor dependent manner. To understand this, we stimulated or infected macrophages with HIV_{JAGO}, respectively, in the presence and absence of increasing doses of 17β-estradiol or SDG. Whole cell and cytoplasmic lysates, mRNA and conditioned medium were collected at various time points. We found that 17β-estradiol and SDG suppressed neurotoxin production and viral replication from HIV infected macrophages in an estrogen receptor dependent manner. Given these studies, estrogen signaling may reduce oxidative stress and inflammation seen during neuroinflammatory disorders, such as HIV-associated neurocognitive disorders.

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Poster

744. Neuroinflammation: HIV and Infections

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Support: NIH Grant DA013137
NIH Grant HD043680
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Title: A promising diagnostic and prognostic biomarker for HAND: Prepulse inhibition

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Abstract: In 2007, the nosology for HIV-1 associated neurocognitive disorders (HAND) was updated to a primarily neurocognitive disorder. However, currently available diagnostic tools

lack the sensitivity and specificity needed for an accurate diagnosis for HAND. Scientists and clinicians, therefore, have been on a quest for an innovative biomarker to diagnose (i.e., diagnostic biomarker) and/or predict (i.e., prognostic biomarker) the progression of HAND in the post combination antiretroviral therapy (cART) era. The translational prepulse inhibition (PPI) experimental paradigm is commonly utilized for the assessment of temporal processing, a construct analogous to speed of information processing, and which has been implicated as a potential elemental dimension of HAND. The potential utility of PPI as a diagnostic and/or prognostic biomarker for HAND was examined using intact male and female F344/N HIV-1 transgenic (Tg; *N*=20 litters) and control rats (*N*=17 litters). First, discriminant function analyses (DFA) and receiver operator characteristic (ROC) curves, complementary statistical techniques, were utilized to assess the utility of PPI as a diagnostic biomarker. In the HIV-1 Tg rat, PPI accurately diagnostics the presence of the HIV-1 transgene, relative to control animals, with both high sensitivity (i.e., 89.3-100%) and high specificity (i.e., 79.5-94.1%); results which generalize across experimental paradigms, the functional lifespan, sensory modalities, and biological sex. Second, regression analyses were conducted to examine the potential utility of PPI as a prognostic biomarker. Early alterations in PPI (i.e., Postnatal Day 30 and 60) accurately predict later neurocognitive impairments in higher-order cognitive domains, including sustained attention, flexibility, and inhibition, with regression coefficients (i.e., *r*) greater than 0.8. Thus, PPI heralds an opportunity for the development of a brief, non-invasive diagnostic and prognostic biomarker for milder forms of NCI in the post-cART era. Funded by NIH grants DA013137, HD043680, MH106392, NS100624.

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Poster

744. Neuroinflammation: HIV and Infections

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Program #/Poster #: 744.10/D23

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Title: Rat model of prenatal Zika virus infection and associated neural and behavioral consequences in the offspring

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Abstract: Zika virus (ZIKV), a mosquito-borne flavivirus, has been associated with microcephaly and other neurological disorders in infants born to infected mothers. Despite being declared an international emergency by the World Health Organization, comparatively very little is known about the pathogenesis, mechanisms, or behavioral consequences of maternal ZIKV infection in the offspring. Our lab is interested in developing a working animal model to answer

some of these questions. Here, we use a rat model of prenatal ZIKV infection to measure the level of infectivity, as well as the rate of viral clearance in both the mother and her pups. We examine various aspects of brain development in pups, including cortical thickness, microglia morphology, apoptosis, and neurogenesis. Further, we use this model to investigate the impact of prenatal ZIKV infection on hippocampal and non-hippocampal dependent learning as well as motor learning in the juvenile and adult offspring. Given that pregnancy is associated with significant immunomodulation, we are also interested in the role that pregnancy has on the impact of ZIKV infection, therefore we compare viral infectivity between both pregnant and non-pregnant female rats. In this study, we show that prenatal ZIKV infection results in an increase in cell death and reduces hippocampal and cortical volumes in the neonatal rat brain. For the first time, we demonstrate the efficacy and validity of a rat model for maternal ZIKV infection with vertical transmission to the fetus. This model will allow us to 1) better understand the mechanisms underlying ZIKV infection and transmission to the fetus, 2) determine the impact of ZIKV infection on the developing male and female fetal brain, and 3) measure behavioral deficits and investigate potential sex differences associated with fetal ZIKV infection later in life.

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Poster

744. Neuroinflammation: HIV and Infections

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Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: FAPESP Grant 2015/22327-7
Unimed Ribeirão Preto

Title: Herpetic lesions in encephalitis are fully reversed by Aciclovir: A case report

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Abstract: Herpetic encephalitis is the most common sporadic viral encephalitis among adults worldwide. Here, we report a case of 63-year old male patient that was admitted to the hospital with abnormal behavior and epileptic seizures. Some days before admission, the patient searched for a health facility reporting peaks of fever, dysuria and lumbar pain. He was oriented to take ciprofloxacin (every 12 hours). Upon admission, the patient had Glasgow 12, ocular aperture of 3, motor responses of 5, verbal responses of 4, confused and disoriented. Video-EEG

examination revealed moderated symmetric disorganization in basal activity due to a diffuse increase in slow theta waves. Also, rare acute type epileptiform discharges were observed in the left front-temporal region. Cephaloraquidian liquor presented a slight increase in glucose (116 mg/dl) and a high increase in protein (89.4 g/dl), together with IgG immunoglobulins for *Herpes* types 1 and 2 and for *Varicela zoster*. Magnetic resonance showed many supratentorial intraparenquimal lesions that were diffusely spread in the cortex and many subcortical structures. The patient was kept in the intensive care unit were ciprofloxacin was replaced by ceftriaxone (2 g, every 12 hours), acyclovir (10 mg/kg) and phenytoin (250 mg, e.v.). One week after admission, all medications were stopped. Eleven days after admission, the patient recovered completely and was discharged from the hospital. Magnetic resonance was repeated after three weeks and all the lesions had disappeared. Since we did not find changes in cephaloraquidian liquor that would suggest bacterial infections, we hypothesized that the patient had an inflammatory response due to a viral infection and apparently, that was the case. We conclude that acyclovir is an effective drug to rapidly treat herpetic encephalitis since it can fully reverse inflammatory lesions, behavioral impairment and seizures induced by these viruses.

Disclosures: **A.D. Cunha:** None. **A.O. Cunha:** None.

Poster

744. Neuroinflammation: HIV and Infections

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 744.12/D25

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: 5UL1GM118973
1R29NS31857

Title: A proposed mechanism for selective vulnerability in the brain of the HIV-1 transgenic rat

Authors: *F. J. DENARO, M. WORTHINGTON;
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Abstract: Since the introduction of the HIV-1 Transgenic rat (HIV-1TGR) (1) over 100 papers have been published using this model in HIV/AIDS studies. Experience with this model has demonstrated its effectiveness particularly for the study of HIV comorbidities. In humans, HIV associated comorbidities exist even with the use of very effective antiviral therapy. It is believed that the cells of viral reservoirs continue to secrete viral proteins even with treatment. Because this model produces chronic levels of HIV proteins (in particular Gp-120) it has a number of similarities to patients that are on antiviral therapy. One interesting observation in the HIV-1TGR is the selective vulnerability of differ cell types. A body of growing evidence on the cellular pathology in the HIV-1TGR has been reported and it reflects what is seen in the patient.

The observation of selective cell vulnerability is even more marked in the brain. Our early observations revealed abnormalities to the motor system. This led to examination of the Basal ganglia and the Substantia nigra. Further studies have also revealed behavioral and motor problems consistent with our earlier observations of the neuropathology. In the present study, we investigate the distribution of the HIV receptors CXCR4 and CCR5 which can bind to GP-120. There is marked homology between the rat receptors and the human receptors. Therefore, the presence of these receptors on specific cell types can provide a rationale for the observed selective vulnerability. The consequence of GP-120 binding to the receptors could lead to negative downstream effects of cell functions. The CXCR5 receptor have been previously mapped in the rat brain. In the present study we also identify the receptors and are correlating the receptors with the pathology The expression of CCR5 is a bit different. It is expressed during embryotic development but only in low levels in the adult. But in instances of inflammation this receptor is upregulated. The different characterizes of these two receptors offers a hypothesis for the development of increased pathology over time. Initially CXCR5 contributes to cell death and dysfunction, this could result in an immune response. The immune response is followed by upregulation of CCR5 with increased GP120 binding and increased pathology. Therefor the identification of HIV receptors in the HIV-1TGR offer a mechanistic rationale for the development of the neuropathology and its apparent increase over time. 1. Reid W., Sadowska M., Denaro, F. et al. An HIV -1 Transgenic Rat that Develops HIV -1 related Pathology and Immunological Dysfunction. *Proceedings of the National Academy of Science,* 2001, **98** (16): 9271-9276.

Disclosures: F.J. Denaro: None. **M. Worthington:** None.

Poster

744. Neuroinflammation: HIV and Infections

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 744.13/D26

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: NIH R01 NS095994
NIH R01 NS095994-01S1
Arizona Biomedical Research Commission ADHS14-082991

Title: *Toxoplasma gondii* interactions and electrophysiology differences in the central nervous system

Authors: *O. A. MENDEZ[1], A. A. KOSHY[2];
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Abstract: *Toxoplasma gondii* is a neurotropic intracellular parasite that causes a life-long latent infection in the brain. *T. gondii's* asymptomatic persistence in the central nervous system (CNS) is unusual, leading some investigators to postulate that this chronic infection might change CNS physiology. To date, these studies have been limited to understanding global neurotransmitter changes, as no mechanism existed to interrogate the single infected neuron *in vivo*. We developed a novel mouse model that allows us to permanently mark and track CNS host cells that have been injected with parasite effector proteins, parasite proteins that are secreted into host cells and manipulate host cell signaling. As the marking of these cells depends only on the injection of a *T. gondii* protein and does not require active infection, we can identify injected host cells, even if these cells do not harbor parasites. Using this system, we have previously shown that in the CNS, *T. gondii* primarily injects neurons, which we call *T. gondii*-injected neurons (TINs). Using a custom MATLAB-based mapping program, we have found that TINs are not homogenously distributed throughout the brain but instead are primarily found in the cortex and striatum. In addition, we have found that TINs co-localize with Ctip2, a medium spiny neuron marker. Given these findings (localization in the striatum and co-localization with Ctip2), we sought to define TINs physiology in the dorsal striatum because the majority of the neurons in this area are medium spiny neurons, allowing us to leverage the well-defined electrophysiology of these cells. Using *ex vivo* slices, we have found that dorsal striatum bystander neurons, neurons near a TIN but not injected with parasite protein, show only minor changes in the passive electrophysiology properties compared to dorsal striatum neurons from uninfected mice. Conversely, the passive electrical properties of TINs are vastly abnormal, including depolarized resting membrane potentials and the need for increased current injection to induce firing. These data suggest that, *in vivo*, interacting with *T. gondii* changes neuron firing properties. Current studies are aimed at determining the mechanism leading to these drastic electrophysiological changes in TINs, including apoptotic labeling and establishing an *in vitro* system that mimics these *in vivo* findings.

Disclosures: O.A. Mendez: None. **A.A. Koshy:** None.

Poster

744. Neuroinflammation: HIV and Infections

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 744.14/D27

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: DA32444
DA15014
DA040519
MH100972
MH105329

NS065957

Title: Morphine modulation of endolysosomal iron stores leads to FHC upregulation and dendritic spine deficits in cortical neurons

Authors: *E. IROLLO[1], B. NASH[1], E. E. RIGGS[1], P. HALCROW[2], G. DATTA[2], J. D. GEIGER[2], O. MEUCCI[1];
[1]Pharmacol. and Physiol., Drexel Univ. Col. of Med., Philadelphia, PA; [2]Biomed. Sci., Univ. of North Dakota Sch. of Med. and Hlth. Sci., Grand Forks, ND

Abstract: Opioid abuse continues to be a severe public health problem and is prevalent among HIV+ individuals. Several studies demonstrated that drug use/abuse may accelerate HIV infection and worsen HIV-associated neurocognitive disorders (HAND). Synaptodendritic injury is correlated with neurocognitive decline and thought to be an underlying mechanism of HAND. However, the mechanism by which opioids contribute to HAND is unclear. We have previously shown that morphine decreases dendritic spine density of cortical neurons *in vitro* and *in vivo,* which requires upregulation of ferritin heavy chain (FHC), a novel negative regulator of the dendritic spine promoting CXCL12/CXCR4 chemokine axis. Here, we investigated the mechanism of morphine-mediated FHC upregulation and how various types of dendritic spines are affected using primary cortical neurons and ~4-week old Holtzman rats of either sex. In primary neurons, 24 hour morphine exposure dose-dependently increased FHC levels, and decreased the density of mushroom and thin dendritic spines. Both outcomes were blocked by inhibiting μ-opioid receptor activation with CTAP, or Gαi-protein signaling with pertussis toxin. Layer 2/3 medial prefrontal cortex neurons in morphine-treated rats also showed increased FHC levels, and decreased density of mushroom and thin dendritic spines. In primary neurons, morphine did not alter FHC transcript expression. As iron also post-transcriptionally regulates FHC, we next examined if iron was involved downstream of morphine. Both FHC and FLC (ferritin light chain), which assemble to form the ferritin iron storage complex, were upregulated by iron loading and morphine. Interestingly, morphine upregulated FHC faster than iron loading, suggesting that morphine mobilizes iron from an intracellular store. Indeed, morphine simultaneously decreased endolysosomal iron content and increased cytosolic iron levels prior to FHC upregulation. Further, chelation of endolysosomal iron with DFO blocked morphine-mediated FHC upregulation and dendritic spine deficits, whereas extracellular iron chelation with DTPA had no effect on this pathway. These studies reveal a novel interaction between opioid receptor signaling and neuronal iron metabolism that may contribute to synaptodendritic damage in opioid-using patients with HAND and in other neurodegenerative disorders with reported dysregulation of iron.

Disclosures: E. Irollo: None. **B. Nash:** None. **E.E. Riggs:** None. **P. Halcrow:** None. **G. Datta:** None. **J.D. Geiger:** None. **O. Meucci:** None.

Poster

744. Neuroinflammation: HIV and Infections

Location: Hall A

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Program #/Poster #: 744.15/D28

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: DA15014
DA32444

Title: Examining the contribution of excitatory and inhibitory neurons to CXCR4-induced dendritic spine changes using a lentiviral CRISPRi approach

Authors: *J. LUCHETTA, R. BRANDIMARTI, E. IROLLO, C.-T. HO, O. MEUCCI;
Dept. of Pharmacol. and Physiol., Drexel Univ. Col. of Med., Philadelphia, PA

Abstract: The chemokine CXCL12 and its main signaling receptor, CXCR4, play essential roles in the CNS. CXCR4 is expressed in inhibitory neurons during development as it is key to their proper migration; however, expression of CXCR4 in the adult brain seems to be widespread. Our previous *in vivo* and *in vitro* studies have shown that the CXCL12/CXCR4 axis positively regulates dendritic spine density in mature cortical neurons. This effect is mediated by activation of the Rac1/PAK pathway and ensuing actin stabilization. Our findings also show that thin spines, a highly dynamic type of spines implicated in synaptic plasticity, are predominantly affected by the chemokine - *in vitro* as well as *in vivo*. In line with this, CXCL12 stimulation of the CXCR4/Rac1/PAK pathway rescued both dendritic and cognitive deficits in a rat transgenic model of HIV-associated cognitive decline, which is primarily caused by synaptodendritic loss. However, it is presently unclear whether CXCL12 regulates spines by acting directly on excitatory neurons or via inhibitory circuits. This study aims to determine whether CXCR4 signaling on either or both of these neuronal sub-types drives the rescue of dendritic spines. To this end, we generated several lentiviral CXCR4-CRISPRi constructs and tested them in primary cortical neurons from E17 Holtzman rats of either sex, with the intent of selectively silencing CXCR4 in inhibitory or excitatory neurons. First, we determined that the proportion of excitatory to inhibitory neurons in our cortical cultures was similar to previously published studies by immunocytochemical staining against GABA, vGAT, and vGLUT. We also confirmed CXCR4 expression in excitatory and inhibitory cultured neurons. Next, we designed two inducible CRISPRi constructs that use GFP as a reporter for dCas9 expression, and distinct small guide RNAs targeting the CXCR4 promoter near exon 1. To confine CXCR4 silencing to specific neuronal subpopulations, we generated constructs that replaced the tetracyclin-inducible system for dCas9 with excitatory neuron-specific CaMKIIα promoter, or inhibitory neuron-specific mDlx enhancer regulatory elements. We demonstrated that transduction of DIV 21 neurons using the mDlx construct restricted dCas9 to a sub-population of cells. These constructs will be used

for future work examining excitatory and inhibitory CXCR4 contributions to dendritic spine density and ultimately, cognitive performance in animal models of HIV-associated neurocognitive disorders. Additionally, these studies represent an important step toward the identification of network-level effects of CXCR4 signaling in cortical neurons.

Disclosures: J. Luchetta: None. **R. Brandimarti:** None. **E. Irollo:** None. **C. Ho:** None. **O. Meucci:** None.

Poster

744. Neuroinflammation: HIV and Infections

Location: Hall A

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Program #/Poster #: 744.16/D29

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: R01-MH085607
R01-DA039044

Title: HIV-Tat protein expression modulates cognitive performance through induction of a hyperglutamatergic state in the brain

Authors: *T. J. CIRINO, H. M. STACY, S. O. EANS, S. W. HARDEN, C. J. FRAZIER, J. P. MCLAUGHLIN;
Pharmacodynamics, Univ. of Florida, Gainesville, FL

Abstract: Despite improving treatment, the prevalence of HIV Associated Neurocognitive Disorder (HAND) in HIV-positive patients has grown paradoxically worse. We hypothesize that brain exposure to HIV-1 Tat protein alters glutamatergic signaling to promote HAND symptomology. Using the GT-tg bigenic (iTat) mouse model, where brain-selective Tat expression is controlled by activation of a doxycycline (Dox) promotor, we correlated the effects of CNS-expression of HIV-Tat protein on glutamatergic signaling in brain circuits of the prefrontal cortex and hippocampus to Tat's effect on executive function and spatial learning and memory. In preliminary studies, exposure to the HIV-Tat protein significantly decreased rheobase and action potential threshold and increased excitability (in response to injected current) of layer 2/3 pyramidal neurons in the mPFC. These data reveal effects of Tat that may underlie enhanced performance of Dox treated iTat mice in an attentional set shifting assay. In contrast, HIV-Tat protein exposure increased rheobase as observed in hippocampal CA1 pyramidal cells. This effect was associated with reduced firing under low to moderate loads, although maximum firing rate was not significantly affected. These data reveal effects of Tat that may underlie impaired performance of Dox treated iTat mice as observed in a spatial memory task. Pretreatment with the glutaminase inhibitor JHU-083 prevented Tat-associated spatial learning and memory impairment supporting the link between cognitive impairment and a Tat-

induced hyperglutamatergic state. Ongoing efforts are evaluating spontaneous excitatory and spontaneous inhibitory post-synaptic currents (sEPSC/sIPSCs) in both regions after Tat protein exposure, and also evoking glutamate release in order to measure the NMDA / AMPA ratio. Additional preliminary data suggests the NR2B antagonist, ifenprodil , attenuates Tat-protein induced deficits in spatial learning and memory. Overall, these data suggest that expression of HIV-1 Tat protein in the CNS has brain region specific effects on cellular physiology and glutamatergic signaling that may underlie differential effects on behavior, specifically, improving cognitive flexibility associated with enhanced cortical function, while impairing performance in spatial learning and memory tasks associated with dysregulated hippocampal excitability. Characterizing the biological means by which HIV infection may mediate HAND symptomology in the absence of a full viral infection, may provide useful information for clinical intervention, in the current treatment era.

Disclosures: T.J. Cirino: None. **H.M. Stacy:** None. **S.O. Eans:** None. **S.W. Harden:** None. **C.J. Frazier:** None. **J.P. McLaughlin:** None.

Poster

744. Neuroinflammation: HIV and Infections

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 744.17/D30

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: R15-GM117501-01A1

Title: Methamphetamine impairs IgG1-mediated phagocytosis and killing of cryptococcus neoformans by macrophage and microglia cell lines *in vitro*

Authors: *L. ASLANYAN[1], H. LEE[2], V. EKHAR[2], L. R. MARTINEZ[3], R. L. RAMOS[2]; [1]Biomed. Sci., [2]NYIT Col. of Osteo. Med., Old Westbury, NY; [3]Biol. Sci. - Border Biomed. Res. Ctr., Univ. of Texas at El Paso, El Paso, TX

Abstract: The prevalence of methamphetamine (METH) use is estimated at ~35 million people worldwide, with over 10 million users in the United States. Chronic METH abuse and dependence predispose the users to participate in risky behaviors that may result in the acquisition of HIV and AIDS-related infections. METH compromises phagocyte effector functions, which might have deleterious consequences on infection control. In this study, we investigated the role of METH in phagocytosis and antigen processing by J774.16 macrophage- and NR-9460 microglia-like cells in the presence of a specific IgG1 to *C. neoformans* capsular polysaccharide. METH inhibits antibody-mediated phagocytosis of cryptococci by macrophages and microglia, likely due to reduced expression of membrane-bound Fcγ receptors. METH interferes with phagocytic cells' phagosomal maturation, resulting in impaired fungal control.

Phagocytic cell reduction in nitric oxide production during interactions with cryptococci was associated with decreased levels of tumor necrosis factor alpha (TNF-α) and lowered expression of Fcγ receptors. Importantly, pharmacological levels of METH in human blood and organs are cytotoxic to ~20% of the phagocytes. Our findings suggest that METH abrogates immune cellular and molecular functions and may be deadly to phagocytic cells, which may result in increased susceptibility of users to acquire infectious diseases.

Disclosures: L. Aslanyan: None. **H. Lee:** None. **V. Ekhar:** None. **L.R. Martinez:** None. **R.L. Ramos:** None.

Poster

744. Neuroinflammation: HIV and Infections

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 744.18/DP05/D31

ControlExtraData.DynamicPosterDisplay:
Dynamic Poster
Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: The Dr. George F. Haddix President's Faculty Research Fund

Title: Design and evaluation of CNS-targeted antiretroviral nanoparticles

Authors: *A. P. S. KOCHVAR[1], A. M. BACKER[1], M. PON[1], A. SHIBATA[1], S. MANDAL[2], C. J. DESTACHE[2];
[2]Sch. of Pharm. and Hlth. Professions, [1]Creighton Univ., Omaha, NE

Abstract: HIV continues to be one of the most prevalent yet treatable chronic viral infections in the world. While advancements in treatment have increased rates of survival in HIV+ individuals, secondary pathologies such as HIV-associated neurocognitive disorder occur in chronically infected persons due to HIV persistence in the CNS. Other literature also suggests that, when taken orally over decades, antiretroviral (ARV) drugs such as dolutegravir (DTG) induce peripheral neuropathies and neurodegeneration. We are currently in the preliminary stages of developing and testing ARV drug delivery using nanoparticles. Polymeric nanoparticle (NP) ARV drug encapsulations have been shown to decrease drug cytotoxicity, extend release time, and increase the efficacy of drug delivery as compared to oral administrations. Our work focuses on the design of poly-lactic-co-glycolic acid (PLGA) NP encapsulations of DTG conjugated to human holo-transferrin (hhTf), a receptor agonist known to enhance transcellular transport through endothelial cells at the BBB. *In vitro* cell viability assays were used to evaluate the cytotoxicity of NP fabrications compared to drug solution. DTG at varying concentrations (10µg/mL to 0.001µg/mL) was delivered to endothelial and CNS cells in solution or encapsulated NPs (hhTf-PLGA-DTG-NP) for 24, 48, and 96h. Cell viability assays showed

statistically significant differences in cytotoxicity of hhTf-PLGA-DTG-NP versus DTG solution applications at most DTG concentrations. Mean % viability in endothelial HCMEC/D3 cells treated with hhTf-PLGA-DTG-NP showed enhanced viability of 33% at 24h, 58% at 48h, and 39% at 96h at 1ug/mL DTG. Astrocyte viability increased by 35% at 24h, 76% at 48h, and 56% at 96h at 1ug/mL DTG. Microglia cell viability increased at 24 and 48h by 79% and 100% respectively, though by 18% increase at 96h. SH-SY5Y neuronal viability increased by 15% at 24h, 36% at 48h, and 13% at 96h. Immunocytochemistry of primary rat astrocytes, cortical neurons, HCMEC/D3s, and microglial cells exposed to hhTf-PLGA encapsulations tagged with Alexafluor 594 were performed. NP uptake was demonstrated as early as 15 minutes in all cell types. Additionally, hhTf-PLGA-NP-Alexafluor 594 were applied to HCMEC/D3 cells to investigate colocalization of hhTf-NPs to transferrin receptor via immunofluorescent labeling using confocal microscopy. Our data suggest that receptor-ligand colocalization may be occurring as early as 15 minutes in HCMEC/D3s. These results collectively indicate that our NPs may be translocated to the endothelial cells of the blood-brain barrier and improve the cytotoxic effects of DTG to CNS cells.

Disclosures: A.P.S. Kochvar: None. **A.M. Backer:** None. **M. Pon:** None. **A. Shibata:** None. **S. Mandal:** None. **C.J. Destache:** None.

Poster

744. Neuroinflammation: HIV and Infections

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 744.19/D32

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: US Army office of Scientific Research #W911NF-17-1-0559

Title: Latent infection of herpes simplex virus type 1 augments anxiety-like behavior in BALB/c mice (*mus musculus*)

Authors: *I. K. HOUGH[1], M. M. OLESH[2], G. D. GRIFFIN[3];
[1]Biol., [3]Departments of Biol. and Psychology, [2]Hope Col., Holland, MI

Abstract: Nearly 70% of the US population has been infected with HSV-1. Epidemiological research has shown that being seropositive for HSV-1 is associated with a decrease in working memory-related tasks. To test if HSV-1 causes changes in behavior, this work used BALB/c mice to test the hypothesis that HSV-1 infections decreased performance of tasks involving working memory. Male and female BALB/C mice (infected at 6 weeks of age) were tested approximately 238 days post infection (dpi) after being inoculated with 10^5 plaque forming units of the F-strain of HSV-1. Next, mice were evaluated on the open field test and the nestlet test. The infected male mice took longer to enter the center of the field than their uninfected

counterparts ($p<0.05$), while there was no difference for the female mice. For the nestlet test, male mice shredded more than the uninfected male mice ($p<0.05$). These results indicate that HSV-1 increases the expression of anxiety-like behaviors, particularly in male mice. Future work will focus on utilizing tests for anxiety like behaviors and increasing the sample size of BALB/C mice for both males and females.

Disclosures: I.K. Hough: None. **M.M. Olesh:** None. **G.D. Griffin:** None.

Poster

744. Neuroinflammation: HIV and Infections

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Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: AA023165
AA017347
AA017168
NS075097
AG047366
Michael J Fox foundation for Parkinson's research

Title: Aging with HIV infection - Markers for risk of impairment: A comparison with Parkinson’s disease

Authors: *E. M. MULLER-OEHRING[1,2], R. FAMA[1], J.-Y. HONG[2], K. L. POSTON[3], H. BRONTE-STEWART[3], E. V. SULLIVAN[1], A. PFEFFERBAUM[2], T. SCHULTE[2,4]; [1]Stanford Univ. Sch. of Med., Palo Alto, CA; [2]Neurosci. Program - Biosci. Div., SRI Intl., Menlo Park, CA; [3]Dept. of Neurol., Stanford Univ., Stanford, CA; [4]Clin. Psychology, Palo Alto Univ., Palo Alto, CA

Abstract: Effective treatment with antiretroviral therapy (ART) has prolonged the life expectancies of individuals infected with human immunodeficiency virus (HIV) to be comparable to those in the general population. Despite ART and viral suppression, HIV-associated neurocognitive disorder (HAND) occurs frequently. Aging HIV individuals may be at risk for additional motor impairment similar to that in Parkinson's disease (PD), given that both diseases affect corticostriatal pathways subserving motor function. To determine cognitive and motor impairment profiles, 42 older HIV individuals, 41 PD individuals, and 37 age-matched healthy controls (HC) underwent neuropsychological testing including oral information processing speed (IP), executive functions (EF), verbal memory (VM), visuospatial skills (VS), and fine finger motor abilities (MOT). Participants were also rated on the Unified Parkinson’s Disease Rating Scale (UPDRS) for Parkinsonian motor signs and underwent MRI for brain

morphological measures. Composite scores for each category were calculated, Z-transformed, and corrected for age and education based on HC. Impairment was defined as -1.5 SD below HC (mean=0, SD=1) for each functional domain. In HIV 32% were impaired on IP, 39% on EF, 36% on VM, 39% on VS, and 15% on MOT domain scores. PD were tested on dopaminergic medication to reduce the impact of motor disturbances on test scores. In PD 22% were impaired on IP, 10% on EF, 27% on VM, 29% on VS, and 24% on MOT domain scores. In HIV, IP impairment was associated with impairment in all other cognitive and motor domains, whereas in PD it was only related to EF and VM. The subset of HIV individuals with MOT impairment also showed more parkinsonian signs, and as part of the UPDRS reported significantly more daytime sleepiness and disturbed nighttime sleep. In PD, MOT impairment (on meds) was mainly associated with UPDRS clinical motor scores (on and off meds), smaller putamen volumes, and VS impairment. Also, UPDRS-III motor scores off-dopaminergic medication were higher in PD patients with poorer nighttime sleep (rho=.33, p=.02) and more fatigue (rho=.36, p=.01). Together these results highlight that impairment in oral IP speed can serve as a marker for an increased risk of neurocognitive impairment in HIV. Considering that sleep disturbances occur in PD, and often start prior to motor signs, our finding suggests that disturbed sleep and increased daytime sleepiness may render HIV-infected individuals vulnerable to experiencing motor functional decline and developing parkinsonism. **Support:** AA023165, AA017347, AA017168, NS075097, AG047366, Michael J Fox foundation for Parkinson's research

Disclosures: E.M. Muller-Oehring: None. **R. Fama:** None. **J. Hong:** None. **K.L. Poston:** None. **H. Bronte-Stewart:** None. **E.V. Sullivan:** None. **A. Pfefferbaum:** None. **T. Schulte:** None.

Poster

744. Neuroinflammation: HIV and Infections

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Program #/Poster #: 744.21/D34

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: US Army Office of Scientific Research #W911NF-17-1-0559
Dow Scholars Science Research Fund, the Hope College Department of Biology

Title: Impact of HSV1 on an *in vitro* model of traumatic brain injury

Authors: *N. WEIGLE[1], C. DA SILVA[1], K. RUSSELL[1], G. D. GRIFFIN[2];
[2]Departments of Biol. and Psychology, [1]Hope Col., Holland, MI

Abstract: Infection of Herpes Simplex Virus Type I (HSV-1) has been associated with the exacerbation of neurodegenerative pathologies. More specifically, *in vitro* and *in vivo* studies have revealed that HSV-1 can augment levels of the phosphorylated form of tau, a modified

cytoskeletal protein that is enriched in neurofibrillary tangles and forms of dementia such as Alzheimer's disease. HSV-1 is a neurotropic virus that establishes and maintains latency in sensory neurons. Physiological and emotional stressors have been shown to reactivate the virus from this latent stage and spread to the central nervous system. In an *in vitro* model of Vero cells, our data has shown increased levels of hyperphosphorylated tau as a result of HSV-1 infection. Ongoing analysis is being performed to further understand the impact of HSV-1 infection on the phosphorylation of tau in rat hippocampal neurons.

Disclosures: **N. Weigle:** None. **C. Da Silva:** None. **K. russell:** None. **G.D. Griffin:** None.

Poster

744. Neuroinflammation: HIV and Infections

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Program #/Poster #: 744.22/D35

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: Institute of Human Virology

Title: Examining metabolic stress and inflammation in a murine model of HIV-associated PCNSL

Authors: S. ANDHAVARAPU[1], J. BRYANT[2], *D. PATEL[1], A. KATURI[1], H. DAVIS[2], A. HEREDIA[2], T. K. MAKAR[1];
[1]Dept. of Neurol., Univ. of Maryland, Baltimore, Baltimore, MD; [2]Inst. of Human Virology, Baltimore, MD

Abstract: Background: HIV-associated primary central nervous system lymphoma (PCNSL) is a malignant diffuse large B-cell lymphoma that occurs in 3-5 % of HIV patients. Studies using animal models are critical to better understanding HIV-associated PCNSL pathogenesis and to investigate potential therapeutic strategies. Symptoms of HIV PCNSL include loss of cognitive function such as memory loss. Because the hippocampus plays a crucial role in cognitive ability, we analyzed cellular and metabolic changes in the hippocampus of the HIV-1-associated PCNSL mouse model.
Methods: The transgenic mouse line TgN (pNL43d14)26Lab (Tg26) was generated by deleting 3kb sequences of gag and pol genes from the 7.4kb HIV proviral transgene. The colony developing lymphoma was generated by cross breeding heterozygous Tg26 mice with skin lesions. 25% of HIV Tg26 mice spontaneously developed lymphoma in the CNS, whereas 75% of the mice developed systemic lymphomas. Cells from the systemic lymphomas were injected intravenously into a new set of Tg26 mice, where 2% of mice developed PCNSL. Paraffin sections of brain tissue from 3 types of mice were prepared: Wild type (WT), Tg26, and Tg26 + PCNSL. Immunohistochemical staining and brightfield microscopy were used to observe the

expression of CD45, GFAP, NFκB, TNF-α, SIRT1, and PGC1-α. ImageJ was used for histological quantifications, and Prism software was used for statistical analysis.
Results: CD45, GFAP, NFκB, TNF-α, and SIRT1 were all were significantly elevated in the hippocampal regions of the Tg26 mice and further upregulated in the Tg26 + PCNSL mice in comparison to the WT. PGC1-α was downregulated in the Tg26 mice but upregulated in the Tg26 + PCNSL mice in comparison to WT.
Conclusion: Increased GFAP signifies that there is increased glial activation in the hippocampal regions of Tg26 mice with PCNSL. Glial cell activation breaks the integrity of the blood-brain-barrier, resulting in enhanced cellular infiltration as seen with CD45 levels. NFκB is implicated with various signaling pathways in the cell including TNF-α and SIRT1, a regulator of PGC1-α. While future research will help to elucidate the interplay between these proteins, we show that there is a link between the inflammatory response and metabolic changes in the disease pathology, suggesting that targeting NFkB and SIRT1 may present a novel therapeutic approach for HIV-associated PCNSL.

Disclosures: S. Andhavarapu: None. **J. Bryant:** None. **D. Patel:** None. **A. Katuri:** None. **T.K. Makar:** None.

Poster

744. Neuroinflammation: HIV and Infections

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 744.23/D36

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: NIH Grant R00 DA039791
The University of Mississippi School of Pharmacy

Title: HIV-1 Tat interacts with selective estrogen receptor modulators to influence morphine-conditioned place preference

Authors: *A. N. QRAREYA, S. MOHAMMED, F. MAHDI, J. J. PARIS;
Bimolecular Sci., The Univ. of Mississippi, University, MS

Abstract: Opioid abuse is a common route of transmission for human immunodeficiency virus (HIV), involved in 13.8% of new infections among women and 8.3% of new infections among men. We have found that the HIV-1 regulatory protein, trans-activator of transcription (Tat), can potentiate the rewarding properties of cocaine or morphine in male mice. Tat also potentiates cocaine reward in female mice and these effects are estrous cycle-dependent. But how Tat interacts with sex steroid targets to influence opioid reward is not well-understood. We hypothesized that estradiol would potentiate Tat-mediated opioid reward and that these effects would be differentially modulated by estrogen receptor α (ERα)- and β (ERβ)-acting selective

estrogen receptor modulators (SERMs). Ovariectomized Tat-transgenic mice were treated with vehicle, a physiological regimen of estradiol (0.09 mg/kg, QOD for 12 d), the ERα-selective SERM, propylpyrazole triol (PPT; 0.09 mg/kg, QOD for 12 d), or the ERβ-selective SERM, diarylpropionitrile (DPN; 0.09 mg/kg, QOD for 12 d) and assessed for morphine reward in an unbiased conditioned place preference (CPP) paradigm. Complementary *in vitro* studies were performed on primary C57BL/6HNsd mixed glial cells that were treated with vehicle, Tat (100 nM), morphine (500 nM), estradiol, PPT, and/or DPN (0.01-10 nM) and assessed for reactive oxygen species (ROS) formation via CM-H_2DCFDA assay. All mice demonstrated morphine-CPP and induction of Tat alone did not influence this effect. However, the combination of Tat and estradiol significantly increased morphine-reward. The ERβ-selective SERM, DPN, did not influence basal morphine-CPP; however, the ERα-selective SERM, PPT, attenuated morphine-CPP in both Tat-transgenic mice and their wildtype counterparts. In primary mixed glia, Tat significantly increased the formation of ROS (~10-15% above baseline) and physiological concentrations of estradiol (0.01-1 nM) significantly attenuated this effect with or without morphine co-exposure. Of interest, the highest estradiol concentration (10 nM) significantly interacted with morphine to increase ROS production (~20% above baseline), irrespective of Tat. Similarly, DPN or PPT attenuated Tat-mediated ROS; however, these effects were notably greater with PPT. Like estradiol, both DPN and PPT significantly interacted with morphine to increase ROS, but the effects occurred at lower concentration for DPN (1 nM) and to greater effect (~30% above baseline) than PPT (at 10 nM, ~11% above baseline). Thus, estrogen receptors may serve as important targets for Tat/opioid interactions.

Disclosures: A.N. Qrareya: None. **S. Mohammed:** None. **F. Mahdi:** None. **J.J. Paris:** None.

Poster

744. Neuroinflammation: HIV and Infections

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 744.24/D37

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: NIH Grant R00 DA039791
The University of Mississippi School of Pharmacy

Title: HIV-1 Tat protein and oxycodone dysregulate adrenal and gonadal endocrine axes and promote affective and cognitive dysfunction in mice

Authors: *S. MOHAMMED[1], A. N. QRAREYA[2], F. MAHDI[2], J. J. PARIS[2];
[1]BioMolecular Sci., Univ. of Mississippi, Oxford, MS; [2]BioMolecular Sci., Univ. of Mississippi, University, MS

Abstract: Human immunodeficiency virus (HIV) is associated with co-morbid affective and neurocognitive disorders that afflict ~50% of infected individuals. One factor that may contribute to neuropathology is the HIV regulatory protein, trans-activator of transcription (Tat), which promotes neuroinflammation and neurotoxicity that can be exacerbated by opioids. We and others have observed steroid hormones, such as estradiol and/or progesterone, to attenuate Tat-mediated neurotoxicity in cell culture; however, their interactions with opioids and their protective effects in a whole-animal model are unknown. We hypothesized that doxycycline-inducible expression of Tat in transgenic mice would interact with the opioid, oxycodone, to induce psychomotor, anxiety-like, and depression-like behavior and to dysregulate adrenal and gonadal steroid hormones. When administered acutely, oxycodone (3 mg/kg) increased psychomotor behavior in an open field and induction of HIV-1 Tat protein significantly potentiated these effects. Tat expression also potentiated the anxiolytic-like effects of oxycodone, increasing entries into the center of the open field, but only among females in the diestrous phase of the estrous cycle. Tat increased depression-like behavior among proestrous, but not diestrous, females. When administered repeatedly, oxycodone (3 mg/kg, QD for 5d) interacted with Tat protein to decrease cognitive performance in a novel object recognition test among all mice with the exception of proestrous control mice. These data suggest that induction of Tat potentiates psychomotor and anxiety-like effects of acute oxycodone and either Tat induction or repeated oxycodone perturb cognitive performance. Manipulations also influenced adrenal and gonadal endocrine status in a cycle-dependent manner. Tat or oxycodone increased circulating corticosterone in all mice acutely and repeated administration produced greater elevations. Tat increased circulating estradiol and progesterone among diestrous mice and decreased estradiol among proestrous mice. Oxycodone increased estradiol and progesterone among diestrous mice when administered acutely, but only elevated estradiol when administered repeatedly. Thus, neuroendocrine function may be an important target for HIV-1 Tat/opioid interactions.

Disclosures: S. Mohammed: None. **A.N. Qrareya:** None. **F. Mahdi:** None. **J.J. Paris:** None.

Poster

744. Neuroinflammation: HIV and Infections

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 744.25/D38

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: RO1DA039005

Title: High content analysis of the neuropathogenesis of SIV infection in the presence of dopamine

Authors: *H. S. JOHNSON[1], K. RUNNER[2], H. S. FOX[3], P. J. GASKILL[2];
[2]Pharmacol. and Physiol., [1]Drexel Univ. Col. of Med., Philadelphia, PA; [3]Pharmacol. and Exp Neuroscie, Univ. of NE Med. Cente, Omaha, NE

Abstract: Globally, around 37 million people are infected with HIV, despite advancements in antiretroviral therapy. HIV enters the central nervous system (CNS) rapidly after initial infection, resulting in a variety of neurological effects collectively known as NeuroHIV. These effects are thought to result, at least partially, from infection of CNS macrophages, the primary targets for HIV in the brain. NeuroHIV is altered by drug abuse, a common comorbidity in the HIV-infected population. While different types of drugs have distinct mechanisms of action, all drugs of abuse increase dopamine. Our research shows increased dopamine both enhances HIV infection and increases production of inflammatory mediators in macrophages. To better understand the impact of increased dopamine in HIV neuropathogenesis, Rhesus macaques were inoculated with SIV in the presence or absence of selegiline, which increases CNS dopamine, and sacrificed after 2 weeks to analyze early changes in brain tissue. CNS tissues were processed and analyzed by both immunofluorescent staining and HPLC to determine how regional changes in CNS dopamine influence the progress of NeuroHIV. In dopamine-rich regions such as the caudate, nuclear localization of the transcription factor NF-κB was increased in macrophages. This suggests that dopamine may enhance inflammation by increasing the release of NF-κB regulated cytokines, such as IL-6 and IL-1β, and correlates with our published data in primary human macrophages. We are currently examining the amount of infection in these regions to determine whether elevated dopamine increases SIV infection in macrophages. These data suggest an interaction between dopamine and SIV enhancing the development of NeuroHIV, a hypothesis supported by previous *in vitro* studies. Understanding the relationship between CNS dopamine and HIV infection will help us to define the impact of substance abuse on HIV neuropathogenesis, leading to more effective treatments for NeuroHIV in drug abusers.

Disclosures: H.S. Johnson: None. **K. Runner:** None. **H.S. Fox:** None. **P.J. Gaskill:** None.

Poster

744. Neuroinflammation: HIV and Infections

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 744.26/D39

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: R01 DA039005

Title: Dopamine-mediated conformational changes in CCR5 in HIV infection of myeloid cells

Authors: *S. MATT[1], Y. RONG[1], M. O'CONNOR[2], N. RADIO[3], P. J. GASKILL[1];
[1]Pharmacol. and Physiol., [2]Div. of Infectious Dis. and HIV Med., Drexel Univ. Col. of Med., Philadelphia, PA; [3]ThermoFisher Scientific Cell. Imaging and Analysis, Carlsbad, CA

Abstract: Although combination antiretroviral therapy (cART) has greatly reduced HIV-related mortality, there are still 37 million people worldwide infected with HIV. Even with cART, infected cells within the central nervous system (CNS) can produce new virus and release neurotoxic factors that may contribute to NeuroHIV. In addition, drug abuse is disproportionately prevalent within the HIV-infected population, and may exacerbate the pathology associated with NeuroHIV. Aberrant regulation of dopamine, which is elevated by the use of all illicit drugs, can also play a role in HIV progression. Our lab has previously shown that dopamine can increase HIV entry in human monocyte-derived macrophages (MDM), suggesting that drug-induced increases in CNS dopamine could accelerate the spread of infection, but the precise mechanism is unknown. One possible mechanism is dopamine-mediated changes in CCR5, the primary co-receptor used by HIV to enter myeloid cells. CCR5 can adopt many conformations, specifically in the second extracellular loop and N-terminal regions, to differentially regulate the accessibility or binding affinity to HIV, which can alter efficiency of HIV entry. Conformationally distinct CCR5 subpopulations also show different affinities with lipid rafts, which could also influence the HIV entry process. Our results demonstrate that dopamine increases the relative abundance of different CCR5 conformations on the MDM surface, and we are currently examining whether these changes also occur in microglia. We are also determining whether these dopamine-induced changes in specific CCR5 epitopes impact HIV entry. Further, our data show that CCR5 conformations differentially colocalize with lipid rafts, although this does not seem to be influenced by dopamine. A detailed understanding of dopamine-mediated changes in CCR5 will be critical to effectively tailor cART regimens that may be more beneficial in HIV+ individuals who abuse drugs. These data will support future projects targeting specific CCR5 conformations for use as novel HIV inhibitors in at risk populations, as these may be more effective in preventing HIV entry. Ultimately, our findings could also have broader implications for how dopamine can shift protein conformations in relation to other disease states.

Disclosures: S. Matt: None. **Y. Rong:** None. **M. O'Connor:** None. **N. Radio:** None. **P.J. Gaskill:** None.

Poster

744. Neuroinflammation: HIV and Infections

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 744.27/D40

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: DA039005

Title: Role of dopamine in the modulation of macrophage-mediated inflammation: Implications for NeuroHIV and drug abuse

Authors: *P. J. GASKILL, R. A. NOLAN, K. RUNNER, Y. RONG;
Pharmacol. and Physiol., Drexel Univ. Col. of Med., Philadelphia, PA

Abstract: Drug abuse is an important comorbidity in HIV infection, affecting 10 - 20% of HIV infected individuals. Abuse of drugs exacerbates peripheral HIV infection and has been linked to the development of NeuroHIV, as HIV-infected drug abusers have a higher risk of neurocognitive impairment. These effects are seen with all types of drugs of abuse, suggesting a common mechanism by which drug abuse impacts NeuroHIV. One mechanism common to all drugs of abuse is an increase extracellular dopamine in the CNS. Research shows correlations between dopaminergic dysfunction and HIV infection of the CNS, suggesting that inflammation induced by elevated dopamine could enhance the development of HIV-associated neuropathology. However, the precise mechanism(s) by which elevated dopamine could exacerbate the progress of HAND remain unclear. As the primary targets for and responders to HIV in the CNS are myeloid lineage cells, the effects of dopamine on these cells may be a key connection between dopaminergic changes and HIV-associated neuroinflammation.Our data show that dopamine treatment of human macrophages promotes an inflammatory phenotype in these cells by inducing production of the inflammatory mediators IL-1β, IL-6, IL-18, CCL2, CXCL8, CXCL9, and CXCL10. Further, dopamine-mediated modulation of specific cytokines is correlated with macrophage expression of dopamine-receptor transcripts, particularly DRD5, which we show to be expressed at significantly higher levels than other dopamine-receptor subtypes. Mechanistically, these effects may be induced by dopamine-mediated activation of inflammatory pathways, as our data show dopamine activates the NF-κB pathway. This results in increased expression of NF-κB modulated genes including NLRP3 and IL-1βthat prime the NLRP3 inflammasome complex. Thus, elevated CNS dopamine in the context of HIV and/or drug abuse may potentiate neuroinflammation via the NF-κB pathway. These changes may also influence the development or maintenance of addiction in these individuals. Overall, these data will provide more understanding of the role of dopamine in the development of NeuroHIV, and may suggest new molecules or pathways that can be useful as therapeutic targets for HIV-infected drug abusers.

Disclosures: P.J. Gaskill: None. **R.A. Nolan:** None. **K. Runner:** None. **Y. Rong:** None.

Poster

744. Neuroinflammation: HIV and Infections

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 744.28/D41

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: NIH Grant R01DA039005

Title: Dopamine modulates HIV entry into macrophages via G_q-dependent signaling mechanisms

Authors: *E. NICKOLOFF-BYBEL[1], P. MACKIE[4], K. RUNNER[2], R. NOLAN[3], S. MATT[5], H. KHOSHBOUEI[4], P. J. GASKILL[3];
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Abstract: Despite the use of combined anti-retroviral therapy (cART), many individuals with HIV still experience neurocognitive decline and neuropathology. Significant neurologic dysfunction is seen in dopaminergic regions of the CNS, suggesting that dopamine may play a role in the development of NeuroHIV. Our lab has shown that dopamine can increase HIV entry and replication in primary human macrophages, the primary cell type infected in the CNS. However, mechanisms by which dopamine mediates these effects remains unclear. Previously, we demonstrated that activation of both D1-like and D2-like receptors increases viral entry into macrophages, suggesting these receptors may act through a common mechanism to enhance the entry process. Our current data support this hypothesis, showing dopamine stimulates calcium release in human macrophages, and inhibition of this calcium flux prevents dopamine-mediated increases in viral entry. This suggests that dopamine's effects on viral entry is modulated by signaling through a non-canonical dopamine signaling pathway, in which activation of either dopamine receptor subtype leads to IP_3-mediated calcium release and PKC activation. Our data demonstrate the activity of this pathway in human macrophages, showing that dopamine stimulates calcium release and PKC phosphorylation in these cells. The dopamine-mediated increases in both calcium release and PKC phosphorylation were inhibited by treatment with a G_q inhibitor. Additionally, our data show that dopamine receptor activation did not increase cAMP production, suggesting that canonical dopamine signaling is not occurring in these cells. Together, these data indicate dopamine mediates its effects on viral entry into macrophages via a non-canonical signaling pathway. Moreover, these data suggest dopamine may signal through different mechanisms depending on cell type, highlighting a need to re-examine the way we think of the canonical dopamine signaling paradigm. Recent studies indicate dopamine can act as a critical mediator of the neuroimmune axis, and therefore it is critical to understand how dopamine acts in distinct cell types. Future studies will further define these dopamine signaling pathways, both in the context of HIV infection and under non-pathological conditions.

Disclosures: E. Nickoloff-Bybel: None. **P. Mackie:** None. **K. Runner:** None. **R. Nolan:** None. **S. Matt:** None. **H. Khoshbouei:** None. **P.J. Gaskill:** None.

Poster

744. Neuroinflammation: HIV and Infections

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 744.29/D42

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: BT/PR20922/MED/122/37/2016
CSIR fellowship
SERB Young scientist award
IISER-K fellowship
NIH, NIBIB,R01-EB018842

Title: ERp29 a PDI family molecular chaperone: A potential target for host factor altering connexin 43 mediated gap junction intercellular communication in mouse astrocytes

Authors: *A. BOSE[1], D. THOMAS[1], P. MUKHERJEE[1], M. MAULIK[1], M. KOVAL[2], J. DAS SARMA[1];
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[2]Departments of Med. and Cell Biol., Emory Univ. Sch. of Med., Atlanta, GA

Abstract: In the central nervous system (CNS), gap-junctions (GJs) directly connect the cytoplasm between neighbouring cells creating a “panglial syncytium”, critical for metabolic coupling and brain homeostasis. It has been recognised for several years that certain RNA and tumor viruses decrease gap-junctional intercellular communication (GJIC) among infected cells. Recently, we showed in a mouse model of demyelination that Mouse Hepatitis Virus (MHV) infection disrupts Connexin43 (Cx43)-containing GJs predominantly expressed by astrocytes. Specifically, MHV infection repressed Cx43 trafficking to cell surface by a microtubule-dependent mechanism during the acute phase of inflammation following infection. However, the mechanism of depletion of Cx43 at the cell surface as well as its reduced expression at mRNA and total protein level is not well understood. We hypothesize that MHV induces ER stress that amplifies the unfolded protein response leading to defects in Cx43 processing and gap-junction channel formation. Consistent with inducing ER stress, MHV infection upregulated GRP78 (Bip) in a dose-dependent manner in primary astrocytes and DBT astrocytoma cells (N=3). Furthermore, MHV infection down-regulated ERp29, an ER resident PDI family protein known to promote Cx43 assembly and trafficking to the plasma membrane, thus enhancing GJIC. Stable transfection of exogenous ERp29 in DBT cells, that endogenously express internalised Cx43 and mimic retention of Cx43 in the intracellular compartment of infected astrocytes, rescued the trafficking of Cx43 to cell surface. Supporting this observation, treatment of infected primary astrocytes or DBT cells with 4-phenylbutyrate (4-PBA) that is known to upregulate native ERp29 expression, facilitated Cx43 trafficking to the cell surface and re-established GJIC.

Further studies showed increasing exogenous ERp29 expression decreased viral infectivity, fusogenicity and replication both in DBT cells and primary astrocytes. Our findings describe a previously unidentified, viral-induced ER stress pathway involving ERp29 as a potential target to restore proper trafficking of Cx43 and re-establish GJIC in the CNS. It will be interesting to explore the regulatory role of ERp29 and ERp29 rescued Cx43 mediated GJIC in mounting antiviral host response.

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Poster

744. Neuroinflammation: HIV and Infections

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 744.30/D43

Topic: I.01. Molecular/ Biochemical/ and Genetic Techniques

Support: R01 NS 108796

Title: Astrocyte derived HIV evolution in humanized mice

Authors: *H. J. BARBIAN, V. LUTGEN, L. AL-HARTHI;
Rush Univ. Med. Ctr., Chicago, IL

Abstract: HIV infects the brain during acute infection and persists in the CNS despite suppressive antiretroviral therapy. While ample data demonstrates HIV genetic compartmentalization between the CNS and the periphery, it is unclear if HIV undergoes significant evolution within the CNS and whether CNS egress contributes to peripheral HIV quasispecies. We previously developed a humanized mouse model where HIV infected human fetal astrocytes were xenotransplanted into NSG mice and reconstituted with human PBMCs. Using this model, we demonstrated that astrocytes, the predominant brain cell type, support replication competent HIV which can egress from the CNS to peripheral organs (spleen, lymph node). In this study, we assessed genomic changes in HIV that egressed from astrocytes. Using single genome amplification and direct sequencing, the gold standard for HIV quasispecies characterization, we show that virus had evolved, with 24% of spleen sequences showing mutations from the original viral inoculum. The mutated genomes showed random diversification, APOBEC mutations, Poisson distribution, star-like phylogeny, and time to most recent common ancestor analysis correctly identified the duration of infection (95% CI=27-61 days, actual=33 days), suggesting that viral evolution in this model fits the mathematical model of acute HIV-1 diversification in humans. Thus, astrocyte-derived HIV evolves and mimics the viral evolution observed in early peripheral infection and can contribute to peripheral genetic diversity. Ongoing studies are assessing HIV evolution within astrocytes over time.

Disclosures: **H.J. Barbian:** None. **V. Lutgen:** None. **L. Al-Harthi:** None.

Poster

745. Brain Injury, Ischemia, and Epilepsy

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 745.01/D44

Topic: C.10. Brain Injury and Trauma

Support: FAPESP Grant 2017 / 23356-6
NIH Grant P01HD085928

Title: Hypoxia-ischemia during a neonatal sensitive period reduces purkinje neuron dendritic complexity only in males

Authors: *S. E. ARAMBULA[1], A. R. R. LEITE[2], M. PEREZ-POUCHOULEN[1], M. M. MCCARTHY[1];
[1]Pharmacol., Univ. of Maryland Sch. of Med., Baltimore, MD; [2]Morphology, Univ. Estadual Paulista - UNESP, Botucatu, Brazil

Abstract: Neonatal hypoxia-ischemia (HI; concurrent oxygen/blood deprivation) is a major health issue with few effective therapies. HI-related brain injuries occur in approximately 2 out of 1,000 term births and are the leading cause of mortality and disabilities in children. Notably, male infants are at a greater risk for HI and exhibit more extreme deficits than females. Although clinical evidence indicates that neonatal HI impacts the cerebellum, this region has been largely ignored in preclinical models. Cerebellar development is unique as it is one of the first brain structures to differentiate yet one of the last to fully mature; making it particularly vulnerable to developmental injury. Our lab has previously identified the second postnatal week in the rat as a sensitive period of cerebellar development that is dysregulated by inflammatory insults. This period coincides with a time of increased risk for perinatal HI (e.g. birth in human infants). Collectively, these data suggest that neonatal HI could impair cerebellar development by stunting Purkinje neuron complexity. To examine the effect of neonatal HI on Purkinje neurons we used a modified version of the Rice-Vannucci model representative of HI brain injury in the term infant. On postnatal day 1 (P1), Sprague-Dawley rat pups received bilateral intracerebroventricular injections of an AAV that expressed eGFP driven by the CB7 promoter to label Purkinje neurons. On P10, animals underwent unilateral ligation of the internal carotid artery followed by hypoxia (8% oxygen for 1hr). Age-matched, sham-operated animals served as controls for all experiments. Cerebellar vermes were collected on P17, processed for confocal microscopy and Sholl analysis of Purkinje neurons was used to quantify branching characteristics of Purkinje cells. In males, neonatal HI significantly ($P < 0.01$) reduced Purkinje dendritic arbor complexity, such that the dendritic tree branched less frequently. Intriguingly, there was a slight but significant ($P < 0.05$) increase in female dendritic branching, suggesting either that repair

mechanisms are initiated earlier in females or that females are protected from HI. Thus, optimal windows for intervention might differ between the sexes. Additional studies are underway to determine the impact of neonatal HI on other cerebellar cell types, including microglia, and astrocytes. This research fills a knowledge gap by defining the impact of HI on the cerebellum and may lead to novel insights on how sex regulates vulnerability to brain injury.

Disclosures: S.E. Arambula: None. **A.R.R. Leite:** None. **M. Perez-Pouchoulen:** None. **M.M. McCarthy:** None.

Poster

745. Brain Injury, Ischemia, and Epilepsy

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 745.02/D45

Topic: C.10. Brain Injury and Trauma

Support: FAPESP grant 2017/23356-6
NIH grant P01HD085928

Title: Impact of hypoxic ischemic brain injury on astrocytes in the developing cerebellum

Authors: *A. R. R. LEITE[1], S. E. ARAMBULA[2], M. M. MCCARTHY[3];
[1]Morphology, Univ. Estadual Paulista - UNESP, Botucatu, Brazil; [2]Pharmacol., [3]Univ. of Maryland Sch. of Med., Baltimore, MD

Abstract: Neonatal hypoxia ischemia (HI) is the major cause of brain injury in the term infant and occurs when the newborn brain doesn't receive enough oxygen due to blood loss or other complications during delivery. The cerebellum is one of the first brain structures to differentiate and one of the last to mature, making it more vulnerable to perturbations occurring during development. While clinical data shows that neonatal HI impacts the cerebellum, this brain region has largely been overlooked in experimental research. To model HI in the term infant, male and female Sprague Dawley rat pups were subjected to a unilateral internal carotid artery ligation, followed by exposure to 8% oxygen air for 60 min on postnatal day (PN) 10. Control animals for all experiments were sham-operated. On PN17, animals were euthanized and cerebellar vermis were dissected, sagittally sectioned on a cryostat, and processed for immunohistochemistry. Astrocytes are dynamic cells that maintain brain homeostasis and provide structural, metabolic and trophic support to neurons. Moreover, impairment in astrocyte function during brain injury can influence neuronal survival and recent studies have shown that growth factors produced by astrocytes can be critical in regenerating trauma-damaged brain tissues. To examine the impact of HI on cerebellar astrocytes, glial fibrillary acidic protein (GFAP) immunoreactivity was evaluated. Initial analyses using ImageJ indicate that HI does not affect the number or density of cerebellar astrocytes in either males or females one week after HI

brain injury. Further studies are underway to determine how HI affects Purkinje cells and granule cells of the cerebellar vermis.

Disclosures: A.R.R. Leite: None. **S.E. Arambula:** None. **M.M. McCarthy:** None.

Poster

745. Brain Injury, Ischemia, and Epilepsy

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 745.03/D46

Topic: C.10. Brain Injury and Trauma

Support: NIH R37NS109478
DC-IDDRC U54HD090257

Title: Oligodendrocyte differentiation is regulated by Sirt2 in white matter after neonatal hypoxia

Authors: *B. JABLONSKA[1], L.-J. CHEW[1], M. REIBER[1], K. KUSCH[2], K. .-A. NAVE[2], V. GALLO[1];
[1]Children's Natl. Med. Ctr., Washington, DC; [2]Dept. of Neurogenetics, Max Planck Inst. for Exptl. Medicine,, Göttingen, Germany

Abstract: Diffuse white matter injury (DWMI) is a major form of brain injury, which results in chronic neurological and behavioral disabilities in prematurely born infants, including a broad spectrum of cognitive and learning disabilities until young adulthood. Using a mouse model of neonatal hypoxia, we previously demonstrated that hypoxia delayed oligodendrocyte (OL) maturation in white matter by decreasing FoxO1 induced $p27^{Kip1}$ levels. Since Sirt2 is implicated in OL maturation, we determined whether neonatal hypoxia altered Sirt2 expression and function in white matter. Hypoxia reduced Sirt2 expression and the number of $Sirt2^+$ cells in white matter along with the number of $Sirt2^+CC1^+$ and $Sirt2^+Olig2^+$ cells. Since Sirt2 siRNA treatment of cultured OLs reduced percentages of $Olig2^+$, $GalC^+$, and $O4^+$ cells, it is likely that hypoxia-induced decrease in Sirt2 prevents OL differentiation. To investigate the role of Sirt2 in OL differentiation after hypoxia, we performed loss- and gain-of-function experiments in $Sirt2^{fl/fl}PDGFR^{cre}$ and $Sirt2^{Stop}PDGFR^{cre}$ mice, in which Sirt2 was ablated or overexpressed in PDGFR-expressing oligodendrocyte progenitor cells, respectively, after tamoxifen injection at P12. The percentage of $CC1^+$ and $Olig2^+$ cells expressing Sirt2 decreased in white matter of $Sirt2^{fl/fl}PDGFR^{cre}$ mice after normoxia and hypoxia, while the opposite effect was observed in $Sirt2^{Stop}PDGFR^{cre}$ mice. In normoxic $Sirt2^{fl/fl}PDGFR^{cre}$ mice, the total number of $CC1^+$ OLs was reduced, as compared to WT mice, whereas Sirt2 overexpression elevated the number of mature OLs. Under hypoxic conditions, the absence of Sirt2 further reduced OL in white matter, whereas Sirt2 overexpression elevated the percentage of $CC1^+$ and $Olig2^+$ cells. Molecular

analysis revealed that Sirt2 formed complexes with FoxO1 and FoxO3a transcription factors in white matter. The Sirt2/FoxO1 complex and deacetylated FoxO1 were reduced by hypoxia. Instead, hypoxia enhanced formation of the Sirt2/FoxO3a complex, but also reduced deacetylated FoxO3a levels. Since FoxO1 and FoxO3a deacetylation are required for transcriptional activity, these changes induced by hypoxia suggest that reduced Sirt2-mediated deacetylation of FoxO1 and FoxO3a underlie reduced $p27^{Kip1}$ expression in injured white matter. Our findings demonstrate that i) Sirt2 promotes OLs differentiation under normoxic and hypoxic conditions, ii) Sirt2 overexpression partially rescues the effect of hypoxia on OL maturation in white matter iii) the functional involvement of Sirt2 may provide a link between cell cycle inhibitors and delayed OL maturation in hypoxia-induced white matter damage.

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Poster

745. Brain Injury, Ischemia, and Epilepsy

Location: Hall A

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Program #/Poster #: 745.04/E1

Topic: C.10. Brain Injury and Trauma

Support: NRF-2018R1A4A1020922
NRF-2017M3C7A1028937
NRF-2017R1D1A1A09081190
NRF-2016M3C7A1913844

Title: Effects of transient receptor potential cation channel 5 inhibition on global cerebral ischemia-induced neuronal death

Authors: *B. KANG, B. CHOI, A. KHO, S. LEE, D. HONG, J. JEONG, D. KANG, M. PARK, S. SUH;
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Abstract: Increased zinc accumulation in the brain plays a critical role in neuronal death in brain diseases such as ischemia, traumatic brain injury, epileptic seizure and hypoglycemia. During such conditions, vesicular zinc is pre-synaptically released into the synaptic cleft and translocated to the cytoplasm via various cation channels. It causes the production of reactive oxygen species (ROS) and neuronal death. Transient receptor potential cation channel 5 (TRPC5) is a receptor-activated non-selective cation channel. NU6027is known as an inhibitor of TRPC5, which regulate the homeostasis of metal ions. In this study, we tested that whether blocking TRPC5 by using NU6027 shows neuroprotective effects and zinc accumulation following global cerebral ischemia (GCI) in mice. We used C57BL/6J mice (aged 2-3 months)

and performed a GCI model that occluded the bilateral common carotid artery (BCCA) for 30 minutes. NU6027 (1 mg/kg, *i.p.)* was immediately injected and mice sacrificed after 24 hours. Neuronal death, zinc accumulation and oxidative stress were confirmed by Fluoro-Jade B (FJB), N-(6-methoxy-8-quinolyl)-para-toluenesulfonamide (TSQ) and 4HNE staining in the brain hippocampal region. The present study found that GCI induced by BCCA occlusion increased considerably neuronal death, zinc accumulation and oxidative stress. But, administration of NU6027 decreased the number of degenerating neurons, zinc accumulation and oxidative stress in the subiculum, CA1, CA3 and dentate gyrus after GCI, via downregulation of TRPC5 channels. Therefore, this study suggests that NU6027, a TRPC5 inhibitor, may have therapeutic potential for prevention of GCI-induced neuronal death, zinc accumulation and oxidative stress.
Keyword: NU6027, global cerebral ischemia, neuronal death, oxidative stress, transient receptor potential cation channel 5, zinc

Disclosures: **B. Kang:** None. **B. Choi:** None. **A. Kho:** None. **S. Lee:** None. **D. Hong:** None. **J. Jeong:** None. **D. Kang:** None. **M. Park:** None. **S. Suh:** None.

Poster

745. Brain Injury, Ischemia, and Epilepsy

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 745.05/DP06/E2

ControlExtraData.DynamicPosterDisplay:
Dynamic Poster
Topic: C.10. Brain Injury and Trauma

Support: EraNet Neuron MISST
Munich Cluster for Systems Neurology (SyNergy)
Graduate School of Systemic Neurosciences (GSN)

Title: Long-term remote cortical reorganization after experimental ischemic stroke

Authors: S. VALERO-FREITAG[1,4], B. GROSCHUP[1], B. SEKER[1], B. GESIERICH[2], M. DUERING[2], M. DICHGANS[3,4], ***F. HELLAL**[1,4], N. PLESNILA[1,4];
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Abstract: Stroke induces neuronal deafferentation leading to remote anatomical and functional changes (diaschisis) via mechanisms not yet fully understood. The aim of the current study was to characterize the long-term effect of a cortical infarct on contralesional cortical reorganization

and dendritic dynamics and to correlate these changes to sensorimotor behavior and neural activity. To achieve these aims we performed the following experiments: We (i) characterized the consequences of cortical stroke and deafferentation of neurons of origin in the contralesional cortex using anterograde and retrograde viral labeling up to two months after cerebral ischemia. (ii) determined the ipsilesional *versus* contralesional relative expression of GABA and Glutamate synaptic transmission markers. (iii) investigated dendritic spine turnover in the contralesional hemisphere by repetitive 2-photon *in vivo* imaging, in correlation with behavioral analysis using an optimized long term survival mouse model depicting large stroke and sustained sensorimotor deficit. (iv) mapped the contralesional neural activity by functional hyperemia using laser speckle imaging. Two months after stroke, we found significant contralesional cortical thinning (-11%; $p<0.001$) in absence of substantial cell loss or neuronal body shrinkage but a decrease of neuropil fraction (-14%). In parallel with changes in relative excitatory/inhibitory balance between both hemispheres, we also observed decreased contralesional spine density in apical dendrites of transcallosal neurons (-35%). The longitudinal analysis in the contralesional cortex revealed that deafferented neurons displayed dynamic dendritic spine turnover favoring spine replacement. However, their density decreased over the course of stroke recovery which plateaued after 3 weeks (40% residual deficit). This structural reorganization is accompanied by reduced functional hyperemia (-33%) in the homotopic contralateral region of the lesion and a shift of the remaining blood flow response to neighboring tissue further implicating changes in neural activity and synaptic transmission in the contralesional cortex. Our data revealed stroke-induced transhemispheric diaschisis mediated by deafferentation of transcallosal neurons. Impacted transcallosal neurons remodel their dendritic spines and trigger contralesional cortex structural and functional reorganization. Currently, we investigate whether this process can be modulated in order to counteract sustained functional impairments in the chronic phase after ischemic stroke.

Disclosures: **S. Valero-Freitag:** None. **B. Groschup:** None. **B. Seker:** None. **B. Gesierich:** None. **M. Duering:** None. **M. Dichgans:** A. Employment/Salary (full or part-time):; Cluster for Systems Neurology. **F. Hellal:** None. **N. Plesnila:** None.

Poster

745. Brain Injury, Ischemia, and Epilepsy

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 745.06/E3

Topic: C.10. Brain Injury and Trauma

Support: AHA17IRG33430004, RO1 NS44025, CPA PG0816

Title: Effect of NSMase-2 inhibitor on extracellular vesicle release and injury after neonatal stroke

Authors: *M. LECUYER, P. PATHIPATI, J. FAUSTINO, Z. VEXLER;
Neurol., UCSF, San Francisco, CA

Abstract: Perinatal arterial stroke (occurs between the 20th gestation week to 28th day of life) leads to long-lasting cerebral disabilities. Although the inflammatory damage is a major brain injury component in the early postnatal period, microglia could limit injury after neonatal stroke (Faustino et al, J Neurosci 2011). These immune cells are central to the crosstalk between brains' cells. Release of extracellular vesicles (EV) is a largely unexplored mechanism of communication. Neutral Sphingomyelinase 2 (N-SMase2) is a plasma membrane enzyme which mediates EV release.
Aim: To understand the role and the underlying mechanisms of N-SMase2 dependent release and signaling of microglia-derived EV.
To investigate the contribution of N-SMase2 in injury after neonatal stroke, we have chosen to downregulate the gene Smpd3 (Sphingomyelin phosphodiesterase 3), which encodes N-SMase2, using a KO-CRISPR/dcas9. Control or KO-CRISPR/dcas9 was injected intracerebral at postnatal day 7 (P7) and enzyme activity examined daily between P9-P12. Transient middle cerebral artery occlusion (tMCAO) was performed at P9. In treated and non-treated pups enzymatic N-SMase2 activity and cell origin expression were examined by immunofluorescence (IF) and histological outcomes determined 72h after reperfusion. Microglia was isolated from injured/uninjured cortex by magneto-isolation. Released microglia derived EV (MEV) were characterized using Nanosight. MEV protein expression was determined by Western. Results: We observed a developmental increase of N-SMase-2 activity in naïve brain from P10 to P12 ($p<0.016$) and a significant decrease in KO-CRISPR/dcas9-treated mice compared to Control-CRISPR/dcas9 at P12 ($p<0.0062$). tMCAO reduced significantly N-SMase-2 activity in injured regions ($p<0.0043$). Based on IF, N-SMase-2 expression was markedly reduced in neurons within injured regions. Injury volume was significantly reduced by down regulation of Smpd3 ($p<0.0029$). Decreased N-SMase2 activity in Control mice correlated with reduced Glut-1 coverage, an effect in part prevented by KO-CRISPR/dcas9 pre-treatment, and neuro-protection. Microglia isolated and plated 24h after tMCAO proliferated and increase release of MEV. Uptake of MEV differs in microglia from injury region. Conclusion: Downregulation of N-SMase2 protects neonatal brain from stroke, in part due to vasculature preservation. MEV uptake by microglia from injured cortex is increased. In fine, these results will provide a better understanding of the implication of this novel cell-cell communication on severity of neonatal stroke.
Support by: AHA17IRG33430004, RO1 NS44025, CPA PG0816

Disclosures: **M. Lecuyer:** None. **P. Pathipati:** None. **J. Faustino:** None. **Z. Vexler:** None.

Poster

745. Brain Injury, Ischemia, and Epilepsy

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 745.07/E4

Topic: C.10. Brain Injury and Trauma

Support: NRF-2018R1A4A1020922

Title: The anti-oxidant, n-acetyl-l-cysteine attenuates hippocampal neurodegeneration after global cerebral ischemia via inhibition of transient receptor potential melastatin 2

Authors: *D. HONG[1], B. CHOI[1], A. KHO[1], S. LEE[1], J. JEONG[1], B. KANG[1], D. KANG[1], M. PARK[1], K.-H. PARK[2], S. SUH[1];
[1]Physiol., Hallym University, Col. of Med., Chuncheon, Korea, Republic of; [2]Div. of Cardiovasc. Dis., Hallym Univ. Med. Ctr., Anyang, Korea, Republic of

Abstract: A variety of cerebral ischemia induced neurodegenerative mechanisms have been verified and demonstrated such as calcium/zinc influx into cytoplasm, reactive oxygen species (ROS) production and ionic imbalance. Our lab has suggested that excessive zinc influx into neurons after the ischemic condition can be deleterious. During ischemic conditions after stroke or heart attack, vesicular zinc can be released into the synaptic cleft, and then translocated into the cytoplasm via various cation channels. Transient receptor potential melastatins (TRPMs) are non-selective cation channels. These channels have various subunits, one of them, TRPM2 was highly distributed in the central nervous system and it has high sensitivity to oxidative damage. Several previous studies have shown that TRPM2 channel activation attributes to neuroinflammation and neurodegeneration cascades. Therefore, in the present study we verified whether anti-oxidant such as N-acetyl-l-cysteine (NAC) treatment has neuroprotection via regulation of TRPM2 after global cerebral ischemia (GCI). Also, we hypothesized that if we block zinc influx with a TRPM2 channel blocker, ischemia-induced neuronal death can be prevented. To demonstrate our hypothesis, we used a GCI animal disease model. It was induced by common carotid artery occlusion and an isoelectric period set for seven minutes. In the present study, we delivered NAC (150mg/kg) into the intraperitoneal space daily administration for 3 days and 7 days. GCI-induced cell degeneration was estimated by Fluoro-Jade B (FJB); oxidative damage by lipid peroxidation was measured by 4-hydroxy-2-nonenal (4HNE); glial activation was assessed by ionized calcium-binding adapter molecule 1 (Iba-1) and glial fibrillary acidic protein (GFAP); zinc accumulation was detected by N-(6-methoxy-8-quinolyl)-para-toluensulfonamide (TSQ); and TRPM2 channel regulation was assayed by TRPM2 staining. As a result, NAC reduced GCI-induced cell damage cascades, such as hippocampal degenerating neurons, lipid peroxidation, microglia & astroglia activation, free zinc accumulation, as well as

TRPM2 over-activation. Consequently, TRPM2 channel may be a therapeutic target to prevent ischemia-induced neuronal death.

Disclosures: **D. Hong:** None. **B. Choi:** None. **A. Kho:** None. **S. Lee:** None. **J. Jeong:** None. **B. Kang:** None. **D. Kang:** None. **M. Park:** None. **S. Suh:** None.

Poster

745. Brain Injury, Ischemia, and Epilepsy

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 745.08/E5

Topic: C.10. Brain Injury and Trauma

Support: NRF-2016M3C7A1913844
NRF-2017R1D1A1A09081190
NRF-2017M3C7A1028937
NRF-2018R1A4A1020922

Title: The newly-found AMP-activated protein kinase (AMPK) inhibitors reduce hypoglycemia-induced hippocampal neuronal death

Authors: *A. KHO[1], B. CHOI[1], S. LEE[1], D. HONG[1], J. JEONG[1], B. KANG[1], D. KANG[2], M. PARK[1], S. SUH[1];
[2]physiology, [1]Hallym Univ., Chuncheon, Korea, Republic of

Abstract: Severe hypoglycemia (below 35mg/dL) is common in patients who are continuously treated with drugs such as insulin in order to control their blood glucose level. The worst outcomes of hypoglycemia can include unconsciousness, seizure or even death. To treat hypoglycemia, glucose reperfusion, performed to recover low blood glucose level in hypoglycemic state is required, but also acts as a secondary injury, causing aggravated neuronal cell death. Severe and prolonged hypoglycemia causes oxidative stress via NMDA excitotoxicity, inflammation, blood-brain barrier disruption, mitochondrial dysfunction and zinc release. AMP-activated protein kinases (AMPK) is a sensor of AMP: ATP ratio and generally plays a role in cellular energy homeostasis under a normal condition. However, under pathological conditions such as stroke and Huntington's disease, AMPK is found to be abnormally activated. This leads to aberrant neuronal nitric oxide synthase activity which produces peroxynitrite, the strongest oxidizing agent, and exacerbates lactate accumulation, which inhibits the ability of neurons to use lactate as an energy source, contributing to neuronal death. Also, in a previous study, AMPK causes zinc-induced neuronal death via the liver kinases B1 (LKB1)-dependent induction of a pro-apoptotic Bcl-2 homology domain 3-only protein (Bim). AMPK consists of three subunits, α subunits (α1 and α2), β subunits (β1 and β2) and γ subunits (γ1, γ2 and γ3). The α subunit is responsible for the catalytic kinase activity, with α2

acting as the dominant catalytic subunit in neurons. This study was therefore conducted to confirm whether the inhibition of AMPKα2 prevents neuronal cell death, including oxidative stress, zinc toxicity, inflammation and blood-brain barrier (BBB) disruption after hypoglycemia and glucose reperfusion. To evaluate this, we used an insulin-induced hypoglycemia animal model and injected AMPK α2 inhibitors (2G11 and 1H10, respectively 20μg/kg and 5μg/kg, *i.v.*, 1time) immediately after hypoglycemia. When administered as intravenous injections after insult, 2G11 and 1H10 significantly reduced hippocampal neuronal cell death. Therefore, the present study suggests that inhibitors of AMPK could be promising drug development candidates to treat hypoglycemia. (NRF-2016M3C7A1913844, 2017R1D1A1A09081190, 2017M3C7A1028937, 2018R1A4A1020922)
Key word: Hypoglycemia, AMPK inhibition, Oxidative stress, Zinc accumulation, Inflammation, BBB disruption, Neuron death

Disclosures: **A. Kho:** None. **B. Choi:** None. **S. Lee:** None. **D. Hong:** None. **J. Jeong:** None. **B. Kang:** None. **D. Kang:** None. **M. Park:** None. **S. Suh:** None.

Poster

745. Brain Injury, Ischemia, and Epilepsy

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 745.09/E6

Topic: C.10. Brain Injury and Trauma

Title: Gamma knife irradiation induced blood-brain barrier disruption and activation of glial cells in mice

Authors: *B. HE[1], X. WANG[4], P. YU[1], J. JIANG[1], W.-J. LIN[2], Y. TANG[3];
[1]Dept. of Neurology, Sun Yat-Sen Mem. Hospital, Sun Yat-Sen Univ., Guangzhou, China; [2]Dept. of Neurology, Sun Yat-Sen Mem. Hospital, Sun Yat-Sen Univ., Guangzhou city, Guangdong province, China; [3]Dept. of Neurology, Sun Yat-Sen Mem. Hospital, Sun Yat-Sen Univ., Guangdong, China; [4]Dept. of Oncology, The First Affiliated Hosp. of Guangdong Pharmaceut. Univ., Guangzhou, China

Abstract: Background: Gamma knife radiosurgery is a clinically and cost effective treatment for malignant brain tumors,especially for most brain metastases. However, patients may suffer from side effects including encephaledema, delayed cerebral infarction, or cognitive dysfunction. The underlying mechanism remains unclear. Blood-brain barrier (BBB) is likely to be the first to bear the brunt. In this study, we investigated the pathological impact of gamma knife irradiation on blood-brain barrier integrity and the neuroinflammatory response in the mouse model.
Materials and Methods: C57BL/6 and BALB/c mice were irradiated with Leksell Gamma Knife with 55Gy at the 50% isodose delivered to left hippocampal area. The appearance and size of brain lesion were evaluated by 7T MRI at different time points post radiation. Cerebral blood

perfusion of mice which haven't developed lesion in the brain were evaluated by arterial spin-labeling MRI (ASL-MRI). Two-photon microscopy, Evans blue dye, and immunofluorescence staining of fibrinogen were employed to measure BBB permeability. The morphology and number of glial cells were measured and quantified using immunofluorescence staining and ImageJ analysis.**Results:** Our data showed that before the development of brain lesion, the irradiated mice displayed cortical hypoperfusion detected by ASL-MRI . Four weeks after irradiation, the cerebral lesion can be clearly seen by MRI imaging and verified by two-photon microscopy imaging with low molecular weight fluorescent dye. Increase in Evans blue dye extravasation and fibrinogen leakage into the brain in irradiated mice also suggested disruption of BBB. In addition, immunofluorescence staining of Iba1, CD68, and S100βshowed significant increase in activated microglial and astrocytes, especially around the necrotic vessels at the ipsilateral side of the irradiated brains, suggesting the disruption of BBB may further lead to activation of glial cells.**Conclusions:** Gamma knife irradiation mouse models successfully induced disruption of blood-brain barrier and the activation of glial cells surrounding necrotic area.

Disclosures: B. He: None. **X. Wang:** None. **P. Yu:** None. **J. Jiang:** None. **W. Lin:** None. **Y. Tang:** None.

Poster

745. Brain Injury, Ischemia, and Epilepsy

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 745.10/E7

Topic: C.10. Brain Injury and Trauma

Title: Blood brain barrier is disrupted in intraventricular hemorrhage in extremely low preterm infants

Authors: *A. DEL POZO SANZ, Sr, M. VILLA, C. VARGAS, M. MARTINEZ, L. SILVA, J. MARTINEZ-ORGADO, A. GUTIÉRREZ-RODRÍGUEZ;
Hosp. Clinico San Carlos, Madrid, Spain

Abstract: Intraventricular Hemorrhage (IVH) is a frequent condition in extremely low birthweight preterm newborns (ELBW), representing a major risk factor for Cerebral Palsy (CP) with no current treatment. Furthermore, in these patients Blood Brain Barrier (BBB) is disrupted and leukocytes translocation and microglia activation are observed. At present, these data have been observed in other IVH neonatal models, but never in a ELBW model. We aim to determine if IVH brain damage and BBB disruption/hyperpermeability in a ELBW rat model are associated.
IVH brain damage was induced in newborn Wistar rats (1 day-old: P1). At P6, BBB disruption and brain damage was assessed by: Biochemistry [Neuroinflammation: Toll like receptor 4

(TLR-4); Oxidative stress: inducible Nitric Oxidase (iNOS); BBB hyperpermeability: Major Facilitator Superfamily Domain Containing 2a (MFSD2a); BBB disruption: Intercellular Adhesion Molecule 1 (ICAM-1)]; Spectroscopy [Excitotoxicity (Glut/NAA) and Cell metabolism (Lac/NAA)]; Flow cytometry [Total and M1/M2 ratio of microglia / macrophages activated population] studies. Non-IVH group was treated as control.
In IVH group, Biochemical analysis shows an increase of BBB permeability and damage, oxidative stress and neuroinflammation. Moreover, Spectroscopy studies revealed higher levels of excitotoxicity and cell metabolism. Flow cytometry studies revealed an increase of total microglia / macrophages population with a pro-inflammatory phenotype. N per group = 5. These results are observed in the table below.
Our findings provide BBB disfunction in our model is related with the brain damage. Furthermore, BBB could be a possible therapeutic target to prevent CP secondary to IVH in ELBW.

		SHAM	IVH
Biochemistry	*MFSD2a receptor* (1)	108.6 (7.70)	83.77 (7.41) *
	ICAM-1 (1)	88.28 (6.23)	109.4 (2.47) *
	iNOS (1)	95 (4.40)	115 (4.49) *
	TLR-4 (1)	70.55 (6.46)	88.84 (1.50) *
Spectroscopy	*Excitotoxicity* (2)	0.97 (0.25)	1.66 (0.03) *
	Cell metabolism (3)	0.85 (0.01)	1.71 (0.03) *
Flow Cytometry	*Total mic / mac activated* (4)	11.56 (2.01)	30.98 (3.91) *
	M1 mic / mac (5)	2.09 (0.48)	9.28 (3.12) *

Mean (SEM). (1): A.U. (2): Glut/NAA ratio. (3): Lac/NAA ratio. (4) % gated of $Cd11b^{+}$/ $Cd45^{medium/high}$. (5): iNOS/Arg1 ratio of $Cd11b^{+}$/ $Cd45^{medium/high}$ population. Kruskall-Wallis: (*) p<0.05 vs SHM

Disclosures: A. Del pozo sanz: None. **M. Villa:** None. **C. Vargas:** None. **M. Martinez:** None. **L. Silva:** None. **J. Martinez-Orgado:** None. **A. Gutiérrez-Rodríguez:** None.

Poster

745. Brain Injury, Ischemia, and Epilepsy

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 745.11/E8

Topic: C.10. Brain Injury and Trauma

Support: The Lilling Family Neonatal Division As well the Cohen's Children's hospital Neonatal Division

Title: Targeted protective role of azithromycin in a neonatal mouse model for periventricular leukomalacia (PVL)

Authors: *K. R. AYASOLLA[1], N. ZAGHLOUL[2], M. AHMED[2];
[1]Feinstein Inst. For Med. Res., Manhasset, NY; [2]Neonatology Division/ Dept. of Pediatrics, Banner - Diamond Children's Med. Ctr. ; The Univ. of Arizona Col. of Med., Tucson, AZ

Abstract.Abstract1:

Background: PVL is the most common cause of cerebral palsy in premature infants. Inflammation and microglial involvement has a role in its pathogenesis. In this study, we propose that azithromycin administration reduces the inflammatory process leading to decreased brain injury induced by Hypoxia-ischemia (HI) and with better outcome.

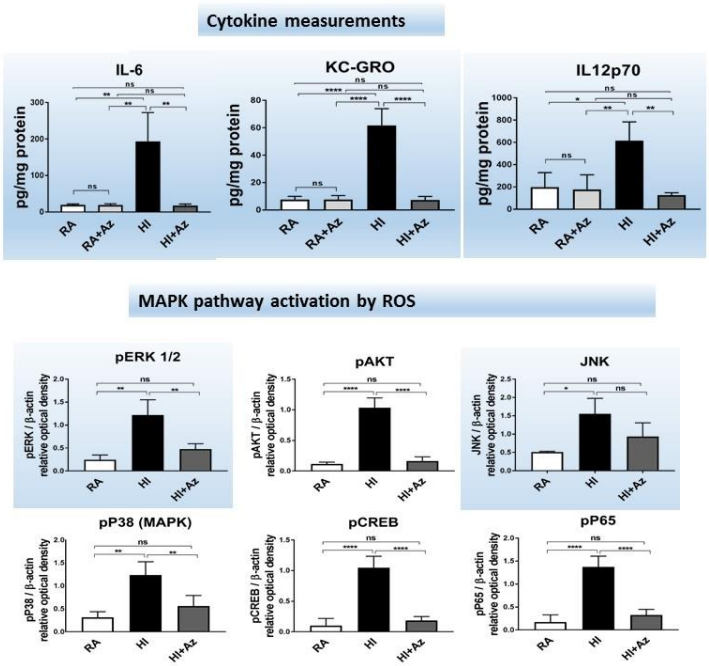
Objective: To examine the neuroprotective function of azithromycin as a new therapeutic approach in neonate mouse model of PVL.

Design/Methods: PVL neonate mouse model was established by temporary bilateral carotid ligation at P5, followed by hypoxia exposure with O2 concentration of 8% for 20 min. Three neonate groups were studied. Room Air Control (RA control), hypoxia Ischemia (HI) + saline injection and (HI) + azithromycin injection. Two doses of Azithromycin were injected IP at a dose of 20mg/kg at P5 (2 hours after HI insult) and at P6. At defined time points following HI, brain inflammatory cytokine markers , immunostaining for various neuronal markers, such as (neurons: NeuN; astrocytes: GFAP; for microglia: Iba1,CD68,arginase 1; oligodendrocyte: CNPase; apoptosis:caspase 3) and western blots for phospho stress kinases such as pAKT, pp38, pSAPK, pERK, pCREB and pP65 were performed. MicroRNA profile panel was studied using a custom designed microarray plate.

Results: Azithromycin treated pups showed minimal paresis and co-ordination deficits as compared to saline treated HI group, which had severe insult. Histopathology showed ventriculomegally, neuronal necrosis and apoptosis in saline treated HI group which was ameliorated in azithromycin treated HI group. There was a significant decrease in IL 12p70, IL6, KC GRO in the azithromycin treated HI vs. saline treated HI. Quantitative immunostaining showed significantly less injury in HI azithromycin treated (more NeuN, olig 2, CNPase and less expression of GFAP, caspase 3) associated with a shift towards an M2 microglial phenotype (increased arginase 1 and decreased in CD68), vs. the saline treated group. There was

a significant decrease in pAKT, pP38, pSAPK, pERK, pCREB and pP65 in the HI azithromycin treated vs. saline treated pup brains. MicroRNA, analysis showed a unique and innovative role of azithromycin in attenuating specific microRNA expression among HI treated group.

Conclusion(s): Azithromycin treatment showed significant reduction in PVL. It shifts microglial inflammation towards an M2 phenotype. Overall it significantly reduces the inflammatory milieu by decreasing pro-inflammatory cytokine release and NF-KB activity and has an innovative role by ameliorating specific microRNA expression which was previously were linked to brain hypoxia and neuro-inflammation.



Disclosures: **K.R. Ayasolla:** None. **N. Zaghloul:** None. **M. Ahmed:** None.

Poster

745. Brain Injury, Ischemia, and Epilepsy

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 745.12/E9

Topic: C.10. Brain Injury and Trauma

Support: NRF-2018R1A4A1020922
NRF-2017M3C7A1028937
NRF-2017R1D1A1A09081190

NRF-2016M3C7A1913844

Title: Effects of cerebrolysin on hippocampal neuronal death and neurogenesis after pilocarpine-induced seizure

Authors: *D. KANG[1], B. CHOI[1], A. KHO[1], S. LEE[1], J. JEONG[1], D. HONG[1], B. KANG[1], M. PARK[1], H. CHOI[2], H. SONG[2], S. SUH[1];
[1]Hallym Univ., ChunCheon, Korea, Republic of; [2]Neurology, Hallym Univ., ChunCheon, Korea, Republic of

Abstract: Epileptic seizure occurs due to the presence of excessive, uncontrolled neuronal activity in the brain. If severe seizure continues, it leads to oxidative stress, zinc release, neuronal death, and cognitive impairment in the brain. Cerebrolysin is a porcine brain peptide that is a unique neurotropic and neuroprotective agent that not only exhibits neurotrophic factor action like to Nerve Growth Factor (NGF) but also can pass the Blood Brain Barrier (BBB), unlike NGF. Cerebrolysin has been reported to increase neuroprotective effects and neurogenesis in head trauma, ischemia, and other CNS diseases. However, the effect of cerebrolysin on seizure was not known. Therefore, this study purposes to investigate the effect of cerebrolysin on neuronal death and neurogenesis in the hippocampus after seizure. To confirm the effect of cerebrolysin, we used a pilocarpine-induced seizure animal model. Lithium chloride (127mg/kg) is injected intraperitoneally 19 hours before pilocarpine injection, scopolamine (2mg/kg) is injected intraperitoneally 30 minutes before pilocarpine injection. After 30 minutes, pilocarpine (25mg/kg) is injected intraperitoneally, seizure was induced for 2 hours. After 2 hours from the seizure induction time point, diazepam (25mg/kg) was injected to finish the induction of the seizure and then cerebrolysin (2.5ml/kg, i.p, once per day for 7 days) was immediately injected. After 1 week, we perfused seizure-induced animals by 0.9% saline and 4% paraformaldehyde and harvest brains. We performed Neuronal Nuclei (NeuN) staining to evaluate any protective effects of cerebrolysin on seizure-induced neuronal death in the hippocampus. Also, we performed bromodeoxyuridine (BrdU) staining to monitor neurogenesis. Here we found that cerebrolysin decreased hippocampal neuronal death. Cell proliferation, which confirmed active neurogenesis, was increased compared to the vehicle treated group after seizure. Therefore, the present study suggests that administration of cerebrolysin can be useful as a therapy to prevent neuronal death and restore cellular function after seizure. Keywords: Epileptic Seizure, Pilocarpine, Cerebrolysin, Neuronal death, Neurogenesis

Disclosures: **D. Kang:** None. **B. Choi:** None. **A. Kho:** None. **S. Lee:** None. **J. Jeong:** None. **D. Hong:** None. **B. Kang:** None. **M. Park:** None. **H. Choi:** None. **H. Song:** None. **S. Suh:** None.

Poster

745. Brain Injury, Ischemia, and Epilepsy

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Topic: C.10. Brain Injury and Trauma

Support: NRF-2018R1A4A1020922
NRF-2017M3C7A1028937
NRF-2017R1D1A1A09081190
NRF-2016M3C7A1913844

Title: Therapeutic effects of carvacrol in hippocampal neuronal death after pilocarpine-induced seizure

Authors: *J. JEONG[1], B. CHOI[1], A. KHO[1], S. LEE[1], D. HONG[1], D. KANG[1], B. KANG[1], M. PARK[1], H. CHOI[2], H. SONG[2], S. SUH[1];
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Abstract: Temporal lobe epilepsy (TLE) is one of the most devastating and common neurological illnesses experienced by young people across the world and is one of the principal causes of cognitive impairment. The underlying cause of epilepsy has not yet been elucidated, but many symptoms arise after brain injury such as stroke and head trauma. Neuronal death after seizure occurs has already been well described. When the brain is injured, free zinc is released from stores in the extracellular membrane into the intracellular space and accumulates. When zinc enters into the intracellular space, zinc is separated from zinc-binding proteins and accumulates as the free zinc form. Our lab has demonstrated that neuronal death after seizure is initiated by excessive accumulation of zinc. Transient receptor potential melastatin 7 (TRPM7) channel is known to be an ion channel to promote calcium entry into the cell. It is also known as a channel that specifically participates in the transport of zinc. Carvacrol is an essential oil extracted from *Origanum vulgare*, which acts as a TRPM7 channel inhibitor. It has been reported that there is a protective effect on neuronal death after brain injury such as ischemia or traumatic brain injury. So, we hypothesized that carvacrol, which inhibits the TRPM7 channel, may have neuroprotective effects by reducing excessive accumulation of vesicular free zinc after seizure. TLE was induced by lithium-pilocarpine in male rats. We injected lithium chloride (125mg/kg, i.p.) 19 hour before administration of pilocarpine. And we injected scopolamine (2mg/kg, i.p.) 30 minutes before pilocarpine. We injected pilocarpine (25mg/kg, i.p.) and performed behavioral testing based on the Racine stage. We injected carvacrol (50mg/kg/day, i.p.) for 3 days after seizure. To confirm the histological evaluation, we proceeded with immunohistochemistry staining. To detect degenerating neurons, oxidative injury, microglia activation and TRPM7

channel activation, we performed Fluoro-Jade B, 4HNE, Iba1, and TPRM7 staining, respectively. We also performed TSQ staining to determine the level of vesicular free zinc. As a result, degenerating neurons, oxidative injury, microglia activation, TRPM7 channel activation, and vesicular free zinc levels were reduced in the carvacrol group after seizure. Therefore, we suggest that carvacrol has neuroprotective effects by inhibiting the TRPM7 channel and thus reduces the abnormally elevated free zinc accumulation after seizure and has potentially therapeutic effects. Keywords: epilepsy; pilocarpine; carvacrol; TRPM7 channel; zinc; neuronal death.

Disclosures: **J. Jeong:** None. **B. Choi:** None. **A. Kho:** None. **S. Lee:** None. **D. Hong:** None. **D. Kang:** None. **B. Kang:** None. **M. Park:** None. **H. Choi:** None. **H. Song:** None. **S. Suh:** None.

Poster

745. Brain Injury, Ischemia, and Epilepsy

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 745.14/E11

Topic: C.10. Brain Injury and Trauma

Support: NRF-2016M3C7A1913844
NRF-2018R1A4A1020922
NRF-2017M3C7A1028937
NRF-2017R1D1A1A09081190

Title: Temporal change of zinc transporters after pilocarpine-induced seizure

Authors: *S. LEE[1], B. CHOI[1], A. KHO[1], J. JEONG[1], D. HONG[1], D. KANG[1], B. KANG[1], M. PARK[1], H. SONG[2], H. CHOI[2], S. SUH[1];
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Abstract: Epileptic seizure is caused by abnormal excitation of the brain and the excessive release of excitatory neurotransmitters. Seizure can destroy neuronal circuits, leading memory loss or cognitive impairment in severe cases. In previous studies, seizure caused oxidative stress, blood-brain barrier disruption, immune cell infiltration and excessive zinc release, leading to neuronal death. Zinc acts in a bidirectional manner. Under normal physiological conditions, zinc (Zn^{2+}) regulates neuronal excitation by blocking the NMDA receptor or other glutamate receptors. However, in pathological conditions such as seizure, zinc homeostasis is disrupted and zinc is excessively released into synaptic craft. This causes the accumulation of zinc in the post synaptic neuron and then acts as to promote excitotoxicity in neurons, leading to neuronal death. Zinc transporters (ZnTs) are a type of membrane transport protein that regulates intracellular and extracellular zinc concentration. ZnT1 is expressed in the plasma membrane of neurons and glia,

which transports zinc from intracellular space to extracellular space. ZnT3 is expressed in the vesicle membrane in neurons, which is necessary for the re-uptake of zinc from the cytosol. After seizure, zinc has profound effects on neuronal death in a short period of time, but it is unclear how it causes cell death. Therefore, it is very important to study on the expression of ZnT1 and ZnT3 and the consequent change in zinc accumulation in the hippocampus after seizure. For the study, we used the pilocarpine-seizure model. Seizure was induced by pilocarpine (25 mg/kg i.p.) injection. Each group was sacrificed at 0 (without diazepam), 6, 12 and 24 hours after seizures induction. To check the expression of ZnT1, ZnT3, and the degree of the neuronal death at each time, we conducted Fluoro-Jade B (FJB) and ZnT1, ZnT3 staining in the hippocampus after seizure. In FJB staining, neuronal death was increased over time and showed the most cell death at 24 hours. In the case of ZnT1 staining, expression was increased up to 12 hours, then to a maximum of 12 hours and decreased significantly from 24 hours. ZnT3 staining also increased as ZnT1 does. These data suggest that the change of zinc transporters (ZnT1 and ZnT3) and zinc level in the presynaptic terminals and hippocampal neurons are related to seizure-induced cell death and it will help to understand how these changes affect oxidative injury, inflammation, blood-brain barrier and neuronal cell death after seizure.
Keywords: Epileptic seizure, zinc accumulation, zinc transporters, neuron death

Disclosures: **S. Lee:** None. **B. Choi:** None. **A. Kho:** None. **J. Jeong:** None. **D. Hong:** None. **D. Kang:** None. **B. Kang:** None. **M. Park:** None. **H. Song:** None. **H. Choi:** None. **S. Suh:** None.

Poster

745. Brain Injury, Ischemia, and Epilepsy

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 745.15/E12

Topic: C.10. Brain Injury and Trauma

Title: Management of AED resistant epilepsy in children

Authors: *O. V. GLOBA[1], L. KUZENKOVA[1], E. SOROKINA[2], V. PINELIS[2], K. SAVOST'YANOV[2];
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Abstract: Childhood epilepsies a heterogeneous group of disorders and syndromes with different anthology, prognosis and treatment. The purpose of study was to recognize the possible reason of failed of AED treatment and to find the way to overcome it.Methods: 96 patients with different forms of epilepsy aged from 3 months to 16 years not the candidate for surgical treatment have been studied. The long duration EEG, high resolution MRI, biochemical, immunoassay, genetic investigations were performed to these childrenResults: In these children different metabolic epilepsies , epilepsies in neurodegeneration diseases, genetical epilepsies were found. Among them- respiratory chain disorders confirmed by mtDNA sequences, glutaric

acuduria type1, propionic acuduria, methylmalonic acuduria,Gaucher type3, glycogenosis type9, ceroud lipofuscinosis tip 2 and type 6, genetic epilepsies with mutation in genes SCN1A, SCN8A, GRIN2A, KCNMA1, SRPX2, duplication 15g11.2g13.3. The evaluation of autoantibodies to NMDA NR2a and AMPA GluR1 revealed the high level even in 4-7 times in children with metabolic epilepsies in compare with others and shows the deterioration in receptors function. In children with metabolic disorders and energy metabolism disorders we use the specific diet, supplements (L-carnitine, vitamins,coenzyme Q10, enzyme replacement or substrate reduction therapy and so on, avoid valproic acid, use phenytoin inpatients with SCN8A mutation . We use hormones as well. These treatments led to reduction in seizures frequency or to seizure remission in some cases with improvement in quality of life of patients.Conclusions: the recognition and diagnostic of underlying etiologies of intractable seizures improve the treatment management in many cases.

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Poster

745. Brain Injury, Ischemia, and Epilepsy

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 745.16/E13

Topic: C.10. Brain Injury and Trauma

Title: EEG transient discharges decomposed using independent component analysis and wavelet transform

Authors: *M. VILLANUEVA, P. GAST;
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Abstract: In scalp-recorded EEG measurement, transient discharges (TDs) are found among clinical populations with identifiable morphology: A sharp wave whose amplitude is 2 -3 times higher than the average background followed by a slow wave which disrupts the EEG from one to several seconds. However, due to the rare and unpredictable nature of these transients, these discharges have been referred to only anecdotally; quantitative investigation has been missing. To overcome this limitation, we conducted a longitudinal study with one participant from whom 19-ch EEG data with TDs located mainly in the left temporal area collected 23 times over 4 years (total 198 min long). The TDs were annotated by two clinical experts. Since these events are rare within a (typically) 10-minute eyes open EEG recording, we annotated each record. We extracted the transients within a 3 second envelope (1.5 before and after the event), then concatenated all the epochs into one data. In analyzing the EEG data, independent component analysis (ICA) was performed on the extended record. Equivalent current dipoles were fitted to each independent component (IC). The ICs from all the recordings were then clustered by their

dipole locations. For each IC clusters, event-related spectral perturbation (ERSP) was computed to perform time-frequency decomposition. The result revealed that the mean occurrence frequency of the TD occurred 2.75 counts per minute (SD 1.54, Range 0.80-6.19). Interestingly, the distribution of the occurrence frequency is skewed to the right as median value being 2.20, indicating that there were more times TDs were infrequent than the mean value. In fact, though based on preliminary observation due to (still) the limited number of data sets, the TD occurrence frequency distribution showed two peaks, one around 1.6 and the other around 3.2. These data suggest that the occurrence frequency of TD is non-normally distributed, indicating presence of a mode whose principle require further investigation. EEG analysis revealed that TD's time-frequency characteristics to be increased power of 12-15 Hz followed by an increase in power in the 4-8 Hz range, confirming the sharp / followed by slow wave morphology. Furthermore, a regression analysis across time points revealed that the effect of 70 neurofeedback training sessions over 4 years turned out to be non-significant. In conclusion, we provided for the first time the distribution characteristics of TD from the longitudinally collected data, and we have underpinned its ICA-decomposed time-frequency characteristics. The EEG result will be useful for building a classifier to detect rare TDs in automatized solutions.

Disclosures: M. Villanueva: None. **P. Gast:** None.

Poster

745. Brain Injury, Ischemia, and Epilepsy

Location: Hall A

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Topic: C.10. Brain Injury and Trauma

Support: This study was funded by the Children's Foundation Research Institute & The Shainberg Neuroscience Fund, Memphis, TN.

Title: Identifying seizure onset zone (SOZ) in electrocorticographic (ECoG) recordings using a dynamical connectivity analysis

Authors: M. NAHVI[1], G. ARDESHIR[1], M. EZOJI[1], J. W. WHELESS[2], ***A. BABAJANI-FEREMI**[2];
[1]Babol Noshirvani Univ. of Technol., Babol, Iran, Islamic Republic of; [2]The Univ. of Tennessee Hlth. Sci. Ctr., Memphis, TN

Abstract: INTRODUCTION: Connectivity analysis can be used to identify the seizure onset zone (SOZ) in electrocorticographic (ECoG) recordings from patients undergoing epilepsy surgery. In previous studies, the dynamic of the connectivity was not considered and the average connectivity over specific time intervals was used to distinguish SOZ and non-SOZ electrodes. We proposed a dynamical connectivity analysis and investigated whether this analysis can

accurately discriminate between the SOZ and non-SOZ electrodes. **METHODS:** We retrospectively analyzed 19 seizures in six patients (4 males; aged 19-40 years), who underwent a Phase II epilepsy surgery evaluation with subdural electrodes. All patients were seizure-free after a minimum 6-month follow-up. Resections were tailored individually based on visual inspection of the ECoG ictal onset in all patients. After preprocessing of ECoG data, dynamical connectivity between subdural electrodes was calculated using Granger causality in a moving window of 10 s with 9 s overlap. We selected two groups of electrodes for our analysis: 1) visually detected electrodes (VDE) as SOZ by epileptologists; and 2) non-resected electrodes (NRE) in seizure-free patients after surgery, presumably electrodes outside of the SOZ. Then we calculated the mean of the intra- and inter-group connectivity for VDE and NRE electrodes. We used a bootstrap resampling approach for the statistical test in this study. **RESULTS:** We found a time interval in all seizures of all patients that the intra-group connectivity of VDEs (VDE→VDE) was significantly larger ($P < 0.05$) than that intra-group NREs (NRE→NRE) or inter-groups (NRE→VDE) connectivity. We also observed that the increase of the VDE→VDE connectivity may occur a short time before or after the seizure onset time (SOT) identified by epileptologists. Since visual identification of the SOT by an epileptologist depends on his/her own personal experience and judgment, this SOT may not be accurate and have a few seconds offset compared to the real seizure onset. **CONCLUSIONS:** Our results show that the dynamical connectivity analysis based on the Granger causality may be able to identify electrodes within the SOZ, and this approach may be used as a complement to the conventional approach of visually identifying the SOZ.

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Poster

745. Brain Injury, Ischemia, and Epilepsy

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 745.18/E15

Topic: C.10. Brain Injury and Trauma

Support: NINDS U54 NS100064 (EpiBioS4Rx)

Title: The pharmacokinetics and brain distribution of potential anti-epileptogenic therapies in a rat model of post-traumatic epilepsy

Authors: *L. COLES[1], P. G. SALETTI[2], C. LISGARAS[2], P. M. CASILLAS-ESPINOSA[3], N. C. JONES[4], S. R. SHULTZ[4], I. ALI[4], C. GOMEZ[5], B. RUNDLE[5], G. SMITH[5], T. P. SNUTCH[7], J. CLOYD[1], R. STABA[6], T. J. O'BRIEN[8], S. L. MOSHE[9], A. S. GALANOPOULOU[10]; [1]Univ. of Minnesota Twin Cities, Minneapolis, MN; [2]Saul R. Korey Dept. of Neurology, Lab. of Developmental Epilepsy, Albert Einstein Col. of Med., Bronx, NY; [3]Med., The Univ. of

Melbourne, Parkville, Australia; [4]Dept. of Neurosci., Monash Univ., Melbourne, Australia; [6]Neurol., [5]David Geffen Sch. of Med. at UCLA, Los Angeles, CA; [7]Michael Smith Lab, UBC, Vancouver, BC, Canada; [8]Dept. of Medicine, RMH, Parkville, Australia; [10]Dept Neurol, [9]Albert Einstein Col. Med., Bronx, NY

Abstract: Background: EpiBioS4Rx aims to identify new therapies to prevent post-traumatic epilepsy (PTE) following traumatic brain injury (TBI). The EpiBioS4Rx project 2 has created a multicenter preclinical therapy screening platform which includes pharmacokinetic (PK) and pharmacodynamic (PD) studies early in the preclinical screening process to determine brain penetration and optimize treatment delivery. As part of these studies, the PK and brain uptake are characterized in naïve animals and in a lateral fluid percussion injury (LFPI) rat model of TBI. **Objective**: To characterize and compare the PK and brain uptake of kineret (IL-1ra, interleukin receptor antagonist), deferiprone (iron chelator), and Z944 (T-calcium channel blocker). These drugs encompass a range of physiochemical properties (for example, molecular weight, lipophilicity) and mechanisms of action. **Methods:** Male 11- week old Sprague Dawley rats were used as either naïve controls or following LFPI induction at the left parietal region, using a 5mm craniotomy and injury parameters optimized to induce severe TBI with a mortality of ~30%. Rats received either a bolus injection (intraperitoneal or subcutaneous), which in LFPI rats was given immediately after injury. Blood was collected from the lateral tail vein at specified timepoints bracketing 0 and 24 hours after the bolus. Parietal cortical samples were collected at similar timepoints. Deferiprone, and Z944 concentrations in plasma and brain were measured using validated HPLC-MS/MS methods. Human IL-1ra was measured using an enzyme-linked immunosorbent assay. Non-compartmental analysis and compartmental PK modeling was completed. **Results:** All drugs exhibited relatively rapid absorption with maximum drug concentrations achieved at 0.5hr for deferiprone and Z944 and 1 hr for kineret. Elimination half-lives ranged from 1-5 hrs with kineret exhibiting the slowest elimination. Z944 exhibited good brain uptake with brain-to-plasma ratios of ~0.8. Kineret has very poor brain penetration with brain-to-plasma ratios <0.001. While drug exposures were similar in the naïve and injured animals, the drug concentrations in the left (injured) cortex were greater than right in LFPI rats. **Conclusions:** The diverse physiochemical properties of the drugs screened resulted in a range of absorption, elimination, and brain penetrations. Obtaining PK information early in the screening allows us to better identify optimal compounds and assist with formulation development and dosing protocols. We can also develop PK/PD models to simulate the effect of drugs on efficacy and safety measurements, guiding optimal treatment protocols in EpiBioS4Rx.

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Poster

745. Brain Injury, Ischemia, and Epilepsy

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 745.19/E16

Topic: C.10. Brain Injury and Trauma

Title: Regulation of behavior sensitization to cocaine administration in NAMPT heterozygous mice

Authors: Q. JIANG, M. NSUMU, L.-Q. ZHANG, ***X.-P. CHU**;
Univ. of Missouri Kansas City, Kansas City, MO

Abstract: Nicotinamide phosphoribosyltransferase (NAMPT), a rate-limiting enzyme in nicotinamide adenine dinucleotide (NAD) biosynthesis in mammals, converts nicotinamide into nicotinamide mononucleotide. NAMPT reveals a critical role in NAD biology, metabolism, aging, inflammation, obesity, liver injury, diabetes, stroke, cancer, and addiction. In this study, we explore the putative role of NAMPT in the regulation of behavioral sensitivity to the psychostimulant cocaine by utilizing NAMPT heterozygous (+/-) mice. Acute cocaine injection at a dose of 20 mg/kg induced an increase in locomotor activities in wild-type (WT) mice. However, cocaine induced a significantly enhanced motor response at this dosage in NAMPT (+/-) mice. In a chronic cocaine administration model (20 mg/kg, once daily for 5 days), a challenge injection of cocaine (20 mg/kg, after 2-week withdrawal) caused a profound behavioral sensitization in the cocaine-pretreated WT mice. This behavioral sensitization to challenge cocaine was also displayed and increased in NAMPT (+/-) mice. Our results demonstrate the important role of NAMPT in the modulation of behavioral sensitization to cocaine. Targeting NAMPT gene might be a therapeutic strategy against cocaine addiction.

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Poster

745. Brain Injury, Ischemia, and Epilepsy

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 745.20/E17

Topic: C.10. Brain Injury and Trauma

Title: Effects of Sox11 on optic nerve regeneration and retinal ganglion cell survival

Authors: *M. NAHMOU[1], K.-C. CHANG[1], M. BIAN[1], A. MADAAN[1], X. XIA[1], Q. WANG[1], L. LIU[1], C. SUN[1], C. KNASEL[1], J. GALVAO[1], B. TANASA[1], Y. HU[3], J. L. GOLDBERG[2]; [1]Ophthalmology, [2]Byers Eye Institute--Ophthalmology, Stanford Univ., Palo Alto, CA; [3]Dept. of Ophthalmology, Stanford Univ. Sch. of Med., Palo Alto, CA

Abstract: Purpose: What are the molecular mechanisms regulating retinal ganglion cell (RGC) survival and optic nerve (ON) regeneration? Failure of RGCs to survive and regenerate after injury or in disease is a leading cause of irreversible blindness worldwide. Previously, transcription factor Sox11 was described to promote regeneration but lead to cell death of a subset of RGCs. In parallel we found that Sox11 desumoylation promotes its nuclear import and efficacy in promoting RGC differentiation from retinal progenitor cells. Here, we study the effects of Sox11 and a non-sumoylatable mutant $Sox11^{K91A}$ on RGC survival and axon growth in vitro and after optic nerve trauma in vivo. **Methods:** We examined the effect of Sox11 and $Sox11^{K91A}$ *in vitro* in primary RGCs isolated from postnatal day 2 mice and transduced with AAV2 viral vectors, examining neurite outgrowth through tracing of axons (n=40-80 cells per group and three independent experiments) and gene expression through bulk RNA sequencing (N=2). To compare the effect of Sox11 and $Sox11^{K91A}$ *in vivo*, we intravitreally injected AAV2-Sox11 and -$Sox11^{K91A}$ into adult mice two weeks before ON crush. Cholera Toxin Subunit B conjugated with Alexa-555 was injected intravitreally at day 12, 2 days before euthanasia, to label regenerating axons. ON regeneration and RGC survival were assayed by measuring CTB-labeled axons in cryosectioned optic nerves and counting RBPMS+ cells in flat-mounted retinas (N=6-8 per group). Data were analyzed by ANOVA with Tukey's test with *P* value of <0.05 considered statistically significant. This research was conducted in compliance with the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research. **Results:** *In vitro*, both Sox11 and $Sox11^{K91A}$ attenuated neurite outgrowth and survival to a comparable extent, compared to AAV-treated controls. *In vivo*, both Sox11 and $Sox11^{K91A}$ enhanced ON regeneration and attenuate cell survival, with a stronger effect on both observed with $Sox11^{K91A}$. RNA sequencing data identified 28 and 11 genes differentially down- and upregulated between Sox11 and $Sox11^{K91A}$-treated RGCs, respectively. **Conclusion:** These data confirm that Sox11 is involved in RGC axon growth and survival. *In vivo*, blocking sumoylation of K91 residue enhances effects of the wild type protein. Further analysis of the downstream-affected genes may reveal how Sox11 oppositely regulates RGC survival and growth, as opposed to more classical "pro-growth/pro-survival" signaling pathways.

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Poster

745. Brain Injury, Ischemia, and Epilepsy

Location: Hall A

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Program #/Poster #: 745.21/E18

Topic: C.10. Brain Injury and Trauma

Support: New York/New Jersey Education Research Center Grant 0253-6526

Title: Respirator use protects against welding-associated changes in white matter microstructure

Authors: *E. RECHTMAN[1], P. CURTIN[1], L. ONYEBEKE[1], D. PAPAZAHARIAS[1], D. HAZELTINE[1], E. DE WATER[1], M. VENKATESH[1], R. LUCCHINI[1], D. GAUGHAN[1], C. TANG[2], M. HORTON[1];
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Abstract: Welding has been associated with structural and functional brain changes and increased rates of neurobehavioral problems. Respirator use has been shown to protect against respiratory morbidity among welders. Little is known regarding the efficacy of respirators to protect welders from the neurotoxicity of welding fumes. In this preliminary study, we used diffusion tensor imaging (DTI) to investigate the association between welding and white matter (WM) abnormalities and determine the effectiveness of respirator use for protecting workers WM microstructure. We hypothesized that associations between fractional anisotropy (FA) and welding fume exposure would be detected as weak contributions from multiple brain regions, and that the use of a respirator would mitigate these effects.
We enrolled 19 welders from labor unions in the New York City area. All welders completed questionnaires to assess occupational and health histories. All subjects completed a DTI acquisition on a 3T Siemens scanner. DTI data was preprocessed using FSL pipeline and a three-tiered analytical strategy was applied: (1) voxel-wise whole brain group comparisons of FA values between respirator users and non-users across the whole WM skeleton, (2) multiple linear models to test for associations between mean FA in 48 regions defined by the ICBM-DTI-81 atlas and respirator usage, and (3) partial least squares discriminant analysis (PLS-DA) to model the divergence of WM microstructures in respirator users compared to non-users. All three approaches showed associations between respirator usage and WM microstructure in numerous regions of the brain with consistency across approaches. Welders who reported not using a respirator showed decreased FA primarily in the superior longitudinal fasciculus, the uncinate fasciculus and the superior cerebellar peduncle compared to workers who used a respirator. To our knowledge, this study is the first to explore the association between respirator usage and WM microstructure. Our findings indicate that multiple WM microstructure tracts are associated with exposure to welding fume. These tracts are part of the neural network enabling both motor and

neurocognitive processes which may explain the heterogeneity of symptoms reported in welders. These findings have implications for occupational safety regulations and policies.

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Poster

745. Brain Injury, Ischemia, and Epilepsy

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Topic: C.10. Brain Injury and Trauma

Support: CONICYT Becas Chile Doctoral Fellowship programme 72160294
SPARKS grant 17UCL01.

Title: AAV gene therapy approach for the treatment of Dravet syndrome

Authors: *J. F. ANTINAO DIAZ[1], J. R. COUNSELL[2], S. SCHORGE[3], M. BERTI[1], J. DAVIDGE[4], S. N. WADDINGTON[1], R. KARDA[1];
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Abstract: Background: Dravet Syndrome (DS) is a genetic childhood epilepsy. Over 80% of the cases are caused by a mutation in the *SCN1A* gene; leading to happloinsufiency of the ion channel $Na_V1.1$. DS has an incidence rate of 1:20,000 to 40,000 live births and patients suffer from fever-sensitive, refractory and generalized seizures and cognitive impairment, which begin at around six months of age. Patients can fall into status epilepticus, which can result in premature death. This disease remains untreatable by either medical or surgical means. Using adeno-associated vectors (AAV) to treat DS presents several challenges: difficulties in propagating wild-type *SCN1A* plasmids in competent cells restrict DNA production and the large transgene (6 Kb) limits incorporation into AAV vectors. Methods: We have designed a bipartite AAV system, in which *SCN1A* is split into two complementary halves between domains 2 and 3, one of which has been codon-optimized. Each construct is driven by a human synapsin promoter. Additionally, we incorporated red and green fluorescent proteins (RFP & GFP) to the first and second halves, respectively. A control carrying only GFP was also produced. A mouse model of DS is used for *in vivo* validation. Results: We confirmed expression of channel protein by western blot in cells co-transfected with both plasmid constructs. AAV8-GFP control vector was delivered via neonatal bilateral intracerebroventricular injection into WT mice, showing widespread brain expression. Knockout Dravet mice received either both treatment vectors

(without fluorescent proteins; n=7) or control AAV8-GFP (n=3) via intracerebroventricular injection in a randomised, blinded study; no difference in survival was found. Follow on electrophysiology suggest functional channels may not be produced.Conclusion: This is the first use of a dual AAV system to restore Nav1.1 expression, as detected by western blot. Optimisation of injection and of the constructs may be carried out to improve expression.

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Poster

745. Brain Injury, Ischemia, and Epilepsy

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Topic: C.10. Brain Injury and Trauma

Support: NIH Grant 4R00NS097620
Cedars-Sinai

Title: Large-scale modulation of motor cortical activity using epidural cerebellar stimulation

Authors: *T. GULATI, P. LAM, J. LEUNG;
Biomed. Sciences, Neurol., Cedars Sinai Med. Ctr., Los Angeles, CA

Abstract: Several neuromodulatory startegies have shown promise in post-stroke motor recovery. These include non-invasive approaches such as repetitive transcranial magnetic stimulation (rTMS), direct current stimulation (tDCS), as well as implantable approaches such as vagal nerve stimulation (VNS), and epidural cortical stimulation (ECS). These studies indicate that- infarct location, integrity of corticospinal tracts, as well as extent of cortical excitability achieved – all are important factors in responsivity to stimulation. Recent work by Andre Machado and colleagues has shown that deep brain stimulation (DBS) of dentato-thalamocortical (DTC) pathway augments post-stroke motor rehabilitation. This pathway originating from deep cerebellar nucleus has a dense projection to several cortical and subcortical areas, and has a capacity to induce widespread cortical modulation. Furthermore, in an ischemic cortical stroke, there is decreased afferent cerebellar input from cortex due to disruption in cerebropontocerebellar tract. This in turn leads to weakened excitatory output to cortex from the cerebellum via the DTN pathway, and makes it particularly attractive for augmentation through neuromodulation. Apart from DBS, even epidural cerebellar stimulation has been shown to modulate cortical excitability as measured through motor evoked potentials (MEPs). While these studies have provided important insight into capacity of cerebellar stimulation to modulate cortical dynamics, it remains incompletely understood as to how cerebellar stimulation affects the ongoing neural activity in the motor cortex.

We have conducted acute experiments in anesthetized rodents to assess how epidural cerebellar stimulation can affect large-scale neural activity in primary motor cortex. We find that 30 minutes of 100 - 150 μA DC stimulation can increase spontaneous firing rates ('positive' modulation) in ~33% of recorded cells while ~12% cells reduced their firing rates ('negative' modulation). These changes were long-lasting (i.e. greater than the typical observation period of 1-2 hours). Our work shows that DC stimulation over cerebellum can result in both long-lasting increases and decreases in neural firing rates. We hope that a better understanding of these phenomena can help optimize neuromodulation to enhance recovery after brain injuries – such as stroke.

Disclosures: T. Gulati: None. **P. Lam:** None. **J. Leung:** None.

Poster

745. Brain Injury, Ischemia, and Epilepsy

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 745.24/E21

Topic: C.10. Brain Injury and Trauma

Support: R01-NS094200
R01-NS096037
R21-HD094085
Trustee grant from Cincinnati Children's Hospital Medical Center

Title: Early inflammation serves as a common pathway to the development of diffuse white matter abnormality (DWMA) in very preterm infants

Authors: *N. A. PARIKH[1], **J. KLINE**[1], L. HE[1], H. LI[1], P. V. S. ILLAPANI[1], M. A. KLEBANOFF[2];
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Abstract: Background: More than 50% of very preterm (VPT) infants exhibit DWMA (aka diffuse excessive high signal intensity) on T2w MRI at term-equivalent age. We previously identified severe retinopathy of prematurity (ROP) and surgery for necrotizing enterocolitis/spontaneous intestinal perforation as risk factors for DWMA in a single-center study.
Objective: Examine antecedent clinical factors of DWMA in a cohort of VPT infants. We hypothesize that inflammation-initiating illnesses are independent risk factors of DWMA development.
Methods: We prospectively enrolled 110 VPT infants (<32 weeks gestational age) from 4 Columbus, Ohio regional NICUs. Infants were imaged on a 3T Siemens Skyra scanner with a high-resolution (1 mm^3) structural MRI protocol at term. We objectively segmented DWMA

regions using our previously-published automated algorithm. We excluded infants with severe brain injury (N=11) or significant motion artifacts (N=1). Clinical variables with $p<0.10$ in bivariable analyses were entered into multivariable linear regression models to evaluate their association with DWMA volume by ordering them temporally (i.e., antenatal first, intrapartum next, postnatal last) and not displacing significant associations ($p<0.05$) by later occurring antecedents.

Results: Several inflammation initiating-illnesses were significantly different between infants with (>75th percentile) and without severe DWMA, including severe ROP, severe bronchopulmonary dysplasia, sepsis, and need for major surgery. In multivariable analyses, severe ROP ($P<0.001$) and severe bronchopulmonary dysplasia ($P=0.006$) remained independent risk factors, while 17-OH progesterone ($P<0.001$) therapy was protective of later DWMA development (Table 1).

Conclusion: We identified several antenatal and neonatal clinical factors that implicate inflammation as a common pathway to DWMA development. These findings enhance our understanding of DWMA pathogenesis and suggest inflammation-associated DWMA as an intermediate biomarker for targeted neuroprotective interventions in high-risk VPT infants.

Table 1. Multivariable linear regression model coefficients of clinical antecedents associated with DWMA volume, objectively-defined on structural MRI at term.

Clinical Antecedent	**Coefficient (95% CI)**	**P**
Maternal 17-OH Progesterone therapy	0.27 (0.14, 0.52)	<0.001
Severe retinopathy of prematurity	7.04 (2.42, 20.49)	<0.001
Severe bronchopulmonary dysplasia	2.73 (1.35, 5.52)	0.006
Gestational age at birth	1.11 (0.97, 1.26)	0.126

Disclosures: **N.A. Parikh:** None. **J. Kline:** None. **L. He:** None. **H. Li:** None. **P.V.S. Illapani:** None. **M.A. Klebanoff:** None.

Poster

745. Brain Injury, Ischemia, and Epilepsy

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 745.25/E22

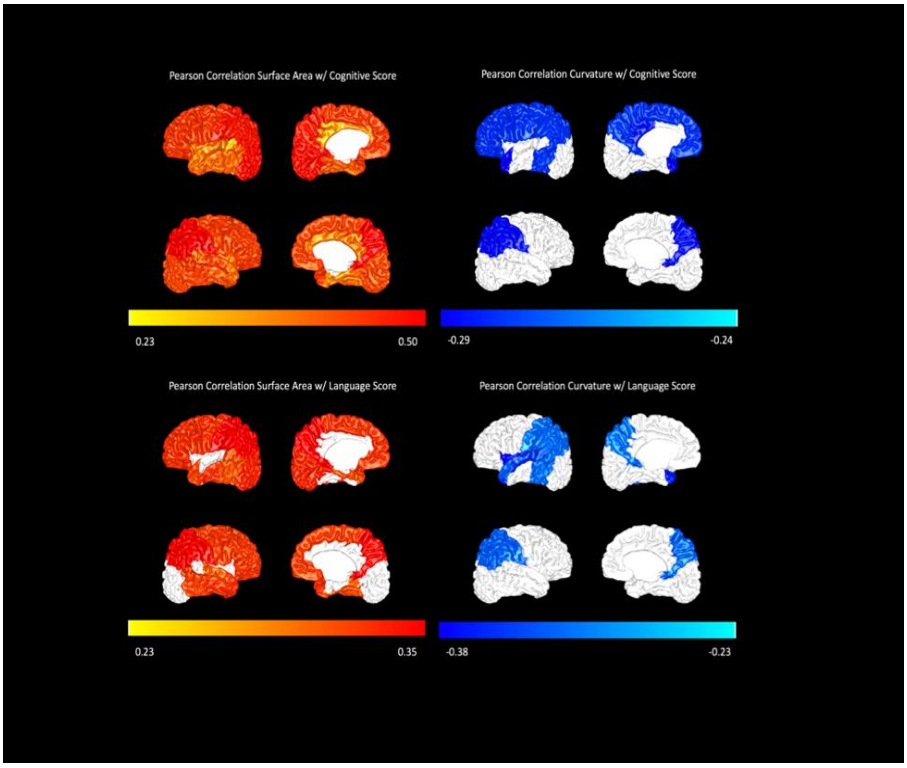
Topic: C.10. Brain Injury and Trauma

Support: NIH R01-NS094200
NIH R01-NS096037
NIH R21-HD094085

Title: Cortical maturational features are altered in very preterm infants at term equivalent age and predict cognitive and language ability at 2-years corrected age

Authors: *J. KLINE, P. V. S. ILLAPANI, L. HE, M. ALTAYE, N. PARIKH;
Cincinnati Children's Hosp., Cincinnati, OH

Abstract: Background: Very preterm infants (VPT;<32 weeks gestational age) are at high risk for neurodevelopmental impairments, including cognitive and language delays. However, there are few validated biomarkers of these impairments at term-equivalent age. Cortical features, including surface area and inner cortical curvature, are altered by preterm birth. These changes may be early developmental biomarkers, but their prognostic ability has not been evaluated.
Objectives: 1) To quantify differences in cortical features on term-equivalent age MRI between a VPT and a full-term cohort. 2) To evaluate the ability of cortical features in the VPT cohort to predict Bayley-III cognitive and language scores at 2-years corrected age.
Methods: We enrolled 110 VPT and 51 full-term infants from 4 level-III NICUs. Structural MRI was performed at term, and Bayley-III language and cognitive testing was performed at 2-years corrected age in the VPT cohort. We quantified group differences in cortical features at term. In the VPT group, we examined the correlation of cortical surface area and curvature with Bayley scores and created multivariable regression models that predicted these scores.
Results: The VPT group had significantly decreased cortical surface area and increased white matter curvature. Their Bayley scores were positively correlated with surface area and negatively correlated with curvature. In multivariable regression, cortical features explained more than one-third of the variance in Bayley scores.
Conclusions: Increased cortical curvature is a new prognostic biomarker that, when combined with cortical surface area, can predict cognitive and language development in VPT infants. Early prediction of domain-specific impairments could facilitate intervention when neuroplasticity is maximal.
Figure 1. Pearson correlation of Bayley cognitive score (top row) and Bayley language score (bottom row) with surface area (left column) and curvature (right column) in the VPT cohort. Correlation strength is shown on a representative subject brain for regions significant at $p < 0.05$.



Disclosures: **J. Kline:** None. **N. Parikh:** None. **L. He:** None. **P.V.S. Illapani:** None. **M. Altaye:** None.

Poster

745. Brain Injury, Ischemia, and Epilepsy

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 745.26/E23

Topic: C.10. Brain Injury and Trauma

Support: Cerebral Palsy Alliance Research Foundation
Johns Hopkins Neurosurgery Pain Research Institute
Kennedy Krieger/Johns Hopkins Intellectual and Developmental Disabilities Research Center

Title: Pain and sensory features in adults with cerebral palsy

Authors: *E. M. CHIN[1], C. LENZ[2], J. JOHNSON[1], X. YE[2], E. STASHINKO[1], C. CAMPBELL[3], A. HOON[1], S. ROBINSON[2];
[1]Kennedy Krieger Inst., Baltimore, MD; [2]Neurosurg., [3]Psychiatry and Behavioral Sci., Johns Hopkins Univ., Baltimore, MD

Abstract: *OBJECTIVE:* Chronic pain and sensory dysfunction are each known to be prevalent in adults with cerebral palsy (CP). However, cortical and primary sensory sensitivity have not been compared, and pain mechanisms in this population are not clear. The aim of this prospective observational study is to define phenotypes of pain and sensory abnormalities in individuals with CP.
METHODS: Early exploratory analysis includes 11 adult subjects with cerebral palsy (Gross Motor Functional Classification Status (GMFCS) I-V) able to self-report and 8 adult volunteers without neurologic or developmental diagnoses. Subjects reported pain interference, intensity, and quality using PROMIS short forms and the PainDETECT neuropathic screening questionnaire. A structured physical examination included quantitative measures of mechanical sensory detection (Von Frey monofilaments) and cortical somatosensory discrimination (JVP dome threshold), qualitative evaluation of pinprick and thermal sensitivity, and an attention screen (digits forward/reversed). Between-group comparisons used a ranksum test, and univariate variance analyses tested F-statistics of linear regressions against a constant model.
RESULTS: Individuals with CP reported significantly ($p<0.05$) greater pain intensity, pain interference, neuropathic qualities, and nociceptive qualities than typical controls. Median between-group difference in pain interference ($\Delta T=8.6$) was approximately two times the previously-published minimally important difference. Individuals with CP had less mechanical (n.s.) and cortical sensory ($p<0.05$) sensitivity.
Motor functioning (GMFCS level) was a poor predictor of pain interference, pain intensity, and neuropathic and nociceptive qualities (R^2_{adj} all <0.05; p all >0.10). Preserved attention functioning may be associated with less neuropathic qualities (R^2_{adj} 0.26; $p=0.09$) and less overall pain intensity (R^2_{adj} 0.16, $p>0.1$).
Anecdotally, individuals with positive PainDETECT neuropathic screens (n=2) had qualitative alterations in cool and pinprick sensation. A third individual with cool/pinprick sensory alterations but preserved attention reported minimal neuropathic pain.
CONCLUSIONS: Neuropathic and nociceptive pain as well as cortical sensory deficits appear to be common in individuals with CP. A subset of individuals with CP have phenotypes suggestive of central pain. Identification of pain-relevant sensory features may be detectable with a quick bedside screening exam. Further exploration of the role of cognitive characteristics in pain in CP is needed.

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Poster

745. Brain Injury, Ischemia, and Epilepsy

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 745.27/E24

Topic: C.10. Brain Injury and Trauma

Title: Congenital malformations in newborns and their relationship with toxic factors during the pregnant stage

Authors: *G. CHÁVEZ-MÉNDEZ[1], J. ARIAS-RICO[2], O. A. JARAMILLO-MORALES[2], R. M. GUEVARA-CABRERA[2], R. C. JIMENEZ-SANCHEZ[2], R. M. BALTAZAR_TELLEZ[2]; [1]Univ. Autonoma del Estado de Hidalgo, Pachuca de Soto, Mexico; [2]Univ. Autonoma del Estado de Hidalgo, Pachuca, Mexico

Abstract: Introduction. Congenital malformations are structural abnormalities in development acquired during pregnancy. To this day, the OMS states that some 276,000 newborns die within 4 weeks of light each year because of congenital anomalies. Associated factors include: poor pregnancy control, acute infectious diseases, multiparity, tobacco and medications, which cause high incidence in child morbidity and mortality with serious sequelae. The so-called neural tube defects (NTD), which group a series of anomalies located in the Central Nervous System, have been considered as the most frequent congenital malformations and with the most serious sequelae, they maintain a global incidence of 1 to 10 per each 1000 newborns, The objective of this study is to identify the relationship of toxins in the incidence of congenital malformations in newborns at a second level hospital in Hidalgo, Mexico. Materials and Methods. Observational, analytical study of cases and controls, retrospective, cross-sectional. The population consisted of 22 newborns, of whom 11 newborns were classified as congenital malformations (cases) and 11 healthy newborns (control). The SPSS version 21 program was used to analyze the data, using descriptive statistics to determine simple, absolute and relative frequencies of the malformations and their distribution. For the analysis of cases and controls, the risk for congenital malformations with OR was calculated (Odds Ratio) with a 95% confidence interval, statistical significance was considered when $p < 0.05$. Result and Discussion. It was observed that the children of mothers exposed to toxins have 17 times more risk for congenital malformations than women not exposed, this risk being statistically significant (OR = 17.5, 95% CI, 1.5-19.1, p = 0.01). In Spain they have reported an OR for congenital defects and toxic exposure (OR = 1.84 IC 95%, 1.15-2.96, p = 0.007) although only 13.6% of malformations were presented in the Central Nervous System compared to ML Martínez Frías I report only two cases in Spain (2017). Conclusion. malformations are multifactorial in origin, prevention is mostly feasible, early diagnosis prevents further sequelae, determining the risk factors for screening and early diagnosis is important as part of preventive strategies.

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Poster

745. Brain Injury, Ischemia, and Epilepsy

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 745.28/E25

Topic: C.10. Brain Injury and Trauma

Support: WV New Faculty Startup Support
WV-INGRE grant; P20GM103434
WV-CTSI; 2U54GM104942
NIH 5T32HL007224-42

Title: Impaired PLA2g6 protects against age-induced vascular stiffening and contributes to preservation of compliant vasculature

Authors: H. PAINTER, K. LAHODA, A. HIJAZI, *J. W. SHIM;
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Abstract: Impairment of phospholipase A2 group 6 (PLA2g6)-dependent calcium (Ca^{2+}) entry in vascular smooth muscle cell (SMC) has been found to protect against age-induced arterial stiffening, but the mechanism and the role of vascular compliance in hydrocephalus are not well understood. Here we tested the hypothesis that impaired PLA2g6 gene could be a previously unknown contributor of preserving compliant vasculature in the brain, thereby, protective against cerebrovascular diseases. Aortic stiffness was assessed in vivo using ultrasound and compared to age-, diet-, and gender-matched (male) mice with constitutive knockout (KO: n=5 to 21) and/or SMC-specific deletion of PLA2g6 (n=3 to 4). Ventricular size of these animals was examined using histological serial sectioning (n=3). Gene expressions of PLA2g6, elastin, and specificity protein 1 (Sp1) were compared in the PLA2g6 KO mice as compared to the age- and diet-matched wild type (WT) controls (n=3). Van Gieson elastic fiber staining was conducted to compare elastin present in the arterial vessels (n=3). We found that aging ($p<0.01$), or high fat high sucrose (HFHS) diet ($p<0.005$) significantly increased pulse wave velocity in WT, but not in PLA2g6 KO mice. Van Gieson staining, quantitative reverse transcription polymerase chain reaction and immunoblot analysis of SMC layer of thoracic aorta from the aged animals revealed significant fragmentation of elastin in WT ($p<0.05$), but not in PLA2g6 KO mice at 24 months. Rather, a significant increase of Sp1 transcription factor was detected in the arterial SMC layer of aged PLA2g6 KO mice as compared to that of WT controls ($p<0.05$). Preservation of elastin content and protection against HFHS diet-induced arterial stiffening can be fully recapitulated in a cell-specific KO mouse model in which impairment of PLA2g6/Ca^{2+} signaling was genetically targeted to SMC. Importantly, there is no ventriculomegaly detected in the KO groups of the constitutive and cell-specific KO mouse model, as compared to the control mice (littermates without inducible PLA2g6 KO at 4 months, and WT at 8 months) at young (4-8 months) and old

(24 months) age, respectively. Our results demonstrate that impairment of PLA2g6 gene does not lead to hydrocephalus and prevents these animals from age-induced elastin fragmentation, thereby, preserving compliant arteries.

Disclosures: H. Painter: None. **K. Lahoda:** None. **A. Hijazi:** None. **J.W. Shim:** None.

Poster

745. Brain Injury, Ischemia, and Epilepsy

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 745.29/E26

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: NINDS Grant NS091213
NINDS Grant NS107365
NIH Grant T32NS7453

Title: Neuroprotection after ischemic stroke using a CXCR2 antagonist

Authors: *A. M. BEDOLLA[1], F. LUO[2], A. CASEY[2], K. A. SCHMIDT[2], Y. LUO[2];
[1]Neurosci., [2]Univ. of Cincinnati, Cincinnati, OH

Abstract: Intro: Ischemic stroke causes weakening of the blood brain barrier allowing a peripheral immune response to respond to the stress and damage in the brain. This can result in secondary damages to the ischemic tissue. Our data showed that the KC/GRO (also called CXCL1/CXCR2) pathway are significantly upregulated during pathological brain edema, which might contribute to expansion of ischemic injury. Previous studies have shown that inhibition of the CXCR2 signaling, which is important for the recruitment of peripheral immune cells, prior to or at the onset of stroke supports a better outcome after ischemia. However, this timeline is not suitable for potential clinical translation. The goal of this current study is to examine whether acute post-stroke treatment of KC/GRO pathway inhibitors still have neuroprotective effects in stroke.
Methods: A transient 60-minute medial cerebral artery occlusion (MCAO) was used to induce ischemia; reperfusion was allowed for 72 hours before sacrificing the animals. The drug Repertaxin (a small-molecule inhibitor of CXCR1 and CXCR2) was administered via subcutaneous injection in two doses (15mg/kg), 3 hours and 12 hours post stroke. MRI was used to assess infarct volume and edema severity at 8 hours, 24 hours, and 48 hours post stroke. Behavioral measurements were used to assess functional outcomes. Number of Neutrophils, T-cells, and natural killer cells were quantified in brain tissue using fluorescent immunohistochemistry.
Results: Our results show that post-stroke treatment of Repertaxin resulted in a decreased mortality rate in the treatment group compared with the control MCAo group (n=18, p=0.04). In

addition, there was a decrease in infarct size and edema severity (n=12, p=0.004) in stroke mice treated with Repertaxin compared with the control MCAo group (n= 12, p=0.003). Adhesive removal test alleviated deficits on motor sensory function in Repertaxin treated mice compared to MCAo control group (n=12, p=0.04).
Conclusion: These results suggest that the protective effects of the KC/GRO pathway inhibitor are still attainable even administered 3 hours after stroke and we are currently investigating the precise underlying molecular mechanisms for the observed beneficial effects in stroke animals.

Disclosures: **A.M. Bedolla:** A. Employment/Salary (full or part-time):; University of Cincinnati. **F. Luo:** A. Employment/Salary (full or part-time):; University of Cincinnati. **A. Casey:** A. Employment/Salary (full or part-time):; University of Cincinnati. **K.A. Schmidt:** None. **Y. Luo:** A. Employment/Salary (full or part-time):; University of Cincinnati.

Poster

745. Brain Injury, Ischemia, and Epilepsy

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 745.30/E27

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Title: Cognitive function and brain morphometry in Mexican workers occupationally exposed to solvents

Authors: *D. ATILANO-BARBOSA[1], E. H. PASAYE-ALCARAZ[1], R. E. MERCADILLO-CABALLERO[2];
[1]Univ. Nacional Autónoma de México, Queretaro, Mexico; [2]Univ. Autónoma Metropolitana-Iztapalapa, Mexico City, Mexico

Abstract: Solvents are volatile substances that evaporate when they encounter the ambient temperature, these substances can be hydrocarbons such as degreasers, refrigerants, anesthetics, etc. Like most aromatic hydrocarbons, the lipophilic and water-soluble property of solvents cause damage to organs of the body such as the brain and spinal cord. It has been reported that solvents causes deficits in coordination, balance, reflexes, language, memory, attention and decision making. Damage to the central nervous system could be the reason for cognitive and motor impairment related to occupational exposure to industrial solvents. Studies have shown that volatile solvents have inhibitory effects on glutamatergic receptors. These findings could explain the symptoms of lethargy, sedation, disarticulated speech and ataxic gait due to occupational exposure. Brain imaging studies have reported ventricular enlargements, brain atrophy and lesions in the cerebral white matter in workers exposed occupationally to industrial solvents. Nevertheless, most of neuropsychological and neuroimaging research related to occupational exposure to solvents have been case studies and group comparison studies with lack of quantitative analysis based on standardized neuropsychological assessments, normalization of

brain images and statistical analysis on brain differences. In addition, developing countries, such as Mexico, have a high number of workers with respiratory disorders due to volatile industrial compounds where the use of some of these substances has been banned in other countries due to health risks. In this sense, occupational exposure to solvents has adverse effects in brain morphometry and cognitive function in mexican workers.To test this hypothesis, we analyzed the cognitive performance and brain morphometry of a group of 10 workers with a mean exposure of 5 years to solvents with a paired control group of 10 non-exposed subjects. For brain morphometry analysis, brain structural images where acquired using MR (magnetic resonance) then VBM (voxel-based morphometry) analysis was implemented using FSL software. Neuropsychological assessment with standardized and validated tests in mexican population was implemented for cognitive performance analysis. We find that the exposed group shows significant decrease gray matter volume in cerebellar cortex compared to control group. Deficit in working memory was present in exposed participants compared to controls. These results indicate that occupational exposure to industrial solvents has adverse effects in cerebellar cortex and working memory performance in a sample of mexican workers.

Disclosures: D. Atilano-Barbosa: None. **E.H. Pasaye-Alcaraz:** None. **R.E. Mercadillo-Caballero:** None.

Poster

746. Brain Injury and Trauma III

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 746.01/E28

Topic: C.10. Brain Injury and Trauma

Support: NIDA Drug Supply Program
The Groff Charitable Fund

Title: Repeated closed-head injury in adolescence impacts oxycodone intravenous self-administration in male and female Sprague-Dawley rats

Authors: *A. K. LEONARD, N. J. SANDSTROM, M. M. CLASEN;
Dept. of Psychology, Program in Neurosci., Williams Col., Williamstown, MA

Abstract: Epidemiological evidence shows that opioid use disorder and traumatic brain injury (TBI), each a serious public health concern in its own right, are highly comorbid. Preclinical studies suggest that inflammation and neuronal damage from TBI increase drug preference and drug-seeking behavior, but with just one prior study investigating opioids. Building on human and rodent evidence that repeated TBI in adolescence may be a particularly strong risk factor for later drug use and abuse, the current study investigated how repeated closed-head injury in adolescent Sprague-Dawley rats affected the intravenous self-administration (IVSA) of

oxycodone in adulthood. Eighteen rats (n = 9 male) received 5 consecutive impacts at 24-hr intervals beginning on PND 40, with 12 (n = 6 male) undergoing a sham procedure. This yielded four groups (FI, FS, MI, and MS, where F or M refers to the sex of the animal [female or male] and I or S refers to the type of head injury [impact or sham]). Of this initial group of 30 rats, 21 remained patent and completed all facets of oxycodone IVSA testing (e.g., the acquisition of oxycodone IVSA, dose-response, progressive ratio, forced abstinence and cue/drug + cue - induced reinstatement; n = 5-6 per group). In most stages, increased variability was observed in FI and MI rats without significantly differing from either FS or MS rats. During drug + cue - induced reinstatement testing, FI rats appeared to respond more than both FS and MI rats, however, these differences were not significantly different ($p = 0.06$). After the conclusion of oxycodone IVSA, neuroinflammation and structural damage were assessed with Iba1 and Cresyl Violet staining. Tissue staining revealed severe neurodegeneration (indexed by ventricle size) in both FI and MI rats, with preliminary analysis suggesting a potential correlation between injury severity and intensity of drug-seeking behavior. Although the small number of subjects utilized limits the conclusion of the present work (n = 5-6 per group), this preliminary research suggests that repeated adolescent TBI increases the variability in oxycodone self-administration in male and female adult rats, and that these effects might be more pronounced in females.

Disclosures: **A.K. Leonard:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); NIDA Drug Supply Program, The Groff Charitable Trust. **N.J. Sandstrom:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); The Groff Charitable Trust. **M.M. Clasen:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); NIDA Drug Supply Program, The Groff Charitable Trust.

Poster

746. Brain Injury and Trauma III

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 746.02/E29

Topic: C.10. Brain Injury and Trauma

Support: IBaCs

Title: Repetitive head trauma induces elevated post-concussive aggression in young-adult male *Drosophila*

Authors: *D. C. LEE[1], K. VALI[2], S. R. BALDWIN[2], J. R. FEQUIERE[2], M. A. FERNANDEZ[2], J. C. FRAGEAU[2], F. LONGO[2], S. S. MADHOUN[2], P. MINGIONE, V[2], T. R. O'TOOLE[2], G. R. TANNER[1];
[1]Physiol. and Neurobio., [2]Univ. of Connecticut, Storrs-Mansfield, CT

Abstract: Repeated concussive head trauma—termed traumatic brain injury (TBI)—can induce chronic traumatic encephalopathy (CTE), a neurodegenerative disease with symptoms ranging from memory loss, to general cognitive deficits, to elevated aggression. We adapted a methodology using a high-impact trauma device (Katzenberger et al., 2013; 2015) that induces TBI while reducing mortality, thus permitting post-TBI behavioral analyses. We subjected young-adult male *Drosophila* of the wild-type Canton-S strain to a battery of TBI-inducing high-impact concussive events on day five post-eclosion as adults. Three days after the TBI protocol ("banging"), pairs of male flies were assayed for aggressive behaviors. Aggression in banged flies was significantly elevated, as compared with that in unbanged flies. These increases in aggressive behavior were not the result of basal motility changes, as measured by a negative geotaxis assay. In addition, the increase in post-TBI aggression appeared to be specific to concussive trauma: neither cold exposure nor electric shock—two alternate types of trauma—significantly altered aggressive behavior in male-male pairs. We conclude that this assay may be used as a model for the study of post-TBI elevations of aggression.

Disclosures: D.C. Lee: None. **K. Vali:** None. **S.R. Baldwin:** None. **J.R. Fequiere:** None. **M.A. Fernandez:** None. **J.C. Frageau:** None. **F. Longo:** None. **S.S. Madhoun:** None. **P. Mingione:** None. **T.R. O'Toole:** None. **G.R. Tanner:** None.

Poster

746. Brain Injury and Trauma III

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 746.03/E30

Topic: C.10. Brain Injury and Trauma

Support: R37HD059288 to ASC

Title: On the application of APP immunohistochemical staining to detect TBI-induced axonal degeneration in the mouse

Authors: *G. XIONG[1], H. METHENY[1], K. A. FOLWEILER[1], A. S. COHEN[1,2];
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Abstract: Immunostaining with an antibody against amyloid precursor protein (APP) has been considered the "Gold-standard" to detect traumatic brain injury (TBI)-induced neuropathology in white matter bundles, shown as intensely stained varicosities and spheroids. It has been suggested that these varicosities/spheroids represent the interruption of axonal transport, which results in APP accumulation and swelling in damaged axons. However, direct evidence for the axonal identity of these APP-stained structures is insufficient. Here we used APP immunofluorescent staining in order to raise the contrast of brain samples after TBI, compared to

the immunoperoxidase protocol widely used. Basal APP staining was routinely seen in both excitatory and inhibitory neuronal cell bodies, without positive staining in axons. Oligodendrocytes also demonstrated basal staining in both naïve and TBI mice. In TBI brains, large-sized varicosities/spheroids or clusters were seen in the external capsule (ec) and fimbria. Many spheroids could also be found in the caudate putamen and stratum moleculare-lacunosum of hippocampal area CA1. Occasionally, pre-terminal axons (with normal-sized varicosities) might be seen in severely damaged cortex. At 3 hr (after TBI) heavily stained axonal blebs were seen connecting their cell bodies via the remaining proximal axons in the cortex and hippocampus. From 10 hr to 2-3 d the remaining axonal segment became very swollen, exhibiting as a spheroid. At 5 and 7 but not 14 d, heavily stained cell bodies with proximal dendrites could be seen in the cortex, hippocampus and thalamus. These findings suggest that the initial injury to proximal axons in gray matter areas may trigger neurodegeneration after TBI. In transgenic mice expressing tdTomato in a subset of neurons, APP-stained varicosities/spheroids in white matter were clearly disdinct from deformed axons labeled with the red fluorescence but negative to APP. We also confirmed this mutually negative staining/labeling pattern in white matter with the axonal marker neurofilament light chain. This piece of negative evidence lead us to costain APP-positive structures with non-axonal markers in white matter. We witnessed multiple large patches of intracerebral hemorrhages using TER, a red blood cell marker. Clusters of densely packed spheroids could be identified at the center of these hemorrhages. They were distributed radially from the blood vessel lumen, suggesting that they might be blood- or vessel-derived structures. The present study suggests that in addition to axonal structures, non-axonal characteristics should be taken into account when interpreting APP immunostaining data after TBI.

Disclosures: G. Xiong: None. **H. Metheny:** None. **K.A. Folweiler:** None. **A.S. Cohen:** None.

Poster

746. Brain Injury and Trauma III

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 746.04/E31

Topic: C.10. Brain Injury and Trauma

Support: NIH-NICD Grant R37HD059288

Title: Impaired pattern separation behavior due to altered activity onto dentate granule cells following mild traumatic brain injury

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Abstract: Cognitive deficits are one of the most common outcomes following mild Traumatic Brain Injury (mTBI) including symptoms of impaired planning ability, memory deficits. In some patients, these symptoms resolve within 3 months, but other patients have persistent cognitive deficits for a year or more after injury. There is currently no way to recognize which patients will have long term deficits and there are no treatments for these cognitive impairments, highlighting the importance of basic research in understanding the effects of mTBI on cognitive abilities. One of the cognitive processes that is affected after injury is pattern separation, which is the ability to discriminate between similar representations. The dentate gyrus (DG), a hippocampal subregion, has been shown to be involved with pattern separation due to the low basal activity levels of the dentate granule cells (DGC's). During pattern separation, a distinct, but small, subset of DGC's are activated for any particular stimulus. The DG is also a region that is especially vulnerable to mTBI. Previously, it has been shown that there is an increase synaptic efficacy following mTBI in the DG. This increased synaptic efficacy is thought to be due in part to a reduced level of inhibition on the DGC's. We hypothesized that more DGC's would be active during a pattern separation task following injury as compared to sham injured animals, which would reduce the effective pattern separation ability of the DG. We hypothesized that the activation of many DGC's would be due to a lack of inhibition following injury. We tested these hypotheses by using the Lateral Fluid Percussion Injury (LFPI) model of mTBI in 6-8 week old mice. One week following injury, we trained the animals on a modified spatial object recognition task in order to test pattern separation behavior. We then took brain sections and stained the DG of these animals for c-Fos expression to determine the activation of DGC's following injury and pattern separation behavior. We also stained the DG for VGAT, a vesicular GABA transporter, to determine the levels of inhibitory activity on the DGC's after this behavioral task. Our results reinforce previous findings that performance on a pattern separation task is impaired after injury, and may be associated with differential activation of DGCs.

Disclosures: R.T. Somach: None. **H. Metheny:** None. **A.S. Cohen:** None.

Poster

746. Brain Injury and Trauma III

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Program #/Poster #: 746.05/E32

Topic: C.10. Brain Injury and Trauma

Support: NIH NS097750 to V.S.
NJCBIR CBIR16IRG017 to V.S.
NJCBIR CBIR19FEL022 to L.C.

Title: Early changes in dentate neurogenesis and network function following concussive brain injury in mice

Authors: *L. CORRUBIA[1], D. SUBRAMANIAN[2], A. IRFAN[2], V. SANTHAKUMAR[2,1]; [1]Pharmacology, Physiol. & Neurosci., Rutgers New Jersey Med. Sch., Newark, NJ; [2]Molecular, Cell and Systems Biol., Univ. of California Riverside, Riverside, CA

Abstract: Traumatic brain injury is a global epidemic that results in a variety of debilitating symptoms such as memory dysfunction and epilepsy. We previously described that rats experiencing brain injury showed a robust early increase in hippocampal adult neurogenesis occurring alongside increases in excitability of the hippocampal dentate gyrus (DG) and seizure susceptibility. Suppressing the aberrant neurogenic burst (Neuberger et al., 2017) attenuated both DG network hyperexcitability 7-days post-injury and subsequent increase in seizure susceptibility, suggesting a role of adult born granule cells (abGCs) in injury induced dentate network pathology. Moreover, abGCs generated after controlled cortical impact in mice exhibit altered morphology and migration, implicating potential for improper network integration (Ibrahim et al., 2016; Villasana et al., 2015). This study was conducted to test the hypothesis that concussive brain injury in mice results in early alterations in the generation and migration of abGCs born after injury, and that abGCs contribute to post-traumatic circuit dysfunction. Adult 6-8 week old mice receiving mild to moderate lateral fluid percussion injury (FPI) at 1.5 atm and age-matched sham-injured controls were examined for cell loss and changes in neurogenesis using immunohistological techniques and stereology. In-vivo local field potential (LFP) recordings were used to examine changes in DG network physiology. Fluoro-Jade staining to reveal degenerating neurons identified an increase in cell death in the ipsilateral dentate hilus and cell layer 4 hours after FPI compared to sham controls. Immunostaining for DCX, a marker for newly born neurons, identified an increase in ectopic expression of DCX+ neurons in the outer 2/3rd's of the granule cell layer on the side of injury as early as 3 days post-injury (N=3/group, p=0.023 by t-test). However, the total population DCX+ neurons in mice 3 days after FPI was not different from controls. Mice 7-9 days after FPI showed a reduction in paired-pulse facilitation of dentate GC population spikes in response to afferent stimulation indicating deficits in feedback inhibition. Kainic acid (7.5 mg/kg, i.p) elicited increased susceptibility and more severe seizures in mice three weeks after FPI compared to controls. These data demonstrate an early dysregulation of dentate neurogenesis and feedback inhibition after FPI in mice. The results provide a strong platform to analyze whether abnormal circuit integration of abGCs born after injury contributes to altered dentate physiology and epileptogenesis after concussive brain injury.

Disclosures: L. Corrubia: None. **D. Subramanian:** None. **A. Irfan:** None. **V. Santhakumar:** None.

Poster

746. Brain Injury and Trauma III

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 746.06/E33

Topic: C.10. Brain Injury and Trauma

Support: NICHD K01HD083759

Title: Unilateral hemisphere-wide damage is dependent upon the interplay between hemorrhage location and seizure duration and may be mediated by an age-dependent upregulation of matrix metalloproteinase-9 in a model of severe traumatic brain injury

Authors: *B. A. COSTINE-BARTELL, G. PRICE, M. LI, J. SHEN, K. J. STALEY, A.-C. DUHAIME;
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Abstract: Hemispheric hypodensity (HH) is a radiological pattern of severe injury where the hemisphere underlying a subdural hematoma (SDH) exhibits damage that evolves over hours to days, spans multiple vascular territories, and often results from abusive head trauma. Using our model of unilateral HH, we tested the effect of age on the amount and distribution of tissue damage in piglets of similar maturity to human infants (1-week-old, "infants") vs. toddlers (1-month-old, "toddlers"). Male, Yorkshire piglets (n = 26) were randomized to receive focal injuries that were scaled to brain size (cortical impact, SDH, mass effect) and focal seizures, global apnea, and hypoventilation, or piglets received sham surgeries. Tissue sections were coded for analysis. Both ages required intensive care, but "infants" had worse neurologic scores and persistent metabolic acidosis. At 24 hours post-injury, "toddlers" had wide-spread hypoxic-ischemic-type damage encompassing most of the ipsilateral cortex with sparing of the contralateral hemisphere while "infants" had less damage that was bilateral. The proportion of piglets that had unilateral HH was greater in "toddlers" vs. "infants" (67 vs. 11%). SDH was not correlated to damage in either age, but indirectly produced a focal subarachnoid hemorrhage that was positively correlated to damage in both ages. Seizure duration was equivalent between ages and positively correlated with hemispheric damage in "toddlers" but not "infants". When piglets were binned into seizure length (greater or less than one hour), unilateral HH only occurred when seizures where greater than 1 hour. "Toddlers" had greater MMP-9 upregulation and blood brain barrier (BBB) disruption than "infants" that was predominately unilateral. In sections with over 30% damage, damage was equivalent between ages, but "toddlers" had greater MMP-9 upregulation and BBB disruption. In plasma, pro-MMP-9 increased in both ages 1-4 hours post-injury and returned to baseline levels by 24 hours, but active-MMP-9 was greater in "toddlers" than "infants" 1-4 hours post-injury and remained elevated at 24 hours. In conclusion, both ages had the same duration of seizures, but damage was positively correlated to seizure duration in "toddlers" that had greater and ongoing conversion of pro- to active-MMP-9 and greater BBB disruption, which may be the mechanism by which damage spreads through the ipsilateral hemisphere with sparing of the contralateral hemisphere. Future studies will determine if inhibition of seizures and/or MMP-9 reduces brain damage in our model potentially resulting in therapeutics for children with severe brain injury.

Disclosures: B.A. Costine-Bartell: None. **G. Price:** None. **M. Li:** None. **J. Shen:** None. **A. Duhaime:** None. **K.J. Staley:** None.

Poster

746. Brain Injury and Trauma III

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Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 746.07/E34

Topic: C.10. Brain Injury and Trauma

Support: NINDS U54 NS100064
NS091170
US Department of Defense W81XWH-13-1-0180

Title: Site and time-specific tau hyperphosphorylation patterns in the rat cerebral cortex after traumatic brain injury: An EpiBioS4Rx Project 2 study

Authors: *P. G. SALETTI[1], C. P. LISGARAS[1], P. M. CASILLAS-ESPINOSA[6], W. B. MOWREY[2], Q. LI[1], W. LIU[1], I. ALI[6], R. D. BRADY[6], G. YAMAKAWA[6], J. C. SILVA[6], E. OZTURK[6], N. C. JONES[6], S. R. SHULTZ[6], T. J. O'BRIEN[6], S. L. MOSHÉ[1,3,4,5], A. S. GALANOPOULOU[1,3,4];
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Abstract: Tau hyperphosphorylation (p-tau) has been implicated in neurodegenerative diseases, and in post-traumatic epilepsy. EpiBioS4Rx Project 2 investigated the temporal patterns of p-tau forms after severe brain trauma induced by lateral fluid percussion injury (LFPI) in rats and whether they are modified by sodium selenate (SS), a protein phosphatase 2 (PP2A) activator. Protein expression was studied using immunochemistries (ICH) [Einstein] or Western blot (WB) [Monash] analyses. Male 11-week old Sprague-Dawley rats were randomized into naïve (n=11, ICH), sham (n=5-6/timepoint/ICH or WB) and LFPI (n=5-6/timepoint/ICH or WB) groups. A left parietal 5mm craniotomy was performed in sham and LFPI rats. LFPI rats were subjected to ~3.1atm pulse at the craniotomy. Rats had the brain either perfused for ICH or frozen for WB, at 2 days, 1, 2, 4 or 8 weeks post-surgery; naïve were age-matched. To determine if SS modified p-tau, LFPI rats (n=5/timepoint/dose) received a bolus injection of SS (0, 0.013, 0.04mg/kg, subcutaneous (sc)) immediately after LFPI followed by minipump to deliver SS (0, 0.33, 1mg/kg/day, sc) for either 2 or 7 days. ICH and WB assays using AT8, AT180, anti-PP2A/PR55 or tau5 antibodies were performed. In ICH, somatic and extrasomatic/extracellular signal densitometry of AT8, AT180, or PR55 immunoreactivity (-ir) was done at the ipsi- and contralateral primary motor (M1) and lateral [somatosensory (S2a,b); granular insular (GI)] cortices using ImageJ. Increase in both somatic and extrasomatic/extracellular AT8-ir was seen

in the left M1 and lateral cortices only at 2 days post-LFPI, compared to other groups. Shams showed increased AT8-ir at the left M1 cortex, 7 days post-craniotomy. In contrast, somatic AT180-ir was increased 8 weeks post-LFPI at the left S2a,b and GI. PR55-ir did not change. For WB, the ratio of AT8, AT180, PR55 or tau5 over GAPDH (glyceraldehyde 3-phosphate dehydrogenase) and PP2A enzymatic activity was determined. Although no differences were found in AT8/GAPDH, AT8/tau5 ratio was increased in LFPI rats at the perilesional cortex at 2 days post-LFPI. No difference in PR55 or tau5 expression was found in WB. In addition, SS did not alter AT8- or AT180-ir after 2 or 7 days of treatment. PP2A activity assays are ongoing. We show site and time-specific p-tau changes which may be candidate for therapeutic targets: an early (2 days) transient focal increase in both somatic and extracellular AT8-ir and a late (8 weeks) increase in somatic AT180-ir at the ipsilateral to LFPI cortex. However, SS treatment up to 7 days did not alter AT8-ir or AT180-ir p-tau. A longer exposure of SS may identify any potential effect of the drug on AT180 site.

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Poster

746. Brain Injury and Trauma III

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 746.08/E35

Topic: C.10. Brain Injury and Trauma

Support: NIH Grant R01 NS111037-01
NIH Grant P20GM103444
SC-SCIRF 2017 B-01

Title: RhoA siRNA local delivery by PgP nanocarrier reduces secondary injury after traumatic brain injury

Authors: C. MACKS[1], D. JEONG[1], M. LYNN[2], ***J. LEE**[1];
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Abstract: Traumatic brain injury (TBI) is one of the leading causes of disability and death following injury. Many studies have demonstrated that diverse extracellular inhibitors of neuroplasticity including both CSPGs (chondroitin sulfate proteoglycans) and MAIs (myelin associated inhibitors) in the CNS may act through common intracellular signaling pathway, RhoA and Rho kinase (ROCK) and neurite growth inhibition in response to MAIs and CSPGs

can be overcome by Rho/ROCK inhibitors. In addition, levels of the cyclic adenosine monophosphate (cAMP) drop due to increased degradation by phosphodiesterases 4 (PDE4) following TBI. Rolipram (Rm), a hydrophobic drug, prevents the degradation of cAMP and is able to inhibit production of neurotoxic cytokines and reduce the apoptosis. The goal of our work is to develop neuron-specific nanotherapeutics for combinatorial delivery of Rm and siRNA targeting RhoA. To achieve this goal, we synthesized cationic, amphiphilic copolymers (poly(lactide-co-glycolide)-g-polyethylenimine : PgP) as Rm and siRhoA carrier. In our previous study, we demonstrated that RhoA knockdown by PgP/siRhoA nanoparticles can maintain knockdown for up to 4 weeks accompanied by a reduction in apoptosis, cavity size, and astrogliosis. In this study, we investigated the effect of RhoA knockdown by the PgP/siRhoA on secondary injury such as inflammatory response, apoptosis, and neuronal cell death in a rat TBI model. The TBI model was generated by controlled cortical impact (CCI) devise armed with a 3 mm tip (3.5 m/sec, depth: 2mm). Animals were divided to 4 groups: 1) Sham, 2) TBI, 3) PgP/siRhoA (20 ug siRhoA), and 4) PgP/siNT (20 µg siRNA negative control). Immediately after injury, nanoparticle solution (20 µl) were injected in the lesion site and brains were harvested at 7 days post-inury for RhoA gene expression by RT-PCR. For histological analysis, rats were euthanized at 7days post-injury by caridac perfusion with 4% PFA. Brains were collected, fixed in 4% PFA, and cryosectioned (30 um). Sections were stained with cresyl violet for lesion volume and IHC was performed using antibodies against ED1 (macrophages/microglia) and GFAP (astrocytes). TUNEL assay was performed for apoptosis. We observed significant knockdown of RhoA expression with PgP/siRhoA compared to saline injection group at 7days post-injury. We also observed that RhoA knockdown by PgP/siRhoA polyplex nanoparticle decreases lesion volume, improves neuronal survival, reduces inflammation cell infiltration, and reduces astrogliosis compared to untreated TBI group. In the future, we will evaluate the synergistic effect of rolipram and siRhoA on secondary injury in a rat TBI model.

Disclosures: C. Macks: None. **D. Jeong:** None. **M. Lynn:** None. **J. Lee:** None.

Poster

746. Brain Injury and Trauma III

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 746.09/E36

Topic: C.10. Brain Injury and Trauma

Title: Automated and manual brain mapping and neuroinflammation in striatum and hippocampus following alcohol exposure and traumatic brain injury

Authors: *L. A. SHAPIRO[1], A. WANG[2], S. DEY[2], S. MUKHERJEE[4], K. O'NEILL[3], W. DAVIS[3], M. RAMIREZ[3], G. HOLLINGSWORTH[3], K. MIMS[3], X. WANG[1], J. WANG[1];

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Abstract: In the United States, Traumatic Brain Injury (TBI) accounts for approximately 2.5 million visits to the Emergency Room (ER) each year. Many TBI patients who present in the ER have alcohol in their blood. For example, a study looking at a community hospital from 1994 to 2004 found that approximately 37%-51% of patients with a TBI had alcohol in their system. Numerous other studies support these findings. Therefore, understanding the impact of alcohol on a TBI is important to understand altered risk factors.

Alcohol use may not only be a contributing factor for TBI, but also might be a co-morbidity, as previous studies have shown an increased risk of alcohol abuse after a TBI. Considering the large numbers of patients that have alcohol present in their system at the time of a TBI, and the fact that TBI increases alcohol usage, it is important to better understand how alcohol use prior to, and after a TBI, might alter TBI pathogenesis.

TBI is known to induce a significant neuroinflammatory response, in the acute, sub-acute and more chronic time points after injury. Alcohol has also been shown to alter inflammatory trajectories, and studies examining alcohol use in the context of TBI support an altered neuroinflammatory response. However, the influence of alcohol before and after a TBI, on neuroinflammation, has not yet been fully explored. We tested the hypothesis that alcohol use before and after a TBI, will alter the neuroinflammatory response in the hippocampus and striatum.

Twenty male C57BI/6 mice were individual housed and allowed free access to water and 20% ethanol (EtOH) solution, every other day, for six weeks. Alcohol consumption was monitored and considered when separating the mice into sham and TBI treatment groups, to an ensure equal distribution of alcohol consumers in both groups. TBI or sham was induced under anesthesia, after which mice were allowed to recover for 3 days, followed by ad libitum access to alcohol, every other day, for four more weeks. One week prior to sacrifice, behavioral tests were conducted followed by sacrifice.

Perfused brains were sliced on a vibratome, and immunolabeled for astrocytes (anti-GFAP) and microglia (anti-IBA-1). Using custom automated brain mapping software, we quantified dopamine D1 or D2 receptor-expressing neurons throughout the entire brain, and also performed manual counts of the astrocytes and microglia in the hippocampus and striatum. The results revealed that alcohol use before and after a TBI results in behavioral deficits, as well as prolonged neuroinflammation in the hippocampus and striatum. Thus, alcohol consumption may alter the post-traumatic pathogenic trajectory.

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Poster

746. Brain Injury and Trauma III

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 746.10/E37

Topic: C.10. Brain Injury and Trauma

Title: Neurodegenerative disease markers coincide with diffuse axonal injury in a mouse model of traumatic brain injury

Authors: D. F. HAVLICEK[1], Y. TONG[1], E. JOSE[1], J. F. CRARY[2], ***P. J. BERGOLD**[3]; [1]Physiol. and Pharmacol., SUNY-Downstate Med. Ctr., Brooklyn, NY; [2]Pathology, Icahn Sch. of Med. At Mount Sinai, New York, NY; [3]SUNY-Downstate Med. Cen., Brooklyn, NY

Abstract: Traumatic brain injury (TBI) selectively damages white matter and increases the risk of developing neurodegenerative disorders, including Alzheimer's disease and Parkinson's disease. Alzheimer's disease is characterized by aggregates of hyperphosphorylated tau (pTau) and amyloid beta (Aβ), while Parkinson's disease is characterized by aggregates of α-synuclein (α-syn). Tau, Aβ, and α-syn are normally located in axons and presynaptic termini, suggesting that axonal injury following TBI may alter the cellular localization of these proteins, leading to their pathological aggregation. We are testing this hypothesis in sham and injured C57BL/6 mice 14 days after experimental closed head injury (CHI). A unilateral dorsal impact by CHI produced a diffuse white matter injury in both hemispheres. We assessed white matter damage across the brain using Bielschowsky silver stain to visualize axons and luxol fast blue stain to visualize myelin. These studies showed that CHI produced a heterogenous white matter injury, yet consistently damaged axons and myelin in the cingulum, thalamus, ventral olfactory tract, ventral striatum and basal forebrain. The hippocampal CA2 region was also selectively damaged. These areas were also immunopositive for aggregates of pTau, Aβ, and α-syn. These results suggest that markers of neurodegeneration coincide with diffuse axonal injury. Our laboratory previously showed that the drug combination of minocycline and N-acetylcysteine prevents white matter injury after TBI (Haber et al. 2017; Sangobowale et al. 2018). We are currently evaluating if these drugs also prevent the aggregation of pTau, Aβ and α-syn after CHI.

Disclosures: **P.J. Bergold:** None. **D.F. Havlicek:** None. **Y. Tong:** None. **E. Jose:** None. **J.F. Crary:** None.

Poster

746. Brain Injury and Trauma III

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 746.11/E38

Topic: C.10. Brain Injury and Trauma

Title: Microglia markers: Distinguishing surveillance and reactive states with immunohistochemistry

Authors: *J. B. BAUN[1], B. TIPTON[2], C. ZURHELLEN[3], H. T. YORK[3], L. S. BELAYEV[4], R. C. SWITZER III[1];
[1]Neurosci. Associates Inc, Knoxville, TN; [2]Lab., [3]Neurosci. Associates, Knoxville, TN; [4]Neurosci. Ctr., LSUHSC, New Orleans, LA

Abstract: Assessing neuroinflammation based on immunohistochemical (IHC) displays of microglia and astrocytes is a key dimension in characterizing different disease states and the results of physical or chemical perturbations to the brain and spinal cord.The antibody Iba1 (ionized calcium-binding adapter molecule) has proven to be a real workhorse for assessing the state of microglia in that it is not species restricted and the antigen is robust and not susceptible to long term exposure to formaldehyde fixative. Iba1 allows visualization of the full range of morphologic changes: surveillance states, ‘reactive’ hypertrophy, amoeboid. The reactive morphologic states span a wide range of extremes: barely different than surveillance state to gnarly processes. To quantify degrees of reactivity across such a gradient of morphologic changes is a considerable challenge. Some image analysis systems can characterize the range by examining individual microglia.Other histologic IHC markers for microglia preceded the discovery of Iba1 and others have emerged since. In the course of applying some of these other antibodies to tissues from a rat MCAO stroke model we found that the OX42 clone of CD11b antibody robustly stained reactive microglia in and around the affected ischemic zone in rats but microglia on the contralateral side were less visible to varying degrees suggesting different degrees of expression of the antigen detected by OX42. The gradient of change of microglia visibility and hypertrophy observed with the OX42 was much ‘steeper’ than with Iba1; that is, a much improved signal to noise across the spectrum of change. This attribute allows image analysis methods to parse out different degrees of reactivity and provide more clear cut quantitative data.We strove to find a clone of CD11b that would perform similarly in mice. Only one of those that we tried (Life Sciences LSC294688) came close to matching the performance of the OX42.Antibodies against CD68, a lysosome marker, are often used to indicate microglia reactivity, but as we reported earlier (SfN: C.Segovia et.al.; abstract 726.10/w8; 2013) not all hypertrophied microglia are necessarily CD68-positive. CD68+ve microglia were a subset of those positive for OX42 in the rat stroke model, but in the mouse, using a transgenic AD model, the CD68+ve microglia appeared to be equal in number to those positive for the LSC

antibody.Another marker not usually considered to identify reactive microglia is ferric iron. Taken together, these different markers for reactive states of microglia provide the means to make a multidimensional assessment of neuroinflammation.

Disclosures: **J.B. Baun:** None. **B. Tipton:** None. **C. Zurhellen:** None. **H.T. York:** None. **L.S. Belayev:** None. **R.C. Switzer III:** None.

Poster

746. Brain Injury and Trauma III

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 746.12/E39

Topic: C.10. Brain Injury and Trauma

Title: BCAS1 expression demonstrates a reduction in early myelinating oligodendrocytes following traumatic brain injury

Authors: *A. AVITUA[1], T. DISTEL[2], B. FORD[2];
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Abstract: Currently, there are over 5 million Americans living with a disability as a result of traumatic brain injury (TBI). This number grows with over 2.5 million TBIs occurring in the U.S. each year. Following TBI, individuals may experience a number of impairments such as: migraines, tinnitus, learning and memory deficits, post-traumatic epileptogenesis, and problems with motor function to list a few. Unfortunately, we lack the clinical interventions necessary to prevent these symptoms from manifesting. Through this research, we aim to have a better understanding of endogenous repair and regeneration following TBI in order to minimize the effect of these symptoms and help those suffering with a TBI-related disability live a better quality life. In this study, we utilized the controlled cortical impact model of TBI and examined brain tissues 24 and 72 hours following injury. Histology was performed to visualize neuronal damage and oligodendrocytes following TBI. At 24 hours and 3 days post-TBI, we observed numerous injured neurons as measured by fluorojade B staining in the perilesional area. Using an antibody that labels myelinating oligodendrocytes, anti-breast carcinoma amplified sequence 1 (BCAS1), we observed potential sites of active myelination. The BCAS labeling was colocalized with expression of Olig2, a marker for oligodendrocytes. BCAS expression was found in cerebral cortex and throughout the brain compared to naïve animals. The numbers of BCAS1 positive cells decreased at 24 and 72 hours following TBI. This data demonstrates markers of cell death and BCAS1-positive cells in post-mortem tissue following TBI. These results are valuable in contributing to our knowledge of the role of BCAS1-positive cells in repair and regeneration and may aid in the development more effective treatments to reverse or prevent disabilities that can arise following TBI.

Disclosures: **A. Avitua:** None. **T. Distel:** None. **B. Ford:** None.

Poster

746. Brain Injury and Trauma III

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Program #/Poster #: 746.13/E40

Topic: C.10. Brain Injury and Trauma

Support: NIH-NINDS Grant U01NS086659
NIH-NIA Boston University Alzheimer's Disease Center Grant P30-AG013846

Title: Ultrastructural analysis of microvascular injury and neuroinflammation in traumatic brain injury and chronic traumatic encephalopathy

Authors: *K. J. BABCOCK[1], M. ERICSSON[2], E. S. FRANZ[1], O. MINAEVA[1], J. A. MONCASTER[1], B. R. HUBER[3], A. C. MCKEE[1], L. E. GOLDSTEIN[1];
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Abstract: Traumatic microvascular injury (TMI) and neuroinflammation are hallmark features of traumatic brain injury (TBI) and sequelae, including chronic traumatic encephalopathy (CTE). The diagnostic lesion of CTE, a progressive neurodegenerative disease associated with sports- and military-related neurotrauma, is abnormal accumulation of hyperphosphorylated tau protein in a patchy distribution around small blood vessels in the depths of cortical sulci. This neuropathological association points to a mechanistic link between TMI and chronic neurotrauma-related pathologies, including CTE. Previous work from our lab on human and mouse brains indicate that acute neurotrauma disrupts the normal integrity of small blood vessels leading to abnormal blood-brain barrier (BBB) function and perivascular neuroinflammation. This project seeks to confirm and extend these findings by conducting a systematic ultrastructural (transmission electron microscopy, TEM) analysis of postmortem brain samples from neuropathologically-confirmed human CTE cases and mice subjected to lateral closed-head concussive impacts. TEM examination revealed ultrastructural changes consistent with diverse axonal pathologies (abnormal myelination, reduced axoplasm, axon-myelin collapse) as well as microvascular injury (dysmorphic capillaries with thickened and highly tortuous basal lamina encircled by swollen, edematous astrocytic endfeet with dilated endfeet). These results provide further evidence that neurotrauma-induced microvascular and axonal injury are mechanistic drivers underpinning both acute and chronic effects of neurotrauma.

Disclosures: **K.J. Babcock:** None. **M. Ericsson:** None. **E.S. Franz:** None. **O. Minaeva:** None. **B.R. Huber:** None. **A.C. McKee:** None. **L.E. Goldstein:** None. **J.A. Moncaster:** None.

Poster

746. Brain Injury and Trauma III

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 746.14/E41

Topic: C.10. Brain Injury and Trauma

Support: Chinese Natural Science Foundation grants 81870971

Title: Interleukin 13 ameliorates neuroinflammation and promotes functional recovery after traumatic brain injury

Authors: *W. MIAO, Y. GAO;
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Abstract: Objectives: Traumatic brain injury (TBI) is a leading cause of death and long-term disability. In addition to the initial primary insult, secondary brain injuries occur after TBI due to various cellular processes, including the activation of immune cells. Microglia play essential roles in the neuroinflammatory responses after TBI Our previous studies showed that microglia could shift towards pro-inflammatory or anti-inflammatory polarities at different stages after central nervous system injury, which correlated to the functional outcomes. IL-13, as an anti-inflammatory cytokine secreted by microglia, has been reported to protect against white matter demyelination and spinal cord injury through immunomodulation. The function of IL-13 in TBI remains to be investigated. **Methods:** TBI was induced in male C57BL/6J mice by controlled cortical impact system. IL-13 was intranasally administrated immediately after TBI and repeated every day for 6 days. A batch of behavior tests was performed to evaluate the long-term sensorimotor functions after TBI. Microglial phenotype was detected using immunohistochemical staining of M1 marker CD16 and M2 marker CD206. The mRNA expression levels of inflammatory factors were measured by qRT-PCR. Primary cultured microglia was used to evaluate the effect of IL-13 on inflammatory responses and phagocytotic ability of microglia. **Results:** Intranasal administration of IL-13 after TBI accelerated functional recovery after TBI, as revealed by increased time to fall off in Rotarod test, reduced number of foot faults in grid walking test, and improved scores in hang wiring test, up to 28 days after TBI. IL-13 reduced tissue loss at 6 days after TBI. Furthermore, IL-13 inhibited the production of pro-inflammatory factors and reduced the number of proinflammatory M1 microglia at 6 days after TBI. *In vitro* studies confirmed that IL-13 treatment inhibited the production of proinflammatory cytokines in primary microglia in response to LPS stimulation, and inhibited the ability of microglia to engulf PI-labeled dead neurons. **Conclusions:** IL-13 treatment improved neurological outcomes after TBI through inhibiting inflammatory responses and adjusting microglial phenotype. IL-13 may represent a potential immune therapy to promote long-term recovery from TBI.

Disclosures: **W. Miao:** None. **Y. Gao:** None.

Poster

746. Brain Injury and Trauma III

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 746.15/E42

Topic: C.10. Brain Injury and Trauma

Title: Effects of aqueous extract of cola nitida on post-natal behavioural indices and histological alterations in the cerebellum of Wistar rat

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Abstract: *Cola nitida* (CN, kolanut) is popular fruit in Nigeria and West Africa. It is used for industrial, snacking, stimulant and cultural purposes. Pregnant women commonly consume kolanut during the first trimester to alleviate the features of morning sickness and dizziness. There is however, dearth of information on the effect of CN on the developing cerebellum. This study was designed to investigate the effects of graded doses of aqueous extract of CN on the structure of the developing cerebellum in Wistar rats.
Fresh CN fruits were purchased from kola plantation in Sagamu, Ogun State, Nigeria in the month of August, 2015. The fruits of kolanut were identified and authenticated at the Federal Research Institute of Nigeria, with voucher FHI number: 109605. Aqueous extract of CN seed was obtained by wetting prepared cubes of CN with water, milling and filtration. The filtrate was concentrated with rotary evaporator, and stored in the refrigerator at 4°C. Forty pregnant Wistar rats were randomly divided into four groups of ten rats each. They were given crude extracts of CN dissolved in water in graded doses of 400, 600, and 800 mg/kg/body weight orally during pregnancy to day 28 after birth, while the control group received water only. On days 1, 7, 14, 21 and 28 after birth, the pups (n=5) were weighed, sacrificed and perfused with neutral buffered formalin and their brains dissected out, weighed and the cerebellum preserved in 10% formol-saline. Paraffin sections of the cerebellum were stained with haematoxylin and eosin for cerebellar cytoarchitecture, cresyl violet stain for Purkinje cell count, glial fibrillary acidic protein, GFAP, for estimation of gliosis and B-cell lymphoma 2 (Bcl2) for apoptotic neuronal cells. Data were analysed using ANOVA at $\alpha_{0.05}$.
The CN-treated rats had, a significant reduction in the body and brain weights and reduction in behavioural indices compared to the control. Histology showed in the CN-treated group, persistent external granular layer of Post-natal Day (PND) 21 and distortion of Bergmann glial. The Purkinje cells in the treated groups showed reduction in density, loss of dendrites and multiple layering. The white matter of the treated groups showed neurodegeneration depicted by

spongiosis. Treatment also elicited over-expression of GFAP, with evidence of reactive astrogliosis. The intensity estimation for Bcl2 showed increase in all the treated groups. Aqueous extract of *Cola nitida* treatment disrupted the normal cellular development, migration and cyto-architecture of Wistar rat cerebellum.

Disclosures: F.A. Atiba: None. **I. Imosemi:** None. **A. Malomo:** None.

Poster

746. Brain Injury and Trauma III

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 746.16/E43

Topic: C.10. Brain Injury and Trauma

Support: CONACYT Grant 1840

Title: The hepatic regeneration does not induces vesicle pools in locus coeruleus neurons

Authors: A. A. BARRIENTOS BONILLA[1], P. B. PENSADO GUEVARA[1], A. D. C. SÁNCHEZ GARCÍA[2], *D. HERNANDEZ-BALTAZAR[3];
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Abstract: Introduction. During hepatic regeneration, the noradrenaline produced in the *locus coeruleus* favors the synthesis of Hepatocyte Growth Factor and Epidermal Growth Factor. In last years, the model of partial hepatectomy (PH) in rats has been used to determine the cellular processes associated with the anatomical and functional recovery of the liver. An interesting finding is the presence of hepatocelullar intracytoplasmic vesicles in stages of high proliferation, which suggest celullar stress in liver and *locus coeruleus*. **Objective.** In this work, we evaluated the lipid or protein content in the vesicle pools of the hepatic cells and *locus coeruleus* neurons. **Methods.** Male Wistar rats (218-240 g) were distributed in 3 groups (n = 3): Intact group, and PH groups (48 h and 144 h post surgery). Changes in *locus coeruleus* and hepatic citoarchitecture as well as the vesicular content was evaluated by hematoxylin-eosin, oily red, Masson's trichrome stain and immunohistochemistry for tyrosine hydroxylase (TH). **Results**. Forty-eight hours after PH, hepatic cells and neurons immunoreactive to TH do not exhibit patterns of cell death. Unlike the cells of liver, the neurons of the *locus coeruleus* no showed vesicle pools. The hepatocellular intracitoplasmic vesicles not exhibited collagen or lipid content. **Conclusion**. Hepatic regeneration does not favor the accumulation of vesicles in *locus coeruleus* neurons. This study was partially supported by Catedras CONACYT project (ID1840).

Disclosures: **A.A. Barrientos Bonilla:** None. **P.B. Pensado Guevara:** None. **A.D.C. Sánchez García:** None. **D. Hernandez-Baltazar:** None.

Poster

746. Brain Injury and Trauma III

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 746.17/E44

Topic: C.10. Brain Injury and Trauma

Support: NIH/NICHD R01HD083001-01A1 grant to C. Ikonomidou
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UNAM-PAPIIT grants IA104518 and IN107916 to I. Rosado-Mendez and L. Castañeda-Martinez
CONACyT National Researcher (level 3) assistant support to L. Castañeda-Martinez

Title: Quantitative ultrasound and apoptotic death in the neonatal primate brain

Authors: I. M. ROSADO-MENDEZ[1], K. K. NOGUCHI[2], L. CASTAÑEDA-MARTINEZ[3], G. KIRVASSILIS[4], S. H. WANG[6], S. CAPUANO III[7], K. BRUNNER[8], K. CROSNO[8], H. SIMMONS[8], A. F. MEJIA[8], J. ZAGZEBSKI[4], T. J. HALL[4], ***C. IKONOMIDOU**[5];
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Abstract: Apoptosis is triggered in the developing mammalian brain by sedative, anesthetic or antiepileptic drugs during late gestation and early life. Whether human children are vulnerable to this toxicity mechanism remains unknown, as there are no imaging techniques to capture it. Apoptosis is characterized by distinct structural features, which affect the way damaged tissue scatters ultrasound compared to healthy tissue. We evaluated whether apoptosis, triggered by the anesthetic sevoflurane in the brains of neonatal rhesus macaques, can be detected using quantitative ultrasound (QUS). Neonatal (n=15) rhesus macaques underwent 5hr of sevoflurane anesthesia. QUS images were obtained through the sagittal suture at 0.5 and 6hr. Brains were collected at 8hr and examined immunohistochemically to analyze apoptotic neuronal and oligodendroglial death. Significant apoptosis was detected in white and gray matter throughout the brain, including the thalamus. We measured a change in the effective scatterer size (ESS), a QUS biomarker derived from ultrasound echo signals obtained with clinical scanners, after sevoflurane-anesthesia in the thalamus. Although initial inclusion of all measurements did not reveal a significant correlation, when outliers were excluded, the change in the ESS between the

pre- and post-anesthesia measurements correlated strongly and proportionally with the severity of apoptotic death. We report for the first time *in vivo* changes in QUS parameters, which may reflect severity of apoptosis in the brains of infant nonhuman primates. These findings suggest that QUS may enable *in vivo* studies of apoptosis in the brains of human infants following exposure to anesthetics, antiepileptics and other brain injury mechanisms.

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Poster

746. Brain Injury and Trauma III

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 746.18/F1

Topic: C.10. Brain Injury and Trauma

Support: NIH Grant R21NS090131

Title: Tracking secondary injury and recovery in mouse models using 3D optical imaging

Authors: C. D. PERNICI[1,2], B. S. KEMP[2], ***T. A. MURRAY**[2];
[1]Pharmacol. and Toxicology, Univ. of Utah, Salt Lake City, UT; [2]Ctr. for Biomed. Engin. and Rehabil. Sci., Louisiana Tech. Univ., Ruston, LA

Abstract: We have developed a high-resolution, optical system for deep brain imaging in Thy1-YFPH mice to monitor cellular damage and recovery over several weeks after diffuse brain injury. We tracked the same axons in a subcortical white matter track at six time points after traumatic brain injury (TBI). To accomplish this, we developed a high-resolution gradient index (hrGRIN) lens system that is compatible with the fluid percussion injury model and precision, time-lapse multiphoton microscopy. Baseline images acquired before injury were used to normalize post-injury data for each mouse which minimized inter-animal variability and reduced the number of mice required for experiments. As expected for diffuse brain injury, a small percentage of axons developed undulations (Fig. 1, dashed arrow). Later, some of these axons developed varicosities (Fig. 1, arrow) and ultimately detached forming a proximal terminal bulb (Fig. 1, asterisk). Other undulated axons returned to their baseline state. Similarly, a small percentage of axons with varicosities resolved over time (Fig. 1, arrowhead). Notably, secondary injury was also tracked as new damage at each time point. Thus, the hrGRIN system will be useful to monitor both the effect of therapeutics on reparative mechanisms and on mitigation of secondary injury. In another application, the hrGRIN system was used to image microglia in Layers 5-6 of the cortex in Cx3cr1-ROSA26-tdTomato mice before and after middle carotid

artery occlusion, a model of ischemic stroke. Ramified cellular processes were prominent in pre-injury images. After injury, cells became de-ramified, adopting brushy and ameboid morphologies associated with activation. Time-lapse images revealed motile microglia moving around the vasculature. In summary, the hrGRIN system has the spatial resolution to observe varicosities on axons and fine ramified processes of microglial cells. It also has the temporal resolution necessary to observe motile microglial cells over seconds and minutes and also the precision to track the same axons over multiple imaging sessions for up to 80 days.

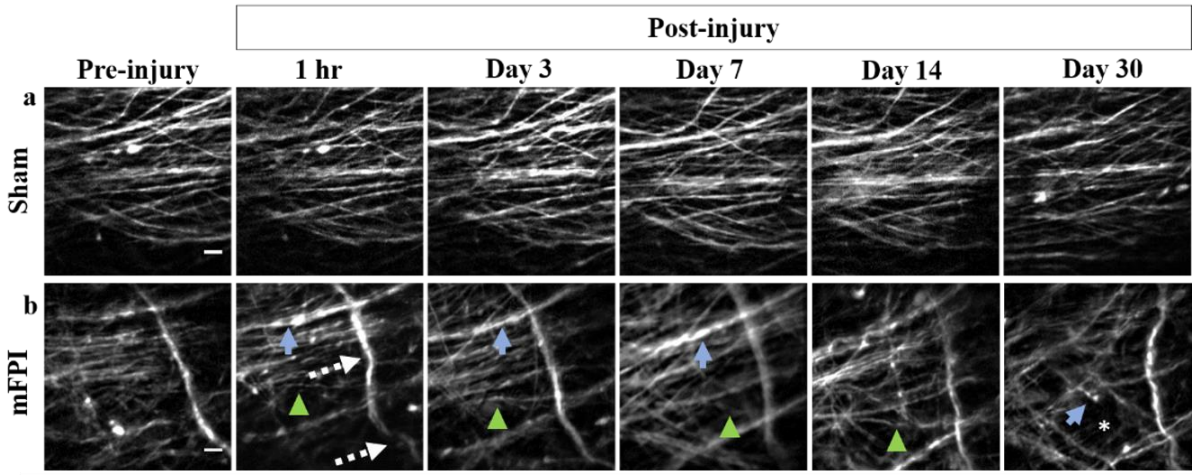


Fig. 1. Time-lapse images following moderate midline fluid percussion or sham injury in Thy1-YFPH transgenic mice. Scale bars denote 10 µm for all images.

Disclosures: **C.D. Pernici:** None. **B.S. Kemp:** None. **T.A. Murray:** None.

Poster

746. Brain Injury and Trauma III

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 746.19/F2

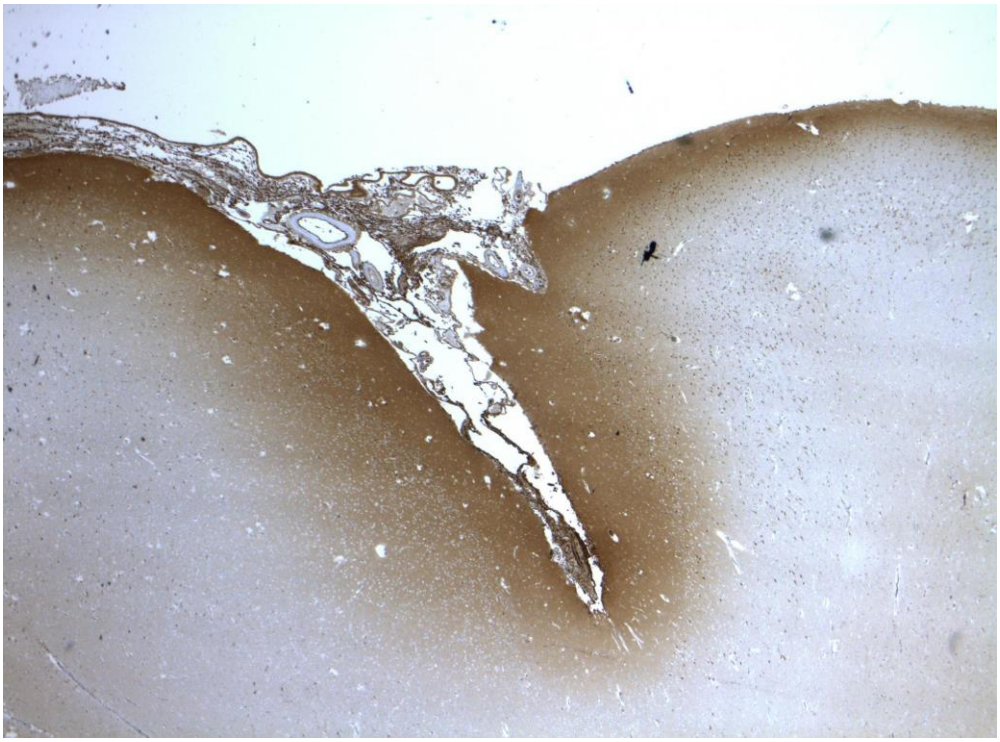
Topic: C.10. Brain Injury and Trauma

Title: Subpial vasogenic edema with rotational trauma in young children

Authors: A. SCHOLL[1], C. J. SCHMIDT[3], *R. J. CASTELLANI[2];
[2]Pathology and Neurosci., [1]WVU Sch. of Med., Morgantown, WV; [3]Wayne County, Detroit, MI

Abstract: The pathophysiology of traumatic brain injury in young children, in particular the massive cerebral swelling and encephalopathy that often occurs in this setting, is poorly understood. As an initial step toward the investigation of complex metabolic cascades in brain injury in young children, we explored brain immunoreactivity for IgG in traumatic brain injury

versus asphyxiation. The study was approved by WVU institutional review board. IgG immunoreactivity in this setting is a surrogate for brain microvascular dysfunction, as IgG traverses the disrupted blood brain barrier. Study subjects included 9 decedents with acute blunt force trauma (age range 2.5 months to 16 months) and 7 subjects with asphyxial deaths due to unsafe sleep environments (age range 0.5 months to 6 months). All subjects presented for autopsy at the Wayne County Medical Examiner's Office in Detroit, Michigan. Among the deaths from blunt force trauma, 5 were associated with subdural hemorrhage, suggesting rotational injury biomechanics. Survival in the trauma subjects ranged from 0 to 38 hours. All asphyxia subjects were found dead. Both the trauma group and the asphyxia group showed variable IgG immunoreactivity around small blood vessels in gray and white matter. This suggests that asphyxia causes measurable changes to the brain microvasculature. In addition, a striking pattern in trauma subjects with subdural hematoma was a pronounced subpial immunoreactivity for IgG (see figure). The basis for this pattern requires additional research, although it is noteworthy that aquaporin 4 expression in astrocytic foot processes is increased in the subpial region. An older study also implicated the subpial region as a means of spreading of brain edema in experimental hypertensive brain injury. The association with subdural hemorrhage suggests a rotational component, possibly with traction on superficial veins that might co-occur with traction on bridging veins and bridging vein rupture. More studies are needed to confirm this finding and elucidate its pathogenic basis.



Disclosures: A. Scholl: None. **C.J. Schmidt:** None. **R.J. Castellani:** None.

Poster

746. Brain Injury and Trauma III

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 746.20/F3

Topic: C.10. Brain Injury and Trauma

Support: NINDS Grant 5P01NS082184-02

Title: The behavioral effects of blocking PDGF-R in a rat model of traumatic brain injury

Authors: *N. KALYNOVSKA[1], M. HAMER[2], P. GIFFORD[1], A. JULLIENNE[1], J. TANG[1], W. PEARCE[1], J. H. ZHANG[1], A. OBENAUS[2], R. E. HARTMAN[1];
[1]Loma Linda Univ., Loma Linda, CA; [2]Univ. of California Irvine, Irvine, CA

Abstract: Traumatic brain injury (TBI) leads to a variety of neurological and behavioral deficits. Prior studies by our group have suggested that platelet-derived growth factor (PDGF) contributes to neuroinflammation following intracerebral hemorrhage (ICH), and that imatinib (a PDGF-R blocker) reduces edema following ICH. We hypothesized that blocking the PDGF receptor would reduce TBI-induced brain edema and improve vascular function, therefore improving behavioral outcomes. Young adult male rats were given a controlled cortical impact TBI or a sham procedure (craniectomy) and treated with imatinib or vehicle (0.1% DMSO). Vehicle-treated rats had increased lesion size that was prevented by imatinib. We also measured behavioral performance on several tests of sensorimotor and neurological function. In general, TBI animals with more severe damage performed worse on a neurological test battery, made more errors on a foot fault test, and traveled less distance on a balance beam. Sham rats performed similarly to naïve controls on the neurological test battery, but TBI rats demonstrated significant deficits at 1d, 3d and 7d post-TBI. Imatinib and vehicle treatment slightly reduced performance 1d and 3d, but by 7d, TBI rats treated with imatinib were performing slightly better than TBI only or TBI+vehicle rats. Sham rats made slightly more foot fault errors than naïve controls, and TBI rats made significantly errors than shams at 1d post-TBI. Imatinib treatment slightly improved performance in both groups. TBI rats still demonstrated foot fault deficits, although attenuated, at 3d post-TBI, but the deficits had dissipated by day 7. On the balance beam test, shams traveled less distance than naïve controls, and TBI rats traveled less than shams 1d, 3d, and 7d post-TBI. Both vehicle and imatinib treatment increased distance traveled in shams, but not TBI rats, at 1d. In summary, the sham procedure induced behavioral deficits, but the addition of TBI made those deficits (observed for up to 7d post-injury) significantly worse. Treatment with imatinib prevented the vehicle (DMSO)-induced exacerbation of the brain injury and tended to improve overall performance, suggesting that blocking PDGF-R may ultimately play a role in preventing brain damage and behavioral deficits observed following TBI.

Disclosures: **N. Kalynovska:** None. **A. Jullienne:** None. **P. Gifford:** None. **J. Tang:** None. **W. Pearce:** None. **J.H. Zhang:** None. **A. Obenaus:** None. **M. Hamer:** None. **R.E. Hartman:** None.

Poster

746. Brain Injury and Trauma III

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 746.21/F4

Topic: C.10. Brain Injury and Trauma

Support: 5P01NS082184-02

Title: Identifying common and distinct behavioral phenotypes associated with 3 types of hemorrhagic brain injury in rats

Authors: *W. HARDEMAN[1], M. HAMER[2], P. GIFFORD[1], J. TANG[1], W. PEARCE[1], J. H. ZHANG[1], A. OBENAUS[2], R. E. HARTMAN[1];
[1]Loma Linda Univ., Loma Linda, CA; [2]UCI, Irvine, CA

Abstract: Brain injuries can induce a variety of behavioral deficits depending on the type of injury, size and location of the lesion, and demographic characteristics of the patient. However, individual variability in responses to brain injury can produce a wide range of deficit profiles, from complete lack of observable deficits despite a large lesion to relatively significant deficits despite a small (or even no) lesion. Additionally, the passage of time can ameliorate or exacerbate behavioral deficits associated with brain damage, depending again on complex interactions between the injury, the environment, and the individual. In this study, adult male rats received one of three forms of hemorrhagic injury (traumatic brain injury [TBI], subarachnoid hemorrhage [SAH], or intracerebral hemorrhage [ICH]), and their performance on a number of behavioral assays was recorded over the course of 7d. In general, specific overall performance profiles were associated with each injury type. For example, TBI, ICH, and SAH rats differed in their grouped (average) on the foot fault assay, balance beam, and wire hang tests. Additionally, the sham procedures associated with each type of brain injury induced behavioral changes, demonstrating the importance of characterizing multiple control groups. However, it was generally impossible to determine the type, extent, or even existence, of a lesion based on the performance of an individual rat on an individual task. Due to biological variability (similar to that observed in humans), control rats sometimes performed worse on tests than rats with even relatively large lesions (and vice versa). However, we provide evidence that, when the overall pattern of behavioral performance across a wide variety of tests is analyzed, the accuracy of predicting the type and extent of brain injury increased dramatically. These data demonstrate that, in both humans with brain injuries and animal models of those injuries, testing a variety of

behavioral domains will allow for more accurate diagnoses, despite the incredibly wide range of performance observed across individuals.

Disclosures: **W. Hardeman:** None. **M. Hamer:** None. **P. Gifford:** None. **J. Tang:** None. **W. Pearce:** None. **J.H. Zhang:** None. **A. Obenaus:** None. **R.E. Hartman:** None.

Poster

746. Brain Injury and Trauma III

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 746.22/F5

Topic: C.10. Brain Injury and Trauma

Support: Phoenix Children's Hospital Mission Support

Title: Microglia elimination recovered peripheral inflammation-induced sleep but prolonged traumatic brain injury-induced sleep in mice

Authors: ***K. R. GIORDANO**[1,2], T. R. F. GREEN[1,2], J. B. ORTIZ[1,2], M. SABER[1,2], Y. HUR[1,2], H. MORRISON[3], J. LIFSHITZ[1,2,4], R. K. ROWE[1,2,4];
[1]Univ. of Arizona Col. of Medicine-Phoenix, Phoenix, AZ; [2]Barrow Neurolog. Inst. at Phoenix Children's Hosp., Phoenix, AZ; [3]Col. of Nursing, Univ. of Arizona, Tucson, AZ; [4]Phoenix VA Hlth. Care Syst., Phoenix, AZ

Abstract: Sleep is regulated by circadian and physiological processes, such that inflammation and cytokine production may disrupt the chemical balance required to maintain a healthy sleep profile. Traumatic brain injury (TBI) initiates inflammation and microglia activation, with subsequent sleep disturbances that can exacerbate inflammation and neurological symptoms after TBI. As such, a dynamic feedback loop links sleep, inflammation, and TBI. We hypothesized that microglia elimination with a CSF-1R inhibitor (PLX5622) would attenuate cytokine levels and differentially regulate sleep after peripheral-induced and TBI-induced inflammation. Mice were administered PLX5622 or control diet (21d) and baseline sleep was measured. PLX5622 eliminated microglia (<0.5% remained) without significant differences in physiological sleep or peripheral cytokine levels (IL-6, TNF-α, IL-1β) compared to mice on control diet. Mice on PLX5622 and control diet received lipopolysaccharide (LPS; 1.2mg/kg i.p) or midline fluid percussion injury (mFPI) and sleep was recorded for 3 days. LPS increased sleep (cumulative minutes/day) regardless of diet ($F(1,8)=11.28$, $p<0.01$). In LPS mice on control diet, sleep remained increased, whereas in mice on PLX5622, sleep returned to baseline by day 3 post-injection, with elevated peripheral IL-6 at day 1 post-injection ($F(2,10)=25.99$, $p<0.0001$). TBI increased sleep regardless of diet ($F(1,4)=17.91$, $p<0.01$). In mFPI mice on control diet, sleep returned to baseline by day 2 post-injury, whereas in mFPI mice on PLX5622, sleep remained higher than baseline over 3 days post-injury. Regardless of diet, peripheral cytokine levels were

not elevated (1 day post-injury). Thus, microglia elimination recovered sleep disturbances after peripheral-induced inflammation, but prolonged sleep disturbances after TBI, which establishes a role for microglia in the feedback loop among sleep, inflammation, and TBI. Microglia represent a plausible therapeutic target to mitigate inflammation, using sleep outcomes as a pharmacodynamic measure in treating TBI and other neuroinflammatory diseases.

Disclosures: K.R. Giordano: None. **T.R.F. Green:** None. **J.B. Ortiz:** None. **M. Saber:** None. **Y. Hur:** None. **H. Morrison:** None. **J. Lifshitz:** None. **R.K. Rowe:** None.

Poster

746. Brain Injury and Trauma III

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 746.23/F6

Topic: C.10. Brain Injury and Trauma

Support: Department of Defense (W81XWH-14-1-0558 to A.K.S.)
The State of Texas (Emerging Technology Fund to A.K.S.).

Title: Human ESC-Derived interneuron precursors grafted into the hippocampus control seizures and cognitive function in a model of temporal lobe epilepsy

Authors: D. UPADHYA[1], S. ATTALURI[1], B. HATTIANGADY[1], B. SHUAI[1], Y. LIU[2], Y. DONG[2], S.-C. ZHANG[2], ***A. K. SHETTY**[1];
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Abstract: Temporal lobe epilepsy (TLE) is drug-resistant in ~35% of patients. An alternative therapy that is efficient for reducing spontaneous recurrent seizures (SRS) is therefore needed. Grafting of mouse/rat medial ganglionic eminence (MGE) interneuron precursors has shown great promise for suppressing seizures in rodent models of TLE. However, clinical translation of MGE cell grafting strategy to TLE patients will require rigorous testing of MGE cells generated from human pluripotent stem cells (hPSCs). In this study, we examined the efficacy of human embryonic stem cell (hESC)-derived hMGE cells grafted into the hippocampus of F344 rats exhibiting Kainate-induced chronic TLE. Chronically epileptic rats (CERs) showing robust SRS received bilateral intrahippocampal grafting of hMGE cells expanded from hESCs transduced with Designer Receptors Exclusively Activated by Designer Drugs (DREADDs, hSyn-hM4D(Gi)-mCherry) through CRISPR/Cas9 technology. Four months after grafting, we employed injections of clozapine-N-oxide (CNO) to activate DREADDs in graft-derived neurons at specific periods during video-EEG recordings or behavioral studies. CNO is a drug that activates DREADDs receptors to block the activity of neurons expressing DREADDs. CNO injections (3 mg/Kg) were given every 8 hours for 2-3 days to activate DREADDs. Video-EEG

recordings were also made for 4-7 days after the washout of CNO. Before CNO injections, CERs receiving grafts displayed considerably reduced frequency of SRS than CERs receiving no grafts and normal hippocampus-dependent cognitive function in an object location test (OLT). Activation of DREADDs by CNO injections resulted in increased SRS activity and impaired cognitive function in an OLT. In contrast, EEG recordings obtained after CNO washout period revealed a pattern of SRS activity that was comparable to the pre-CNO period. Administration of CNO to CERs receiving no grafts did not alter any parameters of SRS, however. Triple immunofluorescence for human nuclear antigen (a marker of all human cells), mCherry (reflecting the expression of DREADDs in hESC-derived cells) and GABA/parvalbumin/neuropeptide Y, revealed the presence of mCherry in virtually all GABA-ergic interneurons derived from hMGE grafts, implying that an increased frequency of SRS after CNO administration correlated with the expression of DREADDs in graft-derived neurons. The results underscore that interneurons derived from hESC-hMGE cell grafts in the hippocampus are directly involved in suppressing SRS and improving hippocampus-dependent cognitive function in chronically epileptic animals.

Disclosures: **D. Upadhya:** None. **S. Attaluri:** None. **B. Hattiangady:** None. **B. Shuai:** None. **Y. Liu:** None. **Y. Dong:** None. **S. Zhang:** None. **A.K. Shetty:** None.

Poster

746. Brain Injury and Trauma III

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 746.24/F7

Topic: C.10. Brain Injury and Trauma

Support: NIH Grant, 1R01NS106907-01 to DJP and AKS

Title: Single intranasal administration of MSC-derived A1-exosomes thwarts moderate TBI-induced long-term cognitive and mood impairments

Authors: *M. KODALI[1], D.-K. KIM[2], B. SHUAI[3], R. UPADHYA[3], A. VOGEL[3], S. ATTALURI[3], D. J. PROCKOOP[3], A. K. SHETTY[3];
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Abstract: A significant percentage of people with moderate or severe traumatic brain injuries (TBIs) develop chronic neuroinflammation and persisting cognitive and mood dysfunction. The chronic effects are driven primarily by excessive inflammation in the early phase, which can prompt tissue damage and chronic neuroinflammation. In patients, the chronic effects produce severe behavioral deficits months or years after recovering from the acute symptoms. Many

drugs have been shown to reduce neuroinflammation following TBI, but none have been incorporated into the standard medical care because of limited functional efficacy or undesirable side effects. Therefore, there is a need for alternative therapeutic strategies. One strategy is to administer exosomes secreted by mesenchymal stem cells (MSCs), which have shown similar or better efficacy than MSCs for modulating inflammation in several disease models. Exosomes are particularly attractive for application in neurological disorders as they can readily cross the blood-brain barrier, quickly get incorporated into neurons and microglia following intranasal (IN) administration, and are unlikely to cause thrombosis. Our previous study showed that intravenous administration of MSC-derived A-1 exosomes is efficacious for reducing inflammation in the hippocampus, and improving learning and pattern separation function in the early post-injury period (Kim et a., PNAS, 2016). In this study, we investigated the efficacy of a single intranasal (IN) administration of A1-exosomes early after moderate TBI for thwarting long-lasting impairments in cognitive, memory and mood function. Nine-week-old mice were first subjected to unilateral controlled cortical impact injury using a velocity of 5m/s, dwell time of 300ms and injury depth of 0.8 mm. Two hours after the induction of TBI, mice received intranasal administration of A-1 exosomes (~5 billion/nostril, total, 10 billion) or vehicle. The mice were examined for cognitive and mood function using a series of behavioral tests at 7 months post-TBI. Animals that received vehicle after TBI displayed cognitive dysfunction, recognition memory problems, pattern separation deficits as well as anhedonia. Remarkably, animals that received A-1 exosome treatment after TBI showed similar cognitive, memory and pattern separation function as naïve control animals. These animals also exhibited a higher level of neurogenesis in the hippocampus contralateral to injury. Analyses of microglia and astrocytes are currently in progress. Thus, IN administration of A-1 exosomes shortly after moderate or severe TBI has promise for preventing long-term cognitive and mood impairments.

Disclosures: **M. Kodali:** None. **D. Kim:** None. **B. Shuai:** None. **R. Upadhya:** None. **A. Vogel:** None. **S. Attaluri:** None. **D.J. Prockoop:** None. **A.K. Shetty:** None.

Poster

746. Brain Injury and Trauma III

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 746.25/F8

Topic: C.10. Brain Injury and Trauma

Support: NIH P30 NS061800
NIH NINDS F32NS106732
VA Merit Review Grant I01-BX002949
DoD CDMRP W81XWH-18-1-0598

Title: Functional analysis of granule cells generated during post-traumatic hippocampal neurogenesis

Authors: *A. K. WILSON[1], E. SCHNELL[2,3];
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Abstract: Individuals with penetrating or severe traumatic brain injury (TBI) are at an increased risk of developing posttraumatic epilepsy (PTE). In a number of animal models, hippocampal neurogenesis increases after TBI, and these new neurons contribute to hippocampal network function. These neurons develop a number of morphologic abnormalities that suggest differential acquisition of inputs during their maturation, which might have functional consequences at the network level. However, it is unclear how different granule cell input pathways might be differentially affected, and whether aberrantly wired granule cells contribute to hippocampal hyperexcitability or alternatively might protect against hyperexcitable circuit function in other regions. To evaluate this, we are using a controlled cortical impact (CCI) model of TBI in conjunction with the transgenic pulse labeling of newborn neurons to identify granule cells born after TBI for both morphologic and functional analysis. Similar to previous results, we find a significantly increased number of labeled neurons in mice after CCI when compared with sham animals, and these neurons demonstrate aberrant cell morphology after TBI. We are using slice electrophysiology to determine how these aberrant cells incorporate into circuits using whole-cell recordings of both newly born neurons as well as target cells. Through this work, we hope to assess the hypothesis that the aberrant development and growth of neurons generated after TBI might lead to hyperexcitable circuit formation.

Disclosures: **A.K. Wilson:** None. **E. Schnell:** None.

Poster

747. Spinal Cord Injury and Repair

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 747.01/F9

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH/NINDS grant R01NS103481
DOD grant SC140089
Shriners grant SHC 86000

Title: Propriospinal neurons mediate rehabilitative recovery of skilled forelimb reaching after cervical injury

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Abstract: Cervical injury to the spinal cord results in diminished or complete loss of skilled forelimb mobility, depending on the severity of the injury. Such, goal-directed reaching and grasping behaviors are primarily driven by corticospinal neurons. After spinal cord injury (SCI), rehabilitation is thought to mediate re-organization and plasticity of spared supraspinal-propriospinal circuits leading to partial recovery of function. Whether plasticity along these circuits is instrumental in promoting recovery of skilled forelimb patterning remains elusive. Bilateral lesions of the corticospinal tract and dorsal columns at C5 results is a 50% loss in pellet retrieval that recovers to normal levels over a 4 weeks period of training. To determine the pathways contributing to recovery, we injected retrograde transportable lentivirus expressing tetracycline-inducible hM4Di-mCherry (inhibitory DREADD) into the rat C6 -T1 spinal cord, the region containing the majority of spinal motor neurons responsible for forelimb targeted reaching and grasping. This virus supports selective up take at synaptic terminals and retrograde transport to their somas. A secondary injection of AAV2-rtTAV16 (Tet-On) into either C3/C4 spinal cord, red nucleus or both limited expression within regional neuronal population innervating the C6-T1 spinal cord. Reversible silencing of C3-C4 propriospinal neurons using clozapine-N-oxide caused partial loss of this recovery with near complete loss of recovery only when both PN and RN pathways were co-silenced. Tracing studies demonstrated that C3/C4 propriospinal neurons not only established vGlut2 + synapses onto C6-T1 spinal motor neurons but also extended an axon branch into the lateral reticular nucleus, thought important in forming an internal motor copy for adjustment of forelimb patterning during movement. Anterograde tracing of the corticospinal tract (CST) shows sprouting of severed CST fibers in the upper cervical spinal cord and red nucleus after training. These finding demonstrate the role of spared pathways on recovery of forelimb reaching behaviors after rehabilitative training.

Disclosures: G.M. Smith: None. **K.M. Keefe:** None. **C. Li:** None. **L.G. Kirby:** None. **I.S. Sheikh:** None.

Poster

747. Spinal Cord Injury and Repair

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 747.02/F10

Topic: C.11. Spinal Cord Injury and Plasticity

Support: MOST 105-2628-B-110-002-MY3
MOST 108-2636-B-110-001

Title: Blockade of $5HT_7$ receptor enhance respiratory recovery following daily acute intermittent hypoxia in rats with chronic cervical spinal contusion

Authors: *K.-Z. LEE, M.-J. WU;
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Abstract: Intermittent hypoxia can elicit respiratory neuroplasticity to augment respiratory motor activities following hypoxia (i.e., long-term facilitation). This type of respiratory neuroplasticity is primarily mediated by activation of Gq-protein coupled 5-HT2 receptors but constrained by Gs-protein coupled 5-HT7 receptors. Accordingly, the present study hypothesized that inhibition of 5-HT7 receptors can enhance the effect of intermittent hypoxia on the respiratory function following cervical spinal cord injury. The ventilatory behaviors of unanesthetized mid-cervical contused rats were measured before, during and after daily acute intermittent hypoxia [10 episodes of 5 min of hypoxia (10 % O_2, 4 % CO_2, 86 % N_2) with 5 min of normoxia intervals for 5 days] at 8 weeks post-injury. Animals were daily received either 5-HT7 receptor antagonist (SB269970, 4 mg/kg, i.p.) or vehicle (DMSO) 5 min before daily acute intermittent hypoxia. The results demonstrated that intermittent hypoxia induced a similar increase in the tidal volume between two groups at the first day; however, the baseline tidal volume was significantly greater in animals received 5-HT7 receptor antagonist at 2-3 days during daily acute intermittent hypoxia. These results suggested that blockade of 5-HT7 receptors can augment intermittent hypoxia-induced respiratory neuroplasticity to enhance respiratory recovery following chronic cervical spinal cord injury.

Disclosures: K. Lee: None. **M. Wu:** None.

Poster

747. Spinal Cord Injury and Repair

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 747.03/F11

Topic: C.11. Spinal Cord Injury and Plasticity

Support: National Institutes of Health/National Institute of Neurological Disorders and Stroke
US Department of Veterans Affairs
Paralyzed Veterans of America

Title: Spinal plasticity at multiple-spinal cord segments in humans with spinal cord injury

Authors: *H. JO[1,2], N. DE LA OLIVA[1], M. A. PEREZ[1,3,2];
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[2]Shirley Ryan Ability Lab., Chicago, IL; [3]Bruce W. Carter Dept. of Veterans Affairs Med. Ctr., Miami, FL

Abstract: A single session of repeated non-invasive stimulation using the principles of spike-timing dependent plasticity (STDP) improves voluntary motor output in humans with spinal cord injury (SCI). Here, we applied the principles of STDP in multiple-spinal cord segments by using transcutaneous electrical stimulation of the spinal cord between L2-L3 and L4-L5 spinal segments timed with transcranial magnetic stimulation (TMS) of the leg representation of the primary motor cortex. Twenty-two individuals with chronic incomplete cervical, thoracic, or lumbar SCI were randomly assigned to the 20 sessions of stimulation (STDP+exercise) or sham (sham STDP+exercise) group. Stimulation or sham sessions were composed of 180 pairs of stimuli applied for ~30 min followed by lower-limb exercise for ~45 min. During STDP, electrical stimuli were applied at spinal cord segments ~1-2 ms after corticospinal volleys evoked by TMS arrived at corresponding corticospinal-motoneuronal synapses. We found that the size of corticospinal responses elicited by TMS and maximal voluntary contraction in targeted muscles increased when exercise was combined with STDP but not sham-STDP. Both measurements were further improved with repeated number of sessions in the STDP group. Clinical functional outcomes improved after both protocols but to a greater extent after STDP than sham-STDP. Our findings indicate that multisegmental stimulation of spinal synapses is an effective strategy to enhance exercise-mediated recovery in humans with SCI.

Disclosures: H. Jo: None. **N. de la Oliva:** None. **M.A. Perez:** None.

Poster

747. Spinal Cord Injury and Repair

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 747.04/F12

Topic: C.11. Spinal Cord Injury and Plasticity

Support: National Institutes of Health/National Institute of Neurological Disorders and Stroke
US Department of Veterans Affairs

Title: Transcutaneous spinal cord stimulation influences cortical and subcortical networks in humans with spinal cord injury

Authors: *F. D. BENAVIDES[1,2], V. EDGERTON[3], Y. P. GERASIMENKO[4], M. A. PEREZ[1,5,2];
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Los Angeles, Los Angeles, CA; [4]Pavlov Inst. of Physiol, St Petersburg, Russian Federation; [5]Bruce W. Carter Dept. of Veterans Affairs Med. Ctr., Miami, FL

Abstract: Transcutaneous electrical stimulation of the spinal cord (TESS) promotes functional recovery in humans with spinal cord injury (SCI) but its mechanisms of action remain largely unknown. We hypothesized that TESS-aftereffects on recovery relate to contributions from cortical and subcortical networks. Here, we examined motor evoked potentials elicited by cortical and subcortical stimulation of corticospinal axons and the activity in intracortical circuits in arm muscles before and after a commonly used TESS protocol (30 Hz pulses with a 5 kHz carrier frequency) and sham-TESS for 20 min between the C5-C6 spinal segments in humans with and without chronic incomplete cervical SCI. We found that the size of subcortically but not cortically evoked motor responses increased in proximal and distal arm muscles for 60 min after TESS, but not sham-TESS, in controls and SCI participants. Intracortical inhibition increased after TESS in both groups. Stimulation at 30Hz, without the 5 kHz carrier frequency, facilitated subcortical motor evoked responses without changing intracortical inhibition, suggesting that the 5 kHz carrier frequency contributed to the cortical effects. Notably, performance in hand and arm functional tasks improved after TESS, but largely, when TESS was used with the 5 kHz carrier frequency. These results demonstrate for the first time parallel effects of TESS on cortical and subcortical networks, having an excitatory effect at the spinal level and an inhibitory effect at the cortical level. We argue that this dual effect supports the recovery of limb function following SCI.

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Poster

747. Spinal Cord Injury and Repair

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 747.05/F13

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Dept. of Defense CDMRP Grant #W81XWH-17-1-0538

Title: Techniques for spinal cord stimulation to restore bladder function in rats

Authors: S. J. ILHAM[1], N. NOLTA[1], C. HARDY[2], P. SMITH[2], ***M. HAN**[1]; [1]Biomed. Engin., Univ. of Connecticut, Storrs Mansfield, CT; [2]Univ. of Connecticut Hlth., Farmington, CT

Abstract: Spinal cord injury (SCI) causes motor and sensory deficits that can severely impact the quality of life including interruption of voluntary bladder control. Epidural electrical

stimulation is a commonly used treatment for emptying the bladder in SCI patients, but low efficacy and incomplete voiding are persistent problems mainly due to the broad spread of the electrical field. Studies in the feline model have shown that chronic intraspinal stimulation of the dorsal gray commissure in the sacral spinal segment can induce micturition by innervating the sacral parasympathetic nucleus and Onuf's nucleus. Applying a similar technique in the rat model may enable refinement of stimulation targets and urodynamic evaluation. We have established robust surgical and measurement procedures in the rat model, including: (1) suprapubic catheterization to the urinary bladder, (2) dorsal laminectomy to expose the lumbar-sacral spinal cord, (3) stimulus target localization comprising of an automated stimulation waveform generation in the perigenital skin and evoked cord dorsum recording with a surface electrode via a differential recording system, (4) cystometric evaluation involving pressure transducer for the bladder pressure and load cell to quantify voiding, and (5) post-mortem immunohistochemical staining of neurons and glial cells. We have completed four non-survival surgeries involving all of these procedures, and confocally-imaged the spinal cord tissues enabling quantification of tissue responses to stimulation. This work will enable testing of a less-invasive focused ultrasound stimulation using a miniatured ultrasound transducer as well as intraspinal stimulation using penetrating microelectrode arrays in both non-survival and survival experiments.

Disclosures: S.J. Ilham: None. **N. Nolta:** None. **C. Hardy:** None. **P. Smith:** None. **M. Han:** None.

Poster

747. Spinal Cord Injury and Repair

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 747.06/F14

Topic: C.11. Spinal Cord Injury and Plasticity

Title: Tracking rehabilitation as an effect mediator, moderator or covariate in spinal cord injury interventional clinical trials: The international spinal cord injury physical therapy - occupational therapy basic data set

Authors: *E. C. FIELD-FOTE[1], K. D. ANDERSON[2], L. A. T. JONES[3], R. RUPP[4], V. K. NOONAN[5], L. A. HARVEY[6], M. W. M. POST[7], S. J. MULROY[8], M. SCHMIDT-READ[9], A. M. BRYDEN[2], M. J. MULCAHEY[9], F. BIERING-SORENSEN[10];
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Abstract: Background & Purpose: Nearly all interventional trials use the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) as the primary or secondary endpoint of neurologic recovery. Since physical and occupational therapies (PT-OT) promote use-dependent plasticity that has the potential to impact the ISNCSCI scores, it is important to consider the influence of these therapies when provided in conjunction with clinical interventional trials.
Methods: To facilitate efficient tracking of therapy content and dose (time), an international workgroup under the auspices of the International Spinal Cord Injury Society (ISCoS) Data Set Committee developed a standardized collection and reporting tool and accompanying syllabus: The International Spinal Cord Injury PT-OT Basic Data Set. During the process of developing the data set, the workgroup solicited input from numerous sources including from PTs and OTs at the institutions where the workgroup members are affiliated, and at the 2017 ISCoS meeting. Taking all feedback into consideration, the workgroup modified the data set over multiple iterations.
Results: The draft version of the PT-OT Data Set contains 7 items. International audience feedback about how the data set and the syllabus meet its goals is invaluable. This poster will provide an interactive opportunity for discussion and feedback will be incorporated into the dataset refinement process.

	ITEM	TIME (in minutes)					
ACTIVITY-DIRECTED INTERVENTIONS							
A	Bed/seated control activities: balance, seated transfers, bed mobility	<10	10-19	20-29	30-44	45-60	>60
B	Standing control activities: standing, balance, standing transfers weight bearing	<10	10-19	20-29	30-44	45-60	>60
C	Walking, stairs (inside, outside)	<10	10-19	20-29	30-44	45-60	>60
D	Gross motor UE: dressing, washing, manual wheelchair mobility	<10	10-19	20-29	30-44	45-60	>60
E	Fine motor UE: grooming, self-feeding, buttoning, zipping, adjustment of clothing	<10	10-19	20-29	30-44	45-60	>60
IMPAIRMENT-DIRECTED INTERVENTIONS							
F	Strength training (including electrical stimulation for strength)	<10	10-19	20-29	30-44	45-60	>60
G	Endurance training (including electrical stimulation for endurance)	<10	10-19	20-29	30-44	45-60	>60
TOTAL INTERVENTION TIME							
	Sum of time spent on individual items	<10	10-19	20-29	30-44	45-60	>60

Discussion & Conclusions: The intent of the PT-OT Basic Data Set is to provide a uniform

mechanism to efficiently track the content and dosing of PT-OT sessions without undue burden on therapists.

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Poster

747. Spinal Cord Injury and Repair

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 747.07/F15

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIDILRR Grant 90SI5016

Title: The troublesome trio of spasticity: Clonus, spasms, stiffness - Characteristics and impact

Authors: E. C. FIELD-FOTE[1], C. L. FURBISH[1], N. TRIPP[2], W. SWEATMAN[3], M. HAYAT[2], *S. P. ESTES[4], A. W. HEINEMANN[5];
[1]Shepherd Ctr., Atlanta, GA; [2]Georgia State Univ., Atlanta, GA; [3]Georgia Gwinnett Col., Lawrencefille, GA; [4]Shepherd Center/Crawford Res. Inst., Atlanta, GA; [5]Northwestern Univ. Feinberg Sch. of Med., Chicago, IL

Abstract: Background: Spasticity is among the most prevalent and problematic secondary conditions following spinal cord injury (SCI). Multiple definitions of spasticity exist, however some have limited relationship with the way this phenomenon is experienced by persons with SCI.
Methods: Investigators at 6 SCI Model System Centers in the US collaborated on a REDCap-based survey study. Questions were intended to identify characteristics of spasticity as experienced by persons with SCI. For example: for hyperreflexia (clonus): “My spasticity causes my legs to shake”; for spontaneous spasms: “My spasticity causes my legs to move on their own”; for hypertonia (stiffness): “My spasticity causes my legs to be stiff”. We quantified relationships among characteristics of spasticity and scores on measures of spasticity-related impact on function and quality of life (SCI-SET and PRISM).
Results: Survey results from 1,200+ individuals with SCI were acquired. Data were collapsed across injury level and severity; only data related to leg spasticity are reported here.
Characteristics of spasticity experienced *Often/Very Often* were [% of respondents]
Stiffness (hypertonia) [64.6%]
Spontaneous spasms [56.9%]
Clonus (hyperreflexia) [50.3%]

Impact of spasticity, based on the SCI-SET query *"During the past 7 days, how have your spasticity symptoms affected…*" elicited *Negative* responses from ≥50% of respondents for 15 of 35 items. The 2 items with highest % of *Negative* responses were *"your feeling of physical comfort* (70.3%)" and *"your feeling of control over your body* (68.8%)". The single item for which respondents most often reported spasticity had a positive influence was *"ability to change positions in bed"* (8.6%).
Impact of spasticity, based on the PRISM query *"In the past 7 days, my abnormal muscle control or involuntary muscle movement…"* elicited responses of *Often/Very Often* from ≥20% of respondents for the items: 1) "*caused me to depend on others",* 2) *"bothered me a lot",* 3) *"made me feel out of control of my body",* 4) "*kept me from being as happy as I could be",* 5) *"made me feel frustrated".*
Discussion: While the classic definition of spasticity (Lance, 1980) is convenient for scientists with its exclusive focus on stretch reflexes, the definition has only a limited relationship with spasticity as experienced by persons with SCI. The comprehensive definition adopted by an international consensus group (the SPASM Consortium, 2005) is a more accurate reflection of the phenomenon. Broader understanding of spasticity would promote efforts to identify interventions that can address this common and problematic secondary sequela of SCI.

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Poster

747. Spinal Cord Injury and Repair

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 747.08/F16

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH grant EB007615

Title: The application of correlational bandits in large decision spaces to spinal cord injury clinical treatments

Authors: *Y. QIN, J. W. BURDICK;
Caltech, Pasadena, CA

Abstract: This work describes the Gaussian process bandits problem's application in the search for the optimal strategy from large decision spaces in a clinical setting. Spinal cord injury patients can achieve partial recovery of lost muscle functions through electrical stimulation applied through an epidural multi-electrode array to the spinal cord. The challenge of this treatment is to determine the stimulus pattern that leads to the best patient performance, as the performances vary significantly when given different stimulus patterns. The optimal stimulus

pattern, which consists of the active electrodes and their polarities, amplitudes, and pulse train frequency, varies significantly across patients and is time-variant. Therefore, the clinicians must determine the optimal pattern from an extremely large decision space for each patient through a laborious approach. This problem, as well as many others, can be modeled as a recommender system with unknown prior distributions. Each decision gives a stochastic reward and new decisions are made based on the previous rewards. To maximize the total reward in a finite number of trials, we need to balance the exploration of various strategies and the exploitation of the currently optimal strategies. Additionally, geometrically similar stimulation patterns are expected to lead to similar rewards since they generate similar electric fields in the spinal cord. We derived this correlational property as the kernel function. The Gaussian process - Upper Confidence Bound (GP-UCB) algorithm was implemented for stimulation pattern selection. We also used supervised learning methods such as Random Forest to extract areas in the spinal cord and their corresponding features that are closely associated with the patients' performances. The performance of the GP-UCB algorithm was evaluated in simulation experiments as well as using offline clinical data collected from two quadriplegic patients with the electrode array implant. We show that the algorithm converges faster in the simulation experiments comparing to the epsilon-greedy method in the independent bandits setting. Given the confined search space of a limited number of stimulation patterns in the clinical data, the GP-UCB algorithm is able to propose the stimulation pattern with the relatively best performance faster than the epsilon-greedy method with no arm correlations.

Disclosures: Y. Qin: None. **J.W. Burdick:** None.

Poster

747. Spinal Cord Injury and Repair

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 747.09/F17

Topic: C.11. Spinal Cord Injury and Plasticity

Title: Compensatory plastic changes in spinal motoneurons after rehabilitation in rats with motor cortex lesion

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Abstract: Several neuropathologies associated with the degeneration of the corticospinal tract show impairment of motor functions. Rehabilitation protocols promote the functional recovery of such pathologies, in part, because they favor the expression of compensatory plastic mechanisms. However, there is little evidence of changes in the synaptic contacts between the terminals of the corticospinal tract and its postsynaptic counterpart in the spinal motoneurons, after a rehabilitation program after anterograde lesion of the corticospinal tract. Stereotaxic lesion with kainic acid in the primary motor cortex was induced in adult female rats. 15 days later, motor function was evaluated in a Rota-rod device and immediately afterwards they were integrated into a rehabilitation protocol in a treadmill type continuous band for 7 continuous days. The following day, the motor performance in the Rota-rod was evaluated. In parallel, the numerical density of dendritic spines was quantified in motor neurons of a thoracic-lumbar segment of the spinal cord. The pharmacological lesion caused a poor motor performance that improved after the rehabilitation stage. Likewise, the density of dendritic spines increased after rehabilitation. The appearance of the clinical symptoms of neurological damage caused by the degeneration of the corticospinal tract is accompanied by spontaneous plastic responses at the synaptic level. In accordance with the present results, such plastic processes were enhanced by induced rehabilitation. This suggests the design of rehabilitation strategies that consider the plastic capacity of the spinal circuits in conditions of Wallerian degeneration of the corticospinal tract.

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Poster

747. Spinal Cord Injury and Repair

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 747.10/F18

Topic: C.11. Spinal Cord Injury and Plasticity

Title: Enhancement of motor function with vagus nerve stimulation following a C7/C8 spinal cord injury

Authors: *M. TORRES[1], M. DARROW[2], Z. HAIDER[6], M. SOSA[3], J. TRAN[6], F. SMITH[6], S. A. HAYS[4], M. P. KILGARD[5];
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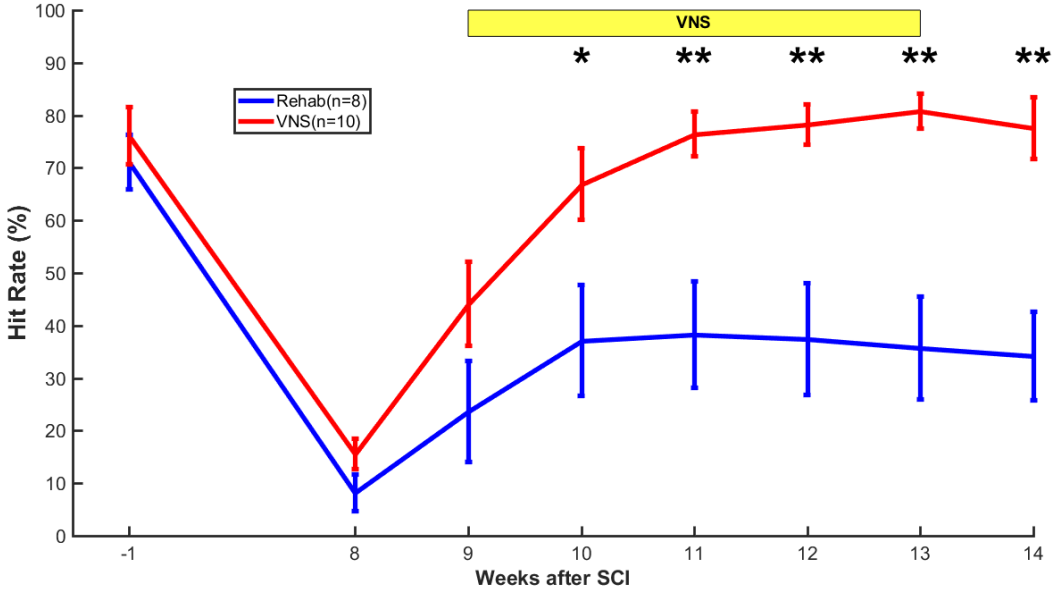
Abstract: There are over 12,000 spinal cord injuries that occur on an annual basis within the United States of America. Recently, we have successfully demonstrated a novel therapy to treat motor dysfunction in animal models of stroke and spinal cord injury (SCI) by pairing motor

training with vagus nerve stimulation (VNS). We describe a design to test the hypothesis that repeated pairing of VNS with a motor behavioral task will drive enhancement of motor function following a bilateral spinal cord contusion injury at C7. VNS repeatedly paired with forelimb movement results in robust neural plasticity in motor cortex. Pairing VNS with the isometric pull task following spinal cord injury to the C5 level has driven significant enhancement or motor function compared to rehabilitation alone. We hypothesize that VNS paired with motor movements will also enhance plasticity and drive recovery on the isometric pull task. This study will determine whether VNS therapy will be effective for patients with an injury to this specific level, or with damage to motor neuron pools, and further assess plasticity. To test whether VNS could improve recovery of motor function after SCI, specifically damaging motor neuron pools, we have trained rats on the isometric pull task, a motor task designed to test forelimb strength. Rats were trained to pull the handle at a force of 120 grams with their right forelimb. After each rat was proficient at the task, the rat underwent surgery during which it will receive a bilateral SCI with the IH impactor at the C7/C8 level (Infinite Horizons impactor). Pairing VNS with the isometric pull task significantly enhanced peak pull force when compared to rats that underwent rehabilitative training on the isometric pull task without VNS. We have also investigated other motor assessments as well as changes occurring in the spinal cord due to plasticity.



Disclosures: **M. Torres:** None. **M. Darrow:** None. **Z. Haider:** None. **M. Sosa:** None. **J. Tran:** None. **F. Smith:** None. **S.A. Hays:** None. **M.P. Kilgard:** None.

Poster

747. Spinal Cord Injury and Repair

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 747.11/F19

Topic: C.11. Spinal Cord Injury and Plasticity

Title: Strengthened descending neural pathways mediate improvements in upper extremity function following transcutaneous electrical stimulation and activity based therapy in an individual with a cervical, complete spinal cord injury

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Abstract: Spinal cord injuries (SCI) at the cervical level leads to severe upper extremity (UE) impairments that decrease independence with daily tasks and impair an individual's quality of life. Transcutaneous electrical stimulation (tcES) is a non-invasive technique of neuromodulation that can be used to facilitate functional recovery after SCI. The aim of this study was to evaluate if tcES delivered to the cervical spinal cord during activity-based-therapy (ABT) can improve UE function and induce plastic changes in an individual with a chronic and complete SCI at the cervical level (C3, AIS A). A 36 y/o male completed a series of 80 training sessions during which he received tcES combined with ABT. Bipolar and modulated (5kHz) current was delivered to the participant's cervical spinal cord for a minimum of 1h per training session with ABT over 80 sessions. Clinical, biomechanical and neurophysiological assessments were completed before, at the mid-point and after training. Clinical assessments included UE touch (monofilament) and temperature discrimination across dermatomes and Capacity of Upper Extremity test (CUE-T). For the biomechanical assessments, we assessed UE kinematics during forward reach and force modulation during hand grip. For the neurophysiological assessments, transcranial magnetic stimulation evoked potentials (MEPs) in UE muscles were measured to assess changes in corticospinal tract integrity; while acoustic startle reflex responses (ASR) were recorded from UE, trunk and leg muscles to assess changes in the reticulospinal pathway. Improvements in touch and temperature discrimination sensation at C6, C7 and T1 as well as an increase in the number of upward reaches performed over 30s were detected. An increase in reaching distance (+80%) and finger displacement velocity (x3) as well as a decrease in shoulder displacement (-45%) were seen during forward reach. Force production during hand grip increased (x3) in both hands. MEPmax increased in 15 out of 18 UE and trunk muscles recorded. The incidence of ASR responses increased in 18 out 22 UE and trunk muscles recorded. Our results indicate that tcES combined with ABT strengthened the spared connections and/or promoted the emergence of new connections along the corticospinal and reticulospinal pathways in an individual with a complete injury. These plastic changes are likely to have contributed to

improvements in the sensory and motor performances detected from the clinical and biomechanical assessments. Further studies are required to evaluate how training interventions that combine tcES and ABT can facilitate neural plasticity and improve UE function after spinal cord injury.

Disclosures: D.M. Rouffet: None. **Y.P. Gerasimenko:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); inventorship rights on intellectual property, Regents of the University of California to NeuroRecovery Technologies and its subsidiaries, shareholder, NeuroRecovery Technologies. **S.J. Harkema:** None. **J.M. D'Amico:** None.

Poster

747. Spinal Cord Injury and Repair

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 747.12/F20

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Wings for Life
Forschungskredit "Candoc" University of Zurich

Title: Deep brain stimulation of the mesencephalic locomotor region to improve motor function after incomplete spinal cord injury

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Abstract: Functionally or anatomically incomplete spinal cord injury (SCI) is characterized by sparing of some fibers still connecting the brain with the spinal cord caudal to the lesion. Loss or severe impairment of motor control and locomotion is common, with limited potential for functional recovery. As a novel strategy for the treatment of large but incomplete spinal cord injuries, we suggest deep brain stimulation (DBS) of the midbrain locomotion center (mesencephalic locomotor region, MLR), which initiates and controls locomotion. Acute electrical stimulation experiments in rats with incomplete spinal cord injury conducted in our lab showed that hindlimb locomotor function improves during DBS of the MLR in chronic SCI. While only limited responses were observed up to seven days after injury, MLR-DBS was able to reestablish a high degree of locomotion five weeks after injury, even in animals with initially very severe functional deficits and white matter lesions up to 80-95%. In order to consider DBS of the MLR as a potential treatment for incomplete spinal cord injury in humans, an evaluation of whether DBS-enabled locomotor training leads to long-term reestablishment of physiological movement patterns under voluntary movement control is necessary. We hypothesized that repeated electrical stimulation-induced locomotion after incomplete SCI can enhance anatomical

rearrangements and thus lead to permanent improvement of motor function. The long-term effects of daily repeated MLR-DBS during physical training after incomplete spinal cord injuries in rats were analyzed. Functional readouts are parameters from kinematic analysis during overground locomotion and BBB scoring. Anatomically, we study the branching pattern of spared reticulospinal fibers (from nucl. gigantocellularis) in the lumbar spinal cord. The project's results are directly translated to a clinical study on MLR-DBS in human patients with chronic SCI.

Disclosures: A. Hofer: None. **M.I. Scheuber:** None. **A.M. Sartori:** None. **M.E. Schwab:** None.

Poster

747. Spinal Cord Injury and Repair

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 747.13/F21

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH R15NS082711
NIH R25GM061331

Title: Using body weight support over ground training system to improve locomotion following contusion spinal cord injury

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Abstract: Body Weight supported treadmill training (BWSTT) has been shown to rehabilitate treadmill walking after spinal cord injury (SCI) in animals. However, whether this form of training has the capacity to translate to over ground walking associated with improved stepping remains unresolved. The circular Bi-ambulatory Rodent Trainer (cBART) is a useful tool to train and to assess the animals in their natural, quadrupedal gait. CBART is constructed with cost effective and easily accessible materials. The rotating arm made from PVC pipe is attached to a caster bracket base. One end of the arm is modified to attach a harness that secures the animal and the other end has adjustable counter weight to provide body weigh support. Sliding the counter weight at one end modifies body support. A video camera is attached on the lever arm to capture continuous rat locomotion. The animals can ambulate with weight body support in a circular path over ground with their right or left hindlimb and forelimb in view (Marvin et.al.,

2015). In this study, we compared the effect BWSTT versus training with cBART on the recovery of locomotor function in spinally contused rats. Spinally contused rats received BWSTT for 8 weeks. One group of rats then received quadrupedal over ground walking using cBART in addition to treadmill training. Following eight weeks of exercise training, tests of locomotor recovery were performed. Preliminary data suggests, forward ankle movement as a measure of initiation of step in the hindlimb, paw placement, plantar paw placement and, hip-ankle-toe (HAT) excursion angle as a measure for multiple joint function improved significantly in the combined BWSTT+ cBART (n=8) trained group when compared to BWSTT(n=8) alone. These results suggest BWSTT combined with cBART over ground training is optimal for improved locomotor recovery in spinally contused rats. Additional analysis is being performed to examine intralimb and interlimb coordination. These findings have implications for improving rehabilitation strategies after spinal cord injury and can address whether current BWSTT therapies alone provide optimal training for locomotor recovery.

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Poster

747. Spinal Cord Injury and Repair

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 747.14/F22

Topic: C.11. Spinal Cord Injury and Plasticity

Support: International Paraplegic Foundation
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Alberta Innovates

Title: Closed loop electrical stimulation technologies to modulate autonomic function after spinal cord injury

Authors: *J. W. SQUAIR[1], M. GAUTIER[1], J. GANDAR[2], E. MARTIN MORAUD[3], N. CHO[4], J. SORIANO[7], M. A. ANDERSON[8], K. BARTHOLDI[4], S. ANIL[1], A. ROWALD[1], N. D. JAMES[5], C. KATHE[9], Z. SARAFIS[1], L. MAHE[1], X. KANG[1], N. VACHICOURAS[1], S. P. LACOUR[6], Q. BARRAUD[10], G. COURTINE[4], A. A. PHILLIPS[7];
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Genève, Switzerland; [3]EPFL, Translational Neural Engin. Lab., Lausanne, Switzerland; [5]SV BMI UPCOURTINE, [4]EPFL, Geneve, Switzerland; [6]EPFL, Lausanne, Switzerland; [7]Univ. of Calgary, Calgary, AB, Canada; [8]Swiss Federal Inst. of Technology, Lausanne, Geneve, Switzerland; [9]Swiss Federal Inst. of Technol. Lausanne, Geneve, Switzerland; [10]EPFL - Ctr. For Neuroprosthetics, Geneve, Switzerland

Abstract: Severe spinal cord injury interrupts descending sympathetic projections that modulate cardiovascular function. This interruption leads to frequent bouts of hypertension (autonomic dysreflexia) and orthostatic hypotension, conditions that lead to increased risk for cardiovascular disease and potentially death. Here, we developed a conceptual and engineering framework to design an electrical spinal cord neuroprosthesis that targets the sympathetic circuitry within the spinal cord in closed loop to prevent the development of these conditions. We first developed a rodent model of sympathetic dysfunction after spinal cord injury. For this, we visualized catecholaminergic fibers originating from the brainstem autonomic centers in TH:Cre rats who underwent a severe upper thoracic contusion. We found a near complete interruption of TH+ descending sympathetic axons, which led to an immediate decrease in resting hemodynamics and to the development of aberrant cardiovascular reflexes. To target the sympathetic circuitry within the spinal cord with epidural electrical stimulation, we mapped the hemodynamic responses to stimulation applied at each level of the thoracic and lumbar segments. We identified highly-specific hotspots that effectively modulated hemodynamics. We then used intersectional neuroanatomical tracing and activity-dependent signalling pathways to uncover the connectome of the spinal cord and splanchnic ganglia circuits engaged by the stimulation. Using optogenetic manipulations, we established causal relationships between the modulation of these circuits and the hemodynamic response to the stimulation. We then combined CT scans, MRI sequences and computational modelling to design a neuroprosthesis that targets cardiovascular hotspots in the spinal cord. This neuroprosthesis was fabricated using e-dura technology. We therefore have termed this implant *autonomic e-dura*. Stimulation via our *autonomic e-dura* can be controlled in closed loop to precisely modulate blood pressure in both acutely and chronically injured animals.

Disclosures: J.W. Squair: None. **M. Gautier:** None. **J. Gandar:** None. **E. Martin moraud:** None. **N. Cho:** None. **J. Soriano:** None. **M.A. Anderson:** None. **K. Bartholdi:** None. **S. Anil:** None. **A. Rowald:** None. **N.D. James:** None. **C. Kathe:** None. **Z. Sarafis:** None. **L. Mahe:** None. **X. Kang:** None. **N. Vachicouras:** None. **S.P. Lacour:** None. **Q. Barraud:** None. **G. Courtine:** None. **A.A. Phillips:** None.

Poster

747. Spinal Cord Injury and Repair

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 747.15/F23

Topic: C.11. Spinal Cord Injury and Plasticity

Support: 2018K000276
NRF-2018K1A4A3A01064257

Title: Exercise accelerates epigenetic changes after spinal cord injury

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Abstract: Spinal cord injury (SCI) is a major devastating lesion which cause various pathophysiological mechanisms. Recent studies reported that epigenetic changes induced by SCI might modulate regeneration-associated genes (RAGs) which control the regeneration capacity and neuronal growth. Epigenetic changes are widely considered to play an important role, but experimental evidence to support this hypothesis has not been addressed. Physical exercise has beneficial effects on the modulation of neuronal plasticity and promoting intrinsic growth capacity through epigenetic modulation in the brain. This study was carried out to investigate whether treadmill exercise affects epigenetic change and functional recovery after SCI. We made contusion models at thoracic spinal cord using adult Sprague-Dawley rats, and performed dot blotting of 5-methylcytosine (5mc) and 5-hydroxymethylcytosine (5hmc), and real-time PCR to analyze the expression level of Ten-eleven translocation (TET) family, RAGs, and pro-inflammatory cytokines as well as histological and functional assessments. Rats which were placed in the treadmill without running were considered as controls. Within the motor cortex of the brain of rats which received treadmill exercise for 12 weeks, the staining intensity and the expression level of 5hmC of cortical neurons were significantly increased. The mRNA levels of TET family (TET1, TET2, and TET3) of brain tissues were also increased more in the exercise group than in control at 12 weeks after SCI. Pro-inflammatory genes including interleukin-1 beta, interleukin-6 and tumor necrosis factor alpha were decreased, and RAGs were increased more in the exercise group. Therefore, we concluded that the 12-week treadmill exercise promotes the epigenetic changes and improves functional recovery after SCI.

Disclosures: **J. Hyun:** None. **J. Hong:** None.

Poster

747. Spinal Cord Injury and Repair

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 747.16/F24

Topic: C.11. Spinal Cord Injury and Plasticity

Title: The problem of whiplash and possible treatment

Authors: *G. HOLSTEGE[1], H. SUBRAMANIAN[2];
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Abstract: Whiplash Associated Disease (WAD) is a disease many people suffering from. More than 75% of the cases are caused by car accidents, in which the car driver, waiting in line in traffic, because of a red traffic light or a traffic block, is hit by another car from behind. In most cases this accident is completely unexpected for the driver of the front car, which means that the neck muscles of this driver were relaxed during the accident. During the collision the body of the driver in the front car is pushed forward with the head staying behind, resulting in a sudden and strong stretching of the relaxed anterior neck muscles. Subsequently, when the front car stops, the body of the driver is pushed backward leaving the head in an anterior position resulting in very strong stretching of the posterior neck muscles. This strong flexion-extension movement often causes large damage of the neck muscles and of the facet joints, capsules and ligaments of the upper cervical vertebrae. These neck muscles and upper cervical facet joints and ligaments send a large amount of information to the spinal cord regarding the position of the head in space. In the upper cervical spinal cord this information is relayed to higher brain levels of which the mesencephalic periaqueductal gray (PAG) and adjoining areas are the most important. Other information regarding the position of the head originates from the vestibular nuclei and from the visual system. Based on this information the mesencephalon determines the position of the head and the eyes. In WAD-patients the damaged neck muscles and upper cervical vertebrae deliver inappropriate proprioceptive information to the PAG, resulting in a mismatch between this information and the incoming information from the undamaged vestibular and visual systems. This mismatch may cause balance disturbances, dizziness, headache, forgetfulness, central hypersensitivity to noise and sound, emotional instability, fatigue and problems with sleep, the common symptoms in WAD patients.The strength of this mismatch differs strongly between patients, probably depending on the strength of the inappropriate information from the upper neck. The solution might be to remove the incoming information from the facet joints, capsules and ligaments of the upper cervical vertebrae to the upper cervical spinal cord (C1-C3). In three healthy cats we have cut the dorsal roots of the C1-C3 spinal cord, which did not result in any problems in these cats. A similar approach in humans might lead to treatments of WAD, a disorder with an estimated yearly cost in Europe of at least 10 billion EUR.

Disclosures: G. Holstege: None. **H. Subramanian:** None.

Poster

747. Spinal Cord Injury and Repair

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 747.17/F25

Topic: C.11. Spinal Cord Injury and Plasticity

Support: MOST 107-2221-E-182-009-MY3

Title: Single joint CPM is beneficial for reducing multi-joint muscle tone in people with chronic SCI

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Abstract: Hypertonia is a common condition in patients with spinal cord injury that might be fluctuated by posture changes. It can be attributed to the adaptation of spinal circuitry and soft tissue property. Previous studies demonstrated that short range ankle CPM with a relatively fast speed could reduce spasticity and decrease H/M ratio. However, whether the effect is focal on a single joint and/or specific to a fixed posture is not clear. The purpose of this study was to evaluate the effect of focal ankle CPM training on reducing muscle tone at sitting/standing postures and on multi-joints of low extremities. Nine individuals with chronic SCI received 8 weeks of ankle CPM with one hour/day, five days/week for 8 weeks. H/M ratio of soleus was tested at sitting and standing with supported by a suspension system. MAS of ankle, knee, and hip flexors/extensors were tested before and after training. The results showed that, after training, the H/M ratio reduced only in sitting but not in standing. MAS decreased in all joints ($p<.05$). This study concludes that single joint ankle CPM can reduce the muscle tone. The treatment effect can be irradiated to multiple joints but is posture specific.

Disclosures: Y. Chang: None. **G. Li:** None. **M. Yu:** None. **C. Fang:** None. **M. Hsu:** None.

Poster

747. Spinal Cord Injury and Repair

Location: Hall A

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Program #/Poster #: 747.18/F26

Topic: C.11. Spinal Cord Injury and Plasticity

Support: FINEP 01.12.0514.00 (FINEP and MCTIC)
CNPq (Siconv #704134/2009) (INCT Program from CNPq and MCTIC)

Title: Surface-based morphometric brain analysis in paraplegic patients after training with brain-machine interfaces, visuo-tactile feedback and assisted locomotion

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Abstract: Traumatic lesion of the spinal cord (SCI) induces anatomical changes in the brain [1]. Structural analysis of the brain of subjects with SCI has shown cortical atrophy and cortical reorganization of the sensorimotor system.
Here we investigate the brain structure of a group of six SCI patients after a long-term multi-step training protocol, called the Walk Again Neurorehabilitation (WANR), that integrates brain-machine interfaces with visuo-tactile feedback and locomotion training [2].
Following this protocol for more than two years, six patients originally diagnosed with chronic complete SCI (AIS A, thoracic lesion, 6-12 years post-injury), experienced significant clinical improvement in the sensory (mean 7.25 dermatomes) and motor (14.6 myotomes) domains. As a result of the training, all patients were reclassified as AIS C.
T1-weighted volumetric brain images were obtained with this group of patients (SCI-W) and compared with a control group of SCI patients naïve to the protocol (SCI-C, all patients classified as AIS A, thoracic lesion, 1-14 years post-injury). We used the Freesurfer processing pipeline to detect statistical differences in cortical thicknesses and volumes between the groups. We found significant cortical thinning (t-test $p<.05$, clustering at $p<.01$) in the SCI-C group compared to SCI-W patients, in the prefrontal regions, cuneus, and fronto-parieto-temporal junctions - therefore association cortex.
A second analysis using the data from 10 healthy subjects (H-C) (OpenfMRI database, Washington University), showed a statistical difference between the H-C and the SCI-C groups in the associative regions and no difference when comparing with the SCI-W group. In other words, we found that the structural frontoparietal network in patients that followed the WANR was closer to the ones of the healthy subjects compared to control SCI patients. These areas are engaged in goal-directed tasks.
We hypothesize that the plastic mechanisms involved in the recovery after the WANR protocol occurred through recruiting of compensating parallel associative networks, instead of enhancing primary cortical pathways. Further longitudinal analysis with a group of SCI patients throughout the WANR protocol will clarify this point.
[1] P. Freund *et al.*, “Disability, atrophy and cortical reorganization following spinal cord injury,” *Brain*, 2011.
[2] S. Shokur *et al.*, “Training with brain-machine interfaces , visuo- tactile feedback and assisted locomotion improves sensorimotor , visceral , and psychological signs in chronic paraplegic patients,” *PLoS One*, vol. 13, no. 11, pp. 1-33, 2018.

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Poster

747. Spinal Cord Injury and Repair

Location: Hall A

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Program #/Poster #: 747.19/F27

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH R01NS103481
SHC 84051
SHC 86000
DOD SC140089

Title: Enhancing propriospinal axon sprouting to promote relay circuits bypassing a spinal cord contusion injury

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Abstract: Contusive spinal cord injuries (SCI) from following traumatic injury cause extensive damage to the spinal cord, which result in the loss of lower limb function. Unfortunately, long projecting supraspinal neurons, like the corticospinal tract (CST), fail to spontaneously regenerate through the lesion or when induced to regenerate only grow short distances. Alternatively, descending propriospinal neurons (DPSNs) bypassing the lesion show a higher potential for reconstruction of a new functional circuits across the injury. Based on our previous result, retrograde genetic tracing shows numerous preserved DPSNs bypassing the contusion lesion site. We are attempting to enhance plasticity along the supraspinal-propriospinal pathway using selective expression of neurotrophins within specific neuronal populations. To target lesioned supraspinal plasticity to propriospinal neurons either NT-3 or BDNF was expressed using retrogradely transported lentivirus injected within the ventral horn within the lumbar spinal cord. Neurotrophin-3 or BNDF has been shown by multiple groups including ours to induce robust sprouting of CST and reticulospinal axons, respectively. To promote propriospinal axon sprouting onto spinal motor neurons, retroAAV encoding Glial Derived Neurotrophic Factor (GDNF) was injected into transient demyelinated sciatic. This method shows robust expression within spinal motor neurons. GDNF promotes the sprouting and regrowth of propriospinal neurons. One week after viral injections a contusive SCI was made at thoracic 10 (T10) using a 200 kilodyne contusive force. After SCI, animals were behaviorally examined weekly using the BBB open field assessment, ladder test, and the ink-blot footprint test. Anterograde and retrograde tracer were injected into the somatomotor cortex or lumbar ventral horn, respectively, 8 weeks after contusion. Three week later, rats were euthanized for analysis of axon sprouting. Our preliminary results indicate GDNF enhanced axon sprouting of DPSNs and enhanced hind limb locomotor function of contused rats after T10 SCI.

Disclosures: **J. Chen:** None. **T.J. Campion:** None. **R. Smit:** None. **I.P. Junker:** None. **E. Kostoff:** None. **G.M. Smith:** None.

Poster

747. Spinal Cord Injury and Repair

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 747.20/F28

Topic: C.11. Spinal Cord Injury and Plasticity

Support: FRQS grant
ERANET Grant

Title: Effects of complex treadmill training on sensorimotor function and on neuropathic pain after an incomplete spinal cord injury: A case series

Authors: *C. DAMBREVILLE, M. GAGNÉ, P. SIMARD, C. RAHN, C. MERCIER, A. K. BLANCHETTE, L. J. BOUYER;
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Abstract: INTRODUCTION: The control of locomotion results from interactions between descending control, spinal pattern generators and sensory feedback. After incomplete spinal cord injury (SCI), gait control is impaired and neuropathic pain often develops. Current gait rehabilitation uses treadmill training to strengthen sensory feedback on spinal circuits. However, locomotor recovery remains incomplete and chronic neuropathic pain often develops. Studies in animal models suggest that locomotor recovery and neuropathic pain might be competing for some shared neural circuits. The aims of this study were therefore twofold: 1) use a more complex treadmill training paradigm that better recruits descending control; and 2) demonstrates the clinical feasibility of this paradigm and evaluate its effects on sensorimotor function and on neuropathic pain. METHODS: 10 participants with an incomplete SCI (AIS C-D; 2-130 mo post lesion) came to the laboratory for 18 sessions (PRE and POST tests plus 16 training sessions) over 4 weeks to undergo complex gait training consisting of stepping onto virtual targets projected on a screen in front of them (80, 100, 120% of step length; pseudo-random order) during treadmill walking. Locomotor recovery (gait speed, 6 min walk test, MiniBest test) and neuropathic pain (International Spinal Cord Injury Pain Basic Data Set) were assessed PRE and POST training. Participants' satisfaction was measured using a custom-designed questionnaire POST training.Finally, the excitability of the corticospinal pathway was assessed PRE-training using TMS (25 MEPs during control walking compared to 25 during stepping onto targets). RESULTS: MEP size increased by 43.9+/-50.3% (n=10; p=0.02) during complex walking compared to control walking. After training, significant improvements ($p<0.05$) were measured in preferred and maximal walking speed, endurance, and dynamic balance. A decrease of 35%+/-22% was measured in the 4 participants that presented neuropathic pain. Participants'

satisfaction regarding this training was excellent (41.8/45 +/- 3.4).CONCLUSION: Complex treadmill training consisting of stepping onto virtual targets that modulate step length is feasible in persons with an incomplete SCI and sufficient to increase descending drive on the locomotor circuits. Complex treadmill training leads to improvement in clinical measures of gait performance and reduction in neuropathic pain when present. It could therefore be used in the clinic to improve sensorimotor function recovery and decrease neuropathic pain in this population.

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Poster

747. Spinal Cord Injury and Repair

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Topic: C.11. Spinal Cord Injury and Plasticity

Support: R01NS107807
R01NS083983

Title: Forced expression of KLF6 in cortical neurons promotes recovery of forelimb function after corticospinal tract injury

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Abstract: Spinal cord injury disrupts communication by severing axon tracts, notably the corticospinal tract (CST), which is responsible for fine motor function. In cases of partial injury, one strategy to enhance recovery is to stimulate sprouting from spared axons, leading to compensatory innervation of distal targets. We showed previously that viral delivery of the transcription factor KLF6 enhances CST regeneration and sprouting after spinal injury. Despite this growth phenotype, however, treated animals showed no improvement in forelimb function on a horizontal ladder task. Here we examined the effect of KLF6 on performance in a fine motor task, pellet retrieval in the Montoya staircase. Adult mice were pre-trained in the retrieval task and then received unilateral pyramidotomy and cortical injection of AAV-KLF6 or control with AAV-EGFP tracer. Mice were then tested twice weekly in the staircase for thirteen weeks post-injury. KLF6 treated mice showed a significant improvement in the skilled forelimb reaching task over time, with behavioral improvement emerging in the last three weeks of testing. Consistent with prior findings, KLF6-treated animals also showed a significant elevation of cross-midline sprouting by CST axons. Notably, behavioral improvements in the KLF6 group were significant but partial, leaving room for further recovery. In ongoing work we are testing

the hypothesis that physical rehabilitation may act to fine tune the innervation by sprouting axons, leading to further gains in function when combined with KLF6 treatment. Together this work aims to identify the tools necessary to achieve behavioral improvement and to direct appropriate axonal integration following central nervous system injury.

Disclosures: A.A. Kramer: None. **G. Olson:** None. **D.M. Gross:** None. **M.G. Blackmore:** None.

Poster

747. Spinal Cord Injury and Repair

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Program #/Poster #: 747.22/F30

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH R01NS096971

Title: Exercise mediated recovery of function after partial spinal cord injury is associated with trunk motor cortex reorganization

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Abstract: Previous work from our lab and recent studies from others have shown that a combination of rehabilitative approaches including exercise and activation of spinal circuits can significantly improve functional outcome in complete SCI animals. This recovery is accompanied by significant reorganization in the trunk motor cortex that is required for functional improvement. To determine if cortex plays a similar role after more clinically relevant contusion injury, we repeated this experiment in a contusion model using treadmill exercise. Importantly, unlike the complete SCI model, rodents and humans with partial SCI injuries are likely to develop chronic neuropathic pain (CNP). It has been suggested that CNP may impede motor learning at the spinal level, limiting recovery of gait, but cortical plasticity may also play a role. **Methods:** In this study, the effect of exercise therapy on functional recovery (locomotion and CNP development) and cortical reorganization was assessed in female Sprague Dawley rats (n=22) with a T10 mid thoracic contusion (SCI). In a subset of animals (n=12), treadmill exercise therapy was initiated 1-week post injury for 25min, 5 days/week for 5 weeks post SCI. At level (trunk) CNP and locomotor recovery (BBB scores) were assessed once a week for 5 weeks post injury. At week 6, all animals underwent motor cortex mapping (ICMS). Average responsiveness score and cortical area devoted to trunk muscle activation were used to evaluate cortical reorganization. **Results:** Consistent with previous work, this level of exercise therapy did not impact neuropathic pain development ((χ^2 (1, 22) =0.105, p>0.05). However, exercise therapy significantly improved locomotor recovery (ANOVA: F (1, 20) =16.946, p=0.001) such

that the injured animals could take weight supported steps with consistent co-ordination (BBB score: 16+/- 2). Regardless of whether the animal had therapy, post SCI ICMS did not elicit activation of hindlimb musculature. Animals that received exercise therapy had significantly higher probability of exclusively activating trunk musculature within the trunk and deafferented-hindlimb motor cortex. In addition, these animals had significant reorganization of the forelimb motor cortex. Preliminary data comparing the trunk representation in animals that developed pain compared to those that did not suggests that CNP may impede the effect of exercise therapy on cortical reorganization of the trunk. **Conclusion:** These results support earlier studies documenting the role of the trunk motor representation after therapy in the recovery of function but also caution that CNP may interfere with this role.

Disclosures: B. Nandakumar: None. **G.H. Blumenthal:** None. **K.A. Moxon:** None.

Poster

747. Spinal Cord Injury and Repair

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Support: NICHD grant K12HD073945
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Wallace H. Coulter Foundation

Title: Intraspinal microstimulation in the ventral horn modulates neural transmission dorsal horn sensory neurons

Authors: *M. F. BANDRES[1,4], V. MELERO[4], L. DA SILVA[4], J. G. MCPHERSON[2,4,3,1]; [1]Biomed. Engin., [2]Physical Therapy, [3]Anesthesiol., Washington Univ. in St. Louis, St. Louis, MO; [4]Biomed. Engin., Florida Intl. Univ., Miami, FL

Abstract: Spinal cord injury (SCI) results in dramatic changes in neural excitability below the lesion, leading to debilitating motor impairments, dysregulation of reflexes, and neuropathic pain. In general, voluntary motor output is reduced below the lesion, whereas the spinal effects of sensory feedback are pathologically increased. Spinal stimulation-based therapies seeking to restore motor impairments after SCI often fail to consider modulation of neural transmission in spinal sensory pathways, including pathways integral to SCI-related neuropathic pain. Here, we characterized the effects of intraspinal microstimulation of the ventral horn (vISMS), an emerging therapeutic approach for motor rehabilitation, on the firing dynamics of sensory neurons in the superficial and deep dorsal horns. All experiments were approved by the FIU IACUC and conducted in adult male Sprague-Dawley rats under urethane anesthesia (n=15). After T13-L2 laminectomy, microelectrode arrays were implanted at the L5 dorsal root entry

zone. Electrodes locations for vISMS targeted Rexed's laminae 8-9 and electrode locations for quantifying transmission in sensory pathways spanned laminae 2-6. Prior to, during, and after vISMS, we mechanically stimulated the L5 dermatome by applying controlled forces ranging from non-painful to painful. Primary outcome measures included the number and type of neurons recruited/derecruited during vISMS, changes in the firing frequency of active neurons, and the spatiotemporal profile of neural activity throughout the ventral and dorsal horns (quantified via stimulus-triggered averages of multi-unit neural data, peristimulus time histograms of single-neuron spike times, and measures of correlation amongst simultaneously active units). We found that even short periods of vISMS could modulate neural transmission in pain and non-pain-related pathways of the dorsal horn. On average, we find that neural transmission is either reduced or unchanged in a majority of identified sensory neurons during and/or after vISMS ~70% of all neurons; approximately evenly distributed), with neural transmission increasing in the remaining third of neurons. Our results suggest that it may be possible to design vISMS paradigms that reduce transmission in spinal pain pathways while continuing to increase spinal motor output. Future work is required to fully characterize the mechanisms by which vISMS modulates spinal pain transmission, to optimize these effects, and to establish limits for avoiding unintended increases in pain transmission.

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Poster

748. Somatosensation: Treatments for Persistent Pain

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 748.01/F32

Topic: D.03. Somatosensation – Pain

Support: R01NS065926

Title: Reversal of peripheral nerve injury-induced neuropathic pain and cognitive dysfunction via genetic and tomivosertib targeting of MNK

Authors: *S. SHIERS[1], J. MWIRIGI[3], G. PRADHAN[3], M. KUME[3], B. J. BLACK[1], G. O. DUSSOR[2], J. J. PANCRAZIO[1], S. KROENER[4], T. J. PRICE[5];
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Abstract: Neuropathic pain caused by nerve injury presents with severe spontaneous pain and a variety of comorbidities, including deficits in higher executive functions. None of these clinical

problems are adequately treated with current analgesics. Targeting of the mitogen activated protein kinase-interacting kinase (MNK1/2) and its phosphorylation target, the mRNA cap binding protein eIF4E, attenuates many types of nociceptive plasticity induced by inflammatory mediators and chemotherapeutic drugs but inhibiting this pathway does not alter nerve injury-induced mechanical allodynia. We used genetic manipulations and pharmacology to inhibit MNK-eIF4E activity in animals with spared nerve injury, a model of peripheral nerve injury (PNI)-induced neuropathic pain. We assessed the presence of spontaneous pain using conditioned place preference. We also tested performance in a medial prefrontal cortex (mPFC)-dependent rule-shifting task. WT neuropathic animals showed strong signs of spontaneous pain and were significantly impaired in the rule-shifting task while genetic and pharmacological inhibition of the MNK-eIF4E signaling axis protected against and reversed spontaneous pain and PNI-mediated cognitive impairment. Additionally, pharmacological and genetic inhibition of MNK-eIF4E signaling completely blocked and reversed maladaptive shortening in the length of axon initial segments (AIS) in the mPFC of PNI mice. Surprisingly, these striking positive outcomes on neuropathic pain occurred in the absence of any effect on mechanical allodynia, a standard test for neuropathic pain efficacy. Our results illustrate new testing paradigms for determining preclinical neuropathic pain efficacy and point to the MNK inhibitor tomivosertib (eFT508) as an important drug candidate for neuropathic pain treatment.

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Poster

748. Somatosensation: Treatments for Persistent Pain

Location: Hall A

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Program #/Poster #: 748.02/F33

Topic: D.03. Somatosensation – Pain

Support: Palmer Center for Chiropractic Research SEED Grant
NIH/NCCIH Grant R15AT009612

Title: Role for endocannabinoids in manipulative therapy analgesia?

Authors: *S. M. ONIFER, R. S. SOZIO, C. R. LONG;
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Abstract: Chronic pain is quite prevalent and causes significant disabilities and socioeconomic burdens. Manipulative therapies are used to manage chronic pain. There is a critical knowledge gap about mechanisms and sites of action in manipulative therapy pain relief, especially the short-term analgesia that occurs following a treatment. Endocannabinoids are an activity-dependent neurotransmitter system that acts as a short-term synaptic circuit breaker. Both

clinical and basic science research evidence suggest that endocannabinoids contribute to short-term manipulative therapy pain relief. Doctors of chiropractic, osteopathic physicians, and physical therapists commonly use spinal manipulative therapy (SMT) to manage chronic low back pain with or without a neuropathic pain component. We previously utilized reverse translation and reductionist approaches to develop an adult rat model of SMT analgesia in peripheral neuropathic pain produced by spared nerve injury (SNI). To begin investigations of endocannabinoids involvement in SMT pain relief, we determined whether modulating the endocannabinoid system systemically has analgesic effects on peripheral neuropathic pain produced by SNI. Our target was the catabolic enzyme fatty acid amide hydrolase (FAAH) of the endocannabinoid anandamide (N-arachidonoylethanolamine), a CB1 receptor agonist. We used URB597 because it is a brain permeant inhibitor of FAAH that when administered intraperitoneally increases rodent brain anandamide levels and AM281, a potent and selective CB1 receptor antagonist/inverse agonist. Male Sprague Dawley rat sciatic nerve tibial and common peroneal branches were transected while sparing the sural branch (SNI). Rats were tested for hindpaw mechanical sensitivity 15-18 days after SNI. Following testing, they were randomly assigned to 4 groups (n = 4 each group) that received 2 intraperitoneal injections separated by 1 minute: 1) vehicle (DMSO: ALKAMULS® EL 620: 0.9% sodium chloride) and vehicle (Vehicle group), 2) AM281 and vehicle (AM281 group), 3) vehicle and URB597 (URB597 group), or 4) AM281 and URB597 (AM281 + URB597 group). Mechanical sensitivity testing was repeated 15, 25, 40, 55, 70, and 90 minutes after the second injection. SNI produced behavioral signs of mechanical hypersensitivity. URB597 significantly reduced mechanical hypersensitivity at 15 - 70 minutes compared to Vehicle and at 15 - 40, 70, and 90 minutes compared to AM281. AM281 + URB597 significantly attenuated this analgesic effect at 15 - 40 and 90 minutes compared to URB597. The results indicate that endocannabinoids are a treatment target for peripheral neuropathic pain produced by SNI.

Disclosures: **S.M. Onifer:** None. **R.S. Sozio:** None. **C.R. Long:** None.

Poster

748. Somatosensation: Treatments for Persistent Pain

Location: Hall A

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Topic: D.03. Somatosensation – Pain

Support: NIH Grant R01 DA040688
NIH Grant R21 NS109862

Title: Cytoarchitectural changes induced by chronic cephalic pain are reversed by HDAC6 inhibition

Authors: *Z. J. BERTELS[1], H. SINGH[2], I. DRIPPS[1], P. SHAH[1], J. CHMURA[2], S. M. BACA[3], M. M. RASENICK[2], A. A. PRADHAN[1];
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Abstract: Migraine is an extremely prevalent neurological disorder and it is estimated to affect 14% of the world population, making it the third most prevalent disease worldwide. Chronic migraine is an especially disabling disorder and is defined as 15 or more headache days a month. Despite its high prevalence migraine therapies are often only partially effective or are poorly tolerated. A greater understanding of migraine pathophysiology would allow for development of novel therapeutic targets. Changes in dendritic morphology and neuroplasticity have been associated with other chronic pain conditions. Microtubules form the backbone for cell morphology, and are made up of heterodimers of α and β tubulin. Tubulin dynamics are regulated by a variety of post-translational modifications, including α-tubulin acetylation. Acetylated tubulin has been correlated with more stable microtubules that are more flexible and less prone to breakage. Endogenously α-tubulin is acetylated by α -tubulin N-acetyltransferase I (αTAT1) and deacetylated through histone deacetylase 6 (HDAC6). The aim of this study was to determine if chronic migraine-associated pain and aura resulted in altered neuronal cytoarchitecture, and if HDAC6 inhibition could reverse these changes and correspondingly alleviated these symptoms. Male and female C57BL/6 mice went through a previously established model of chronic migraine using the human migraine trigger nitroglycerin (NTG). Following the chronic migraine model Golgi stain revealed that in key cephalic pain processing regions there was decreased neuronal complexity that was reversed by the HDAC6 inhibitor, ACY738. Correspondingly, ACY738 also blocked migraine-associated pain. Additionally, we tested the effects of cortical spreading depression (CSD), a physiological correlate of migraine aura, and observed decreased neurite outgrowth in the cortex after repeated CSD events. Pretreatment with ACY738 not only resulted in decreased CSD events, but also reversed cytoarchitectural alterations. Together our results demonstrate that migraine pathophysiology is associated with disrupted neuronal cytoarchitecture and that HDAC6 inhibitors could be a novel therapeutic target for this disorder.

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Poster

748. Somatosensation: Treatments for Persistent Pain

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

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Topic: D.03. Somatosensation – Pain

Support: MOST 105-2314-B-195-003-MY3, TAIWAN
MOST 106-2811-B-195-001, TAIWAN
MOST 107-2811-B-195-001, TAIWAN

Title: *In vivo* and *in vitro* effects of human mesenchymal stem cell exosomes on nerve injury-induced neuropathic pain

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Abstract: Aim of Investigation: Nerve injury-induced neuropathic pain is difficult to treat. In this study, we used purified human umbilical cord mesenchymal stem cell (UCMSC) exosomes as a therapeutic in the L5/6 spinal nerve ligation (SNL) pain model and explored the possible analgesic mechanisms. The cell type-specific localization of exosomes in dorsal root ganglion (DRG) and their effects on SNL-induced glial activation and neuro-inflammation were also examined.
Methods: Male Sprague-Dawley rats (250-300 g) received right side L5/6 SNL, intrathecal catheterization and infusion pump implantation under anesthesia. Von Frey hair and radiant heat tests were used to measure the mechanical and thermal sensitivity of affected hindpaw. Seven days after SNL, rats were sacrificed. L5/6 spinal cord, DRG and peripheral nerves were removed and used for double fluorescent immunohistochemistry and Western blotting assay. PC12 and HEK293 cells were used to test the *in vitro* effects of UCMSC exosomes.
Results: Isolated UCMSC exosomes range in size from 30 to 160 nm and contain CD63, HSP60 and CD81, exosome markers. After SNL, single intrathecal injection exosomes reversed SNL-induced mechanical and thermal hypersensitivities of rat right hindpaw at initial and well-developed pain stages. Moreover, continuous intrathecal infusion of exosomes achieved excellent preventive and reversal effects for SNL-induced pain. Lots of Exo-green-labelled exosomes could be found in ipsilateral L5 spinal cord, DRG and peripheral axons suggesting the homing ability of UCMSC exosomes. They also appeared in the central terminals and cell bodies of $IB4^+$ and $CGRP^+$ nociceptors in DRG. The exosome suppressed SNL-induced up-regulation of c-Fos, CNPase, GFAP, Iba1, TNF-α and IL-1β, while enhanced the level of IL-10, GDNF and BDNF in the ipsilateral L5/6 DRG. *In vitro*, the exosomes not only protected PC12 and HEK293 cells against inflammatory agent formaldehyde acid, but also induce neurite outgrowth of PC12 cells.
Conclusions: We showed the analgesic effects of human UCMSC exosomes may involve their actions on neuron and glial cells, with anti-inflammatory and pro-neurotrophic abilities. Intrathecal infusion of exosomes derived from human UCMSCs may be considered as a novel therapeutic alternative for nerve injury-induced pain.

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Poster

748. Somatosensation: Treatments for Persistent Pain

Location: Hall A

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Topic: D.03. Somatosensation – Pain

Support: DoD SC150162

Title: Recombinant GABAergic cells and locomotor training as a combined treatment to attenuate SCI-induced chronic pain in rats

Authors: *S. JERGOVA, E. DUGAN, M. HERNANDEZ, B. SCHACHNER, S. M. RUTTENBERG, L. E. ROBAYO, M. RESTREPO, J. SAGEN;
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Abstract: Spinal cord injury (SCI) initiates a cascade of pathophysiological events that may lead to development of chronic pain, refractory to pharmacological treatment. Multifactorial approaches targeting key events is necessary to be identified in order to prevent or attenuate development of chronic pain. Reduced inhibitory GABAergic signaling in the spinal pain processing sites, enhanced excitatory NMDA signaling and elevated level of inflammatory mediators represent such key events. The goal of this study was to evaluate the analgesic effect of a multitargeted approach using intraspinal grafts of GABAergic progenitors expressing NMDA antagonist serine-histogranin in combination with intensive physical exercise. Male Sprague Dawley rats underwent spinal clip compression injury and developed hypersensitivity in the hind paws. Treadmill training was initiated at 5 days or 5 weeks post SCI, with GABAergic cells grafted at 4 weeks post SCI. Tactile allodynia, heat and cold hyperalgesia were monitored weekly up to 15 weeks. Our results show that combined treatment significantly reduced established hypersensitivity (with late training) or in some animals even prevented its development (with early training). The behavioral outcome in animals with recombinant grafts was more robust and stable compared to animals with nonrecombinant cells, although both groups show significant recovery from pain related behavior compared with non-transplanted and sedentary controls. The level of inflammatory cytokines in the spinal tissue was reduced in treadmill trained animals and further reduced in animals with combined treatment. Immunohistochemical and biochemical analysis showed the presence of recombinant cells in the spinal tissue as well as the attenuation of GABA loss in the trained animals compared to the SCI controls. Reduced expression of KCC2 transporter involved in GABAergic inhibition in the sedentary SCI rats compared to trained SCI animals further was also detected. Volume analysis of spared tissue in the injury site showed reduced cavitation in the trained animals compared to sedentary ones.Our findings support the hypothesis that the combined approach is beneficial for management of chronic SCI induced pain. Direct intervention within the spinal pain-processing

sites by intraspinal transplants and indirect modulation of the inflammatory response by physical exercise showed the most promising potential for attenuation of chronic neuropathic pain.

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Poster

748. Somatosensation: Treatments for Persistent Pain

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Topic: D.03. Somatosensation – Pain

Support: Medical Research Council grant MR/K022539/1

Title: Selective neuronal silencing using novel synthetic botulinum molecules alleviates chronic pain states

Authors: *M. MAIARU[1], C. LEESE[2], I. ECHEVERRIA-ALTUNA[1], J. ARSENAULT[3], B. DAVLETOV[2], S. HUNT[1];
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Abstract: Previous studies showed that persistent pain states were substantially relieved by targeting and ablating small populations of spinal neurons that convey pain-related information to the brain. Here, we designed botulinum conjugates that are safe to construct, nontoxic, and act relatively quickly after intrathecal injection to silence pain processing neurons in the spinal cord. We have conjugated the silencing domain of BoNT/A, BOT, to either substance P, SP, or dermorphin, Derm, to reversibly inhibit key substance P receptor, NK1R, or mu-opiate receptor, MOR, expressing neurons in the pain pathway and produce a long-term amelioration of persistent pain states. We used two models of persistent pain; a model of an inflammatory pain state, induced by injection of Complete Freud's Adjuvant, CFA, into the ankle joint and a model of a neuropathic pain state, the Spared Nerve Injury model, SNI. SP-BOT and Derm-BOT were injected intrathecally when the pain state was fully developed. The targeting of conjugates was monitored using immunochemistry: lumbar spinal cord sections were stained for cleaved SNAP25 using a specific antibody and tyramide amplification followed by staining for MOR or NK1R to confirm specificity. The injection of SP-BOT or Derm-BOT had no effect on baseline mechanical threshold in naïve mice. However, the injection of SP-BOT, 100ng/3µl, following CFA injection as well as given before or after SNI surgery, reduced the mechanical hypersensitivity typically observed in these pain models. Importantly, the injection of SP-BOT was not effective in alleviating mechanical hypersensitivity when injected in NK1R knockout mice. Derm-BOT conjugates, 100ng/3µl, also reduced the mechanical hypersensitivity when

injected intrathecally after SNI surgery or CFA injection. The reduction in mechanical hypersensitivity was to the same extent as i.t. morphine and no additive effects were seen when morphine was injected i.t into mice pretreated with Derm-BOT. Immunohistochemistry demonstrated subsets of cleaved SNAP 25-positive neurons in the dorsal horn of conjugate injected mice. Double staining with either NK1R or MOR antibodies indicated that uptake of conjugates was specific: cSNAP was found in either NK1R positive neurons following SP-BOT injection or in MOR positive neurons following Derm-BOT treatment. We have shown that a single injection of SP-BOT or Derm-BOT produce long lasting relief in models of inflammatory and neuropathic pain. The data strongly suggests that botulinum-conjugated molecules could represent an opioid-free alternative for the treatment of chronic pain.

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Poster

748. Somatosensation: Treatments for Persistent Pain

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Program #/Poster #: 748.07/F38

Topic: D.03. Somatosensation – Pain

Title: A novel target for osteoarthritis pain

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Abstract: Chronic pain is a significant health problem posing an enormous economic burden to our society. The lack of therapeutic options, particularly for chronic pain, is driving the current opioid epidemic in humans. One of the potential limitations in developing therapeutics is a lack of understanding of the precise mechanisms in the target disease condition. Here, we identified molecular targets using naturally occurring osteoarthritis (OA) in pet dogs and human patients and now going back to investigate the molecular mechanism in a mouse model of OA with an ultimate goal of developing possible therapeutics. Here, we used male mice to study chronic pain – making the plausible assumption that females are intrinsically more variable than males. All behavioral assays were performed blinded. Data are presented as mean ±SEM. For more than two groups, ANOVA was used and for two groups, we performed student's t-test using GraphPad Prism Software to determine the significance. The p-value for significance was set at 0.05. To decipher the molecular signaling cascades in chronic pain, we used an intra-articular injection of monoiodoacetate (MIA) to induce OA in mice and compared them to mice injected with saline (control). Employing cellular, pharmacological, physiological, and mouse behavioral assays, we demonstrate that a peripheral ligand and receptor expressed on sensory neurons are

involved in chronic pain. Next, we showed when ligand injected exogenously into the mouse hind paw could cause widespread pain hypersensitivity, which corroborates with MIA-induced pain hypersensitivity. Finally, we blocked the ligand/receptor interaction using an antibody specific against the receptor and showed attenuation of pain hypersensitivity in mice. Overall, our study provides an underlying mechanism behind chronic pain associated with OA and offers potential new targets for developing therapeutics.

Disclosures: L.M. Minnema: None. **J.J. Wheeler:** None. **S.K. Mishra:** None. **B.D.X. Lascelles:** None.

Poster

748. Somatosensation: Treatments for Persistent Pain

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Program #/Poster #: 748.08/F39

Topic: D.03. Somatosensation – Pain

Support: FAPESP (2018/06877-5)
INCT – Translacional em Medicina (FAPESP nº 465458/2014-9)
CAPES-PROEX
CNPq

Title: Cannabidiol is a potential therapeutic treatment for chronic pain: Analgesic and anxiolytic effects in an animal model of chronic constriction injury (CCI)

Authors: *G. K. CARDOSO[1], A. W. ZUARDI[2], J. A. D. CRIPPA[2], J. E. C. HALLAK[2], C. R. A. LEITE-PANISSI[1];
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Abstract: Emotional and cognitive disorders often accompany chronic pain. In the general population, chronic pain incidence is 6% to 8%, and its impact on the quality of life, mood, and sleep exceeds the burden of its causal pathology. Considering the nociceptive modulation, the cannabinoid system is an important endogenous system participating in circuitry pain sensitivity. In this perspective, the cannabidiol (CBD) is considered to be a promising strategy for the treatment of neuropathic pain. Our study aimed to evaluate the effect of systemic treatment with CBD (3 days) in rats submitted to sciatic nerve constriction (CCI) and submitted to open field (OP) and nociceptive (NT) tests. For this study, 80 rats (220 g) Wistar were used (CEUA - USP # 2018.1.103.58.5). The rats were submitted to the surgical procedure (CCI or false operated / SHAM) on day zero, and the development of neuropathy was followed for three weeks by nociceptive tests (von Frey, hot plate and acetone). On the 23rd day, the animals were submitted to the to the open field test. Nociceptive tests were performed on the 24th day, after 3 days of

CBD treatment. The two-way ANOVA test was used, followed by the Bonferroni test, $p < 0.05$. The results showed that treatment with CBD for three days at different doses (0.3, 3, 10 and 30 mg/kg ip) had an antiallodynic effect (i - von Frey: $F(4, 24) = 237.2$; $P < 0.0001$; ii - acetone: $F(4, 24) = 172.3$; $P < 0.0001$ and iii - hot plate: $F(4, 24) = 375.4$ $P < 0.0001$) in the injured rats. In the open field test the CBD showed an anxiolytic type effect ($F(4, 25) = 6.748$, $P = 0.0008$) in the injured animals. When we evaluated the synergy of the dual profile of the CBD at 3 mg/kg (von Frey, (ii) acetone and (iii) hot plate = $P < 0.0001$ and OP: $P = 0.0005$) was shown to perform better in both the analgesic effect on the nociceptive test battery and the anxiolytic effect in the open field test. These results corroborate with the literature on the analgesic and anxiolytic effects of CBD, emphasizing the dose of 3mg/kg as the dose with better pharmacological performance. This synergistic effect offers favorable perspectives for new pharmacological approaches in the treatment of neuropathic pain.

Disclosures: G.K. Cardoso: None. **A.W. Zuardi:** None. **J.A.D. Crippa:** None. **J.E.C. Hallak:** None. **C.R.A. Leite-Panissi:** None.

Poster

748. Somatosensation: Treatments for Persistent Pain

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Program #/Poster #: 748.09/F40

Topic: D.03. Somatosensation – Pain

Support: Canadian Institutes of Health Research – Foundation Grant #353649

Title: Analgesic efficacy of various NTS2-selective neurotensin(8-13) analogs in a rat model of bone cancer pain

Authors: *C. LAGARD[1], M. VIVANCOS[1], M. CHARTIER[1], R. FANELLI[2], M. DESGAGNÉ[1], A. RENÉ[2], J. CÔTÉ[1], J.-M. LONGPRÉ[1], E. MARSAULT[1], F. CAVELIER[2], P. SARRET[1];
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Abstract: In recent years, the tridecapeptide neurotensin (NT) and its minimal biologically active fragment NT(8-13) have emerged as major modulators of nociceptive transmission. They exert their analgesic activity by interacting with two distinct 7-transmembrane domain receptors termed as NTS1 and NTS2. These receptors are attractive targets for the development of new analgesic compounds that could represent promising alternatives to opioids. However, the NT peptide is also implicated in other physiological functions, such as hypotension and hypothermia, which are exclusively mediated by NTS1 activation. In this context, the NTS2 receptor, which is mainly expressed in the central nervous system, represents a target of interest for the

development of new chemical entities with enhanced analgesic effects and minimal adverse effects. In order to improve NTS2-selectivity, we synthesized a series of linear NT(8-13) analogs harboring reduced amide bond and/or site-specific modifications with unnatural amino acids. We also designed conformationally constrained analogs via ring-closing metathesis macrocyclization between the proline residue in position 10 and the side chain of alkene-functionalized amino acid in position 8. Radioligand binding studies demonstrated that these substitutions or macrocyclization step improved the selectivity towards NTS2 by 1,000- to 10,000-fold over NTS1. Strong analgesic effects were also observed following intrathecal injection (i.t.) in acute (tail-beam) and tonic pain (formalin) models, with no apparent change in body temperature or systemic blood pressure. We thus evaluated if a single i.t. injection of these NTS2-selective compounds could exert analgesic action in a bone cancer pain model, which consists in the injection of syngeneic MRMT-1 breast cancer cells into the femoral bone cavity of female Sprague-Dawley rats. We found that the most promising linear compound named JMV5335 (H-Lys-Ψ[CH2NH]Lys-Pro-*N*-*h*Trp-Ile-TMSAla-OH) exerted powerful and sustained analgesic effects 14 days after surgery, as measured with the von Frey filament test. However, no significant changes were observed in burrowing behaviors, spontaneous pain or postural deficits (dynamic weight bearing), probably attributable to the acute treatment. Effectiveness of macrocyclic compounds has yet to be confirmed. Altogether, these results demonstrate that NTS2-selective compounds have been optimized to have better analgesic effects in acute, tonic and chronic bone cancer pain models, without any significant adverse effects.

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Poster

748. Somatosensation: Treatments for Persistent Pain

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 748.10/F41

Topic: D.03. Somatosensation – Pain

Title: Treatment-based classification system for low back pain combined to dry needling improved symptoms of patients with non-specific low back pain

Authors: *C. FUSARO, A. F. NASCIMENTO, T. A. L. MARQUES;
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Abstract: Non-specific low back pain is one of the most common chronic pain conditions and pharmacological treatment remains a mainstream therapy for it. However, it is not fully efficient, therefore, non-drug therapies, such as Treatment-based classification system (TBC) for low back pain and Dry needling, are of great interest. The aim of this study was to assay efficiency of Dry

needling plus TBC for low back pain in patients with non-specific low back pain. 30 volunteers with low back pain (20 men and 10 women), 18-50 years-old, were selected. Exclusion criteria were Red Flags plus low back surgeries or fractures and neurological diseases. The outcomes were pain (Visual Analogue Scale -VAS), disability (Oswestry disability Index - ODI) and pain related fear (Fear Avoidance Belief Questionnaire - FABQ for physical activities and work). Volunteers were categorized into 1 of 4 subgroups of TBC and randomized in 3 groups (n=10): G1 - TBC for low back pain; G2 - Dry needling; and G3 - TBC for low back pain + Dry needling. Interventions were performed once a week, for 4 weeks, at the School-Clinic of Physiotherapy from São Francisco University, Bragança Paulista, Brazil. VAS, ODI and FABQ were applied before the first session as baseline. VAS and ODI were repeated after the end of each session, and FABQ after the last session. Questionnaires were applied by a blinded tester. Procedures were approved by ethics committee in human's research from Sao Francisco University (2.440.282). Results showed that G1, G2 and G3 improved pain in each of the four sessions when compared to baseline ($p<0.001$, One-way ANOVA, Dunnett's test), but there was no difference among groups ($p>0.05$, One-way ANOVA, Dunnett's test). Disability reduced in the last session of G1 when comparing to baseline ($p=0.0484$, One-way ANOVA, Dunnett's test). There was no reduction in disability for G2 and G3 ($p>0.05$, One-way ANOVA, Dunnett's test). Finally, pain related fear for work reduced in the last session of G2 ($p=0.0051$) and G3 ($p=0.0213$), but not of G1 ($p=0.0911$), when comparing to baseline (paired T-test). Pain related fear for physical activities did not reduce in any group ($p>0.05$, paired T-test). The present study demonstrated that TBC for low back pain and Dry needling are efficient in reducing low back pain when applied alone. However, pain response was not amplified by a combination of both. Disabilities were reduced only by TBC for low back pain, and Dry needling alone or combined to TBC for low back pain reduced pain related fear for work. Together, these findings suggest that in patients with low back pain associated to disabilities and pain related fear the combined use of these therapies is a efficient strategy.

Disclosures: C. Fusaro: None. **A.F. Nascimento:** None. **T.A.L. Marques:** None.

Poster

748. Somatosensation: Treatments for Persistent Pain

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Program #/Poster #: 748.11/F42

Topic: D.03. Somatosensation – Pain

Support: NRF Grant 2016R1A2B400940

Title: p66shc-PLGA nanoparticles alleviate mitochondrial dysfunction mediated pain behaviors

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Abstract: AIMS: Reactive oxygen species has been suggested as a key player in neuropathic pain, causing central sensitization by glia activation and loss of GABAergic interneuron in spinal dorsal horn. However, it remains unclear as to what type of reactive oxygen species changes what aspect of glia activation and GABAergic interneuron for central sensitization in neuropathic pain conditions. In this study, we investigated whether mitochondrial superoxide affects both excitatory in spinal dorsal horn neurons after peripheral nerve injury.
RESULTS: Downregulation of mitochondrial superoxide level by p66shc-PLGA nanoparticles alleviated neuropathic mechanical hypersensitivity caused by L5 spinal nerve ligation. In SNL model (Spinal nerve ligation model), superoxide product DHE and Mitochondrial ROS signal was highest at 9 days postoperatively. In SNL condition, the DHE and Mitochondrial ROS signal, pain behavior and inflammatory cytokine and decreased after p66shc-PLGA nanoparticles in spinal dorsal horn. In addition, Mitophagy regulatory factor and inflammatory cytokine level were attenuated in microglia and neuronal cell line by p66shc-PLGA nanoparticle co-treatment after H_2O_2 treatment.
CONCLUSION: These results suggest that, high levels of mitochondrial superoxide through p66shc in spinal dorsal horn neurons and microglia increase sensory threshold after peripheral nerve injury and contribute to neuropathic mechanical hypersensitivity.
KEY WORDS: Neuropathic pain, Spinal cord ligation, p66shc, Nanoparticle, ROS

Disclosures: N. Shin: None. **H. Shin:** None. **D. Kim:** None.

Poster

748. Somatosensation: Treatments for Persistent Pain

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Topic: D.03. Somatosensation – Pain

Support: NNSFC grant 84870872, 31270882
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NBRP 2013CB531302

Title: GABAergic circuits within DRG filtering nociceptive transmission and as potential target for chronic pain therapeutic

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Abstract: It was discovered in our previous study that DRG cell bodies contain a fully functional GABAergic system that can modulate nociceptive signals before they enter the CNS. Our findings indicated that peripheral somatosensory ganglia may represent a new type of "gate" within the somatosensory system and call for a substantial revision to current understanding of how somatosensory information is generated and processed. However, there is still lack of direct *in vivo* evidence on this hypothesis. In this study, we developed a method of *in vivo* electrophysiological recording from the peripheral and central (dorsal root) branches of the L5 spinal nerve of rats , and demonstrated that i) dorsal root ganglia contain tonic GABAergic function in physiological situation; ii) GABAergic circuit in DRG particularly "gating" peripheral nociceptive inputs induced by various types of noxious stimuli; iii) transplantation of embryonic GABAergic progenitor cells from the mouse medial ganglionic eminence into adult mouse DRG effectively alleviated chronic pain induced by inflammation or peripheral nerve injury.
Keywords: GABA, DRG, pain, transmission, MGE

Disclosures: H. Hao: None. **N. Gamper:** None. **X. Du:** None.

Poster

748. Somatosensation: Treatments for Persistent Pain

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Topic: D.03. Somatosensation – Pain

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KI Rheumatology Foundation
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Title: Neuroinflammation is associated with lower pain intensity and milder symptoms in patients with painful knee osteoarthritis

Authors: *V. PALADA[1], E. FREYHULT[2], A. SIDDIQAH AHMED[1], K. KULTIMA[2], C. I. SVENSSON[1], E. KOSEK[1];
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Abstract: The primary aim was to identify inflammatory substances potentially involved in neuroinflammation and neuroimmune communication between blood and CNS in patients with painful knee osteoarthritis (OA) by novel multiplexed proximity extension assay (PEA) which

allows the simultaneous analysis of 92 human inflammatory proteins. In an exploratory part of the study, we investigated associations between the protein levels in cerebrospinal fluid (CSF) and serum with clinical symptoms.
Methods: OA patients (n=40) were recruited from a waiting list for total knee replacement. The patients rated knee and global pain intensity (VAS) and knee-related symptoms (KOOS). Pressure algometry was used to assess pressure pain thresholds (PPTs) and conditioning pain modulation (CPM) was determined. CSF and serum were collected just prior to the surgical procedure. The samples were analyzed by multiplexed PEA immunoassay using Proseek Multiplex inflammation panel (Olink Proteomics, Uppsala, Sweden). P-values were adjusted for multiple comparisons.
Results: Seven CSF inflammatory proteins were all negatively correlated to VASknee and positively correlated with KOOS. We found higher CSF protein levels in VASknee subgroups of patients without pain or mild pain compared to patients with moderate pain. Furthermore, ten inflammation associated proteins showed significant correlation between CSF and serum. No significant associations were found between protein levels in serum and clinical symptoms.
Conclusion: Our results suggest that inflammatory proteins in CSF are associated with less intense knee pain and milder symptoms in patients with painful knee OA which provides novel targets for pain relief and new insights into the profile of neuroinflammation in OA.

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Poster

748. Somatosensation: Treatments for Persistent Pain

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Topic: D.03. Somatosensation – Pain

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Title: Persistent hyperalgesia modulated by high-fat diet and voluntary physical activity: The role of nucleus accumbens

Authors: *A. D. BRANDÃO, I. J. M. BONET, M. F. PAGLIUSI, JR, G. G. ZANETTI, C. H. TAMBELI, C. A. PARADA, A. S. VIEIRA, C. R. SARTORI;
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Abstract: Persistent hyperalgesia (PH) is highly prevalent among humans with obesity and sedentary lifestyle. It is known that the nucleus accumbens (NAc) is critically involved in PH and in motivation for voluntary physical activity (PA). In addition, high-fat diet (HFD) alters

peripherical and central signaling by increasing inflammatory cytokines and brain gene expression alterations. However, the relationship between HFD, gene expression alterations in NAc, PA, and PH still remain unknown. To address these questions, we used male C57BL/6J mice (at six weeks old) to test whether twelve weeks of HFD facilitates the development of PH by applying a modified model of prostaglandin E2 (PGE)-induced persistent hyperalgesia with a short-term (PH-ST) induction protocol. In this PGE-induced PH-ST protocol, the mice received seven successive daily intraplantar injection of PGE, which produce a non-persistent hyperalgesic state. In a second experimental design, we tested whether six weeks of voluntary PA could prevent the development of PH promoted by HFD. To test this effect, after six weeks on HFD, a second cohort of mice were placed in a home cages with a running wheel, where mice had free access to voluntary PA, before the PH-ST protocol. Finally, we extracted the brain from all mice and microdissected slices to isolate and process NAc samples for transcriptome analysis. All procedures were approved by the animal ethics committee at the University of Campinas (4243-1). The analysis of variance with repeated measures (ANOVA-RM) showed that the HFD-PGE group presented a significative increase of PH when compared to the groups fed with standard diet (SD) ($F_{(2,60)}$=12.52, p<.001). The Newman-Keuls post-hoc test revealed that the HFD-PGE group (3.85 ±0.61g) had increased PH seven days after the end of the PH-ST when compared with the SD-PGE group (0.48 ±0.58g, p=.001). Moreover, the HFD-PGE group presented the same mechanical nociceptive threshold at day 7 when compared to day 1 after the end of PH-ST (p = .89). On the second experimental design, the ANOVA-RM showed that the HFD-PGE-PA group, which did voluntary PA, presented a decreased on PH ($F_{(2,62)}$=4.32, p=.01) from day 1 (3.95 ±0.93g, p=.008) to day 7 after the end of PH-ST (2.5 ±1.38g). Our results corroborate recent findings that the HFD contributes to the development of PH. Furthermore, our results showed that voluntary PA could prevent the development of PH. The analysis of gene expression alterations in NAc through transcriptome technique may reveal the potential target and molecular pathways underling the HFD-induced development of PH, as well, the effects of voluntary PA on preventing this nociceptive sensory response.

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Poster

748. Somatosensation: Treatments for Persistent Pain

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 748.15/F46

Topic: D.03. Somatosensation – Pain

Support: Boston Scientific Corporation

Title: Quantifying the effects of kilohertz-frequency spinal cord stimulation on superficial dorsal horn neurons

Authors: *S.-W. KUO[1], T. ZHANG[3], W. M. GRILL[1,2];
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Abstract: Kilohertz-frequency SCS (KHF-SCS) is applied clinically as a paresthesia-free treatment for chronic pain. The mechanisms of action of KHF-SCS remain elusive but appear to be distinct from those of conventional SCS, as demonstrated by the longer duration of the clinical therapeutic onset of KHF-SCS and the relative inability of KHF-SCS to activate dorsal column axons at intensities below motor threshold. Therefore, we sought to quantify the effects of KHF-SCS on superficial dorsal horn (SDH) neurons directly beneath the SCS electrodes. We previously reported heterogeneous responses from SDH neurons during 30 sec of SCS at either 50 Hz or 10 kHz, which suggested that the minimum amplitude to suppress neuronal activity was frequency- and neuron type-dependent. To investigate further the effects of KHF-SCS, we prolonged stimulation time to 30 min and applied SCS at 50 Hz, 1.2 kHz and 10 kHz in randomized order at 40% motor threshold intensities. Extracellular single-unit recordings, targeting dorsal horn depths <350 μm, were performed in healthy, urethane-anesthetized rats while spinal cord surface temperature was measured using a microprobe-type thermocouple. Neuronal responses were characterized in response to 1 Hz sciatic nerve electrical stimulation applied at 3x C-fiber threshold intensity. Of seven neurons receiving 50 Hz and KHF-SCS, three were low threshold (LT) neurons and four were high threshold (HT) neurons. C-fiber responses (latency > 90 ms) evoked by sciatic nerve stimulation were suppressed in 2 of 4 HT neurons by all SCS frequencies, while the other two HT neurons were non-responders. Of three LT neurons, C-fiber responses were suppressed in one neuron by all SCS frequencies, while the other two were non-responders. No facilitation was observed in either HT or LT neurons. Unconventional mechanisms, such as heating, might contribute to KHF-SCS, but no substantial change in spinal cord surface temperature was detected (<0.1) after either 30 sec or 30 min of KHF-SCS. The results demonstrate heterogeneous effects of KHF-SCS on SDH neurons and indicate the importance of recording such effects in identified neurons to advance our understanding of the mechanisms of action of KHF-SCS.

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Poster

748. Somatosensation: Treatments for Persistent Pain

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 748.16/G1

Topic: D.03. Somatosensation – Pain

Title: Analgesic effect of prolonged gum chewing in patients with burning mouth syndrome

Authors: *N. SEKINE, Y. IMAMURA, A. OKADA;
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Abstract: Purpose: Primary burning mouth syndrome (BMS) is associated with a chronic idiopathic pain in the apparently normal tongue or other oral mucosa. Interestingly, BMS patients do not usually complain of pain during eating, and they often chew gum to reduce their pain. However, the analgesic mechanism has not been elucidated. Therefore, we aimed to investigate the mechanism of analgesic effect following gum chewing in BMS patients. Methods: Twenty nine female BMS patients with and 25 age-matched female controls were recruited at the Orofacial Pain Clinic of Nihon University Dental Hospital. Both groups were randomly divided into two subgroups each, participants chewed a gum for 5 minutes (5 min group) and those who chewed a gum for 20 minutes (20 min group). Twenty min group also imitated a chewing jaw movement without any occlusal contacts for 20 minutes (air chewing) 30 minutes before the real gum chewing. Visual Analog Scale (VAS), concentration of plasma catecholamines (adrenaline, noradrenaline, dopamine), serotonin and progesterone levels and psychological questionnaires including POMS were obtained before and after the intervention. Results: The intensity of pain reduction following gum chewing was more significant than that after air chewing in BMS. There were no differences in the concentrations of catecholamines between the BMS and the control groups at rest. Adrenaline, dopamine and serotonin concentrations significantly decreased after gum chewing, but did not chang after air chewing in BMS patients. Adrenaline was significantly decreased by air and gum chewing in controls. Progesterone concentration and POMS score did not change in both groups. . Consideration: Chewing gum strongly alleviated the pain of BMS patients. Plasma adrenaline might reflect the analgesic effect of gum chewing. From the difference between the results of gum and air chewing, certain factors such as texture and occlusal pressure might have an important role in inducing pain reduction in BMS patients. Chewing duration may be another important factor especially in reducing the level of serotonin, which is a peripheral inflammatory mediator. These results suggest that reduction of serum levels of adrenaline and serotonin is associated with jaw movement not only in BMS patients but also in controls and it may be subsequently related to pain reduction in BMS patients.

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Poster

748. Somatosensation: Treatments for Persistent Pain

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Program #/Poster #: 748.17/G2

Topic: D.03. Somatosensation – Pain

Title: The novel NMDA receptor modulator, NYX-2925, enhances NMDAR-mediated current and LTP, induces changes in cell intrinsic properties, and alters firing properties in layer 5 pyramidal neurons of rat mPFC

Authors: *C. J. KELLY[1], J. R. MOSKAL[1,2], C. N. CEARLEY[1];
[1]Aptinyx, Evanston, IL; [2]Falk Ctr. for Mol. Therapeut., Evanston, IL

Abstract: NYX-2925 is a small-molecule N-Methyl D-Aspartate receptor (NMDAR) modulator capable of enhancing mood, improving cognition, and alleviating centralized neuropathic pain in animal models. We believe the beneficial effects of NYX-2925 are associated with its ability to bind and activate NMDARs and enhance long-term potentiation (LTP) in brain regions involved in learning, executive function, and central control of pain, such as the medial prefrontal cortex (mPFC). Here we show that in the mPFC, NYX-2925 enhances LTP with an inverted U-shaped dose response, with effective concentrations between 1 nM and 500 nM and a loss of effect at a higher concentration of 2 µM. In an effort to understand the mechanistic underpinnings of the observed LTP enhancing effects, we further characterized the NMDA current-enhancing effects of NYX-2925 in rat mPFC layer 5 (L5) pyramidal neurons, and the compound's impact on cell intrinsic properties and firing properties. Using whole-cell patch clamp in L5 pyramidal neurons, we show that NYX-2925 enhances NMDA current maximally at a concentration of 100 nM, with a loss of effect at 2 µM, similar to the LTP effects. At 100 nM, the compound also causes changes in intrinsic membrane properties in these cells, including a slight depolarization of the resting membrane potential and an increase in the hyperpolarization-activated cation conductance (Ih). Ih content within the membrane is known to be upregulated by calcium entry into the cell through NMDARs, which has been shown to result in membrane depolarization, reduced firing, and increased rhythmicity of firing. Consistent with this, our experiments show that NYX-2925 alters firing properties of the L5 pyramidal neurons, leading to a reduction in firing frequency and an increased tendency toward burst firing. Therefore, during LTP induction, we hypothesize that NYX-2925-induced enhancement of Ih contributes to increased rhythmicity of firing and therefore enhanced LTP. These effects are consistent with the long duration of effect of NYX-2925 observed preclinically and support its further investigation as a therapeutic for diseases with disrupted neural plasticity, such as centralized neuropathic pain.

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Poster

748. Somatosensation: Treatments for Persistent Pain

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 748.18/G3

Topic: D.03. Somatosensation – Pain

Support: The Buoniconti Fund
DoD Grant SC150162

Title: Intensive locomotor training provides sustained alleviation of chronic spinal cord injury associated neuropathic pain: A 2-year study

Authors: *B. SCHACHNER[1], E. A. DUGAN[2], S. JERGOVA[3], J. SAGEN[4];
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Abstract: Neuropathic pain often accompanies the functional deficits associated with spinal cord injury (SCI) and further reduces a patient's quality of life. Clinical and pre-clinical research is beginning to highlight the beneficial role that rehabilitative therapies such as locomotor training can have not only on functional recovery but also pain management. Our group has previously developed an intensive locomotor training (ILT) protocol for SCI rats and shown that up to 3 months of ILT alleviated pain symptoms partly through a reduction in inflammatory processes. We have extended these findings in the current study to examine the maintenance of developed pain states in the clip-compression SCI animal model as well as the chronic analgesic benefits of ILT up through 24 months post-SCI. Male Sprague-Dawley rats (200-250g) received a clip-compression SCI at the thoracic 7-8 spinal level which produces consistent and reproducible pain symptoms of thermal hyperalgesia, mechanical allodynia, and cold allodynia. The ILT ramping protocol was initiated 4 weeks post-SCI. Behavioral sensory testing was conducted weekly for 24 months. Experimental groups included: SCI only(n=9), SCI+ILT(n=12), and normal, age matched controls (n=6). Lumbar and lesion spinal cord regions were collected (when possible) and examined for protein expression of pro and anti-inflammatory markers (TNFa, IL10, and IL1b). Correlations between protein expression and end-point behavioral data were made were appropriate. The clip-compression SCI animal model produces consistent thermal hyperalgesia, mechanical allodynia, and cold allodynia for up to 2 years post injury. Animals that received ILT

had a reduction or attenuation of these pain symptoms by 2 months post-SCI that continued for the duration of the study (24 months). Survival rates over the 24 months were increased for animals receiving ILT compared to sedentary animals. The clip-compression SCI produced increased expression of inflammatory markers compared to normal, age matched controls while ILT reduced or normalized protein expression of several pro and anti-inflammatory markers. The clip-compression SCI model can provide maintained pain states for up to 24 months and represents a unique animal model of SCI to examine chronic pain in aging SCI animals. The benefits of chronic ILT suggest that sustained and long-term physical therapy can produce powerful and prolonged management of neuropathic pain, partly through regulation of different inflammatory processes. A comprehensive understanding of the long-term benefits of intensive rehabilitative therapies will provide a more beneficial treatment strategy for SCI patients.

Disclosures: B. Schachner: None. **E.A. Dugan:** None. **S. Jergova:** None. **J. Sagen:** None.

Poster

748. Somatosensation: Treatments for Persistent Pain

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Program #/Poster #: 748.19/G4

Topic: D.03. Somatosensation – Pain

Support: Canadian Institutes of Health Research (CIHR)
Fonds québécois de la recherche sur la nature et les technologies (FQRNT)

Title: CCR2 pepducins alleviate neuroimmune-driven bone cancer pain through allosteric antagonism

Authors: *E. MIDAVAINE, R. L. BROUILLETTE, G. DE ARMAS GUITART, É. BESSERER-OFFROY, V. ZEUGIN, C. MONA, J.-M. LONGPRÉ, E. MARSAULT, P. SARRET;
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Abstract: Bone pain is a profoundly disabling condition with largely unmet analgesic needs for patients coping with bone metastases. The CCR2 receptor along with its chemokine ligand CCL2 are well-known for their role in driving tumor progression and pain hypersensitivity. The CCR2 signaling also orchestrates immune cell recruitment into the sensory nervous system, thus contributing to a heightened pro-inflammatory state and exaggerated nociceptive responses. Decades of failed clinical trials targeting CCR2 at its extracellular orthosteric site provide a rationale for implementing alternative therapeutic strategies. To this aim, we recently developed and characterized CCR2-targeting cell-penetrating palmitoylated peptides (also called pepducins), designed from the intracellular loops (ICL) of CCR2 and acting as allosteric modulators. We investigated the effects of ICL1- and ICL3-derived pepducins on bone cancer

pain development and tumor proliferation. In a MRMT-1 bone cancer pain model in Sprague-Dawley female rats, administration of anti-CCR2 pepducins significantly decreased the allodynic responses as well as the non-reflexive pain behaviors. *In vitro,* pepducins significantly decreased the MRMT-1 cell survival as assessed by WST-1 assay and DAPI cell cycle analysis using flow cytometry. However, pepducins selectively targeting CCR2 were unable to reduce the skeletal tumor burden *in vivo*. Tumor-bearing animals also showed an increase in pain-related neurotransmitters and gap junction protein expression (Cx43) in the lumbar dorsal root ganglia (DRG). This neuronal pain signaling was accompanied by an increased number of $Iba1^+$ and $Iba1^+CD68^+$ activated resident macrophages in DRGs, as well as by an infiltration of peripheral immune cells identified as $CD11b^+CD45^+Iba1^-$ monocytes and $CD3^+$ T cells. Chronic treatment with anti-CCR2 pepducins resulted in a significant decrease in both pain-related neurotransmitter expression as well as bone cancer pain-induced myeloid and adaptive cell infiltration. At the spinal cord level, neurons located in the marginal nucleus showed decreased signaling following CCR2 allosteric modulation, as determined by decreased ERK1/2 and c-Fos activation. Noteworthy, pain hypersensitivity was independent of spinal immune cell infiltration. In conclusion, CCR2 allosteric inhibition may limit tumor burden and improve pain management through decreased peripheral neuroinflammatory signaling.

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Poster

748. Somatosensation: Treatments for Persistent Pain

Location: Hall A

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Program #/Poster #: 748.20/G5

Topic: D.03. Somatosensation – Pain

Support: Department of Defense CDMRP Award W81XWH-15-1-0494
T32 Training Grant T32DA07234

Title: AAV5 particle kinetics in adult and aged mice following intrathecal injection

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Abstract: The intrathecal (IT) delivery of adeno-associated virus (AAV)-based gene therapeutics is increasingly being investigated as a tool for treating both motor and sensory disorders. Previously published studies rely on the expression patterns of reporter genes such as GFP or other fluorescent markers following gene transfer to determine the biodistribution of such therapeutics in mouse populations. However, this only indicates regions of successful transduction, not the entire distribution profile of AAVs following IT injection. Furthermore, the prevalence of motor and sensory disorders increases with age, so we must consider changes of therapeutic distribution in aged populations when developing AAV therapies. However, there is limited information regarding the distribution of viral particles in aged mouse models following IT delivery. To address these gaps in knowledge, we evaluated the pattern of distribution of viral vector particles following IT delivery of AAV5 in mice. Conscious adult and aged male and female ICR-CD1 mice (4 to 20 months) were injected intrathecally with AAV5-ef1alpha-GFP (1.37 x 10(11) vector genomes in 5 microliters) or saline. Over 48 hrs post-injection animals were serially sacrificed, and whole blood and tissues of interest were immediately collected. Tissues and whole blood were then examined using qPCR to detect the presence of viral DNA. Viral particle distribution was also visualized using IHC targeting a viral capsid protein in whole column slices to determine patterns in particle distribution in relation to central and peripheral nervous system tissues. Viral DNA concentration in adult whole blood reaches a maximum at 6 hrs post-injection. Spinal tissue and dorsal root ganglia (DRG) have early increases in viral DNA. Interestingly, lumbar DRG have a secondary spike in viral DNA concentration 24 hours post-injection. In aged mice, whole blood concentrations increase over 6 hrs post-injection with viral DNA concentrations in other tissues following similar patterns as in adult mice. At 1 hr post-injection, AAV5-ir was observed in the region of the pia mater surrounding the spinal cord parenchyma and surrounding adjacent nerve fibers. This pattern was observed at 2, 6, and 12 hours post-injection but not evident at 24 hours. AAV5-ir was observed in cellular profiles in DRG at 0.5, 2, and 12 hours. This research furthers our evaluation of AAV vectors and their distribution in adult and aged populations for clinical translation.

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Poster

748. Somatosensation: Treatments for Persistent Pain

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 748.21/G6

Topic: D.03. Somatosensation – Pain

Title: High frequency kHz spinal cord stimulation (SCS) modulate spinal dorsal horn neurons in neuropathic pain rats

Authors: *K. LEE, D. LEE, Z. KAGAN, K. BRADLEY;
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Abstract: Paresthesia-free 10kHz spinal cord stimulation has Level I clinical evidence demonstrating clinically-superior, long-term pain relief. Recent studies in normal rats have suggested that 10kHzSCS selectively modulates interneurons in superficial dorsal horn (SDH). In order to see how 10kHzSCS might modulate spinal interneurons to relieve neuropathic pain, we investigated brush and von Frey evoked responses of SDH neurons in neuropathic pain model (L5 spinal nerve ligation) rats. 10-14 days after SNL surgery, laminectomy and electrophysiological recordings were made under urethane anaesthesia. In all experiments, bipolar 10kHzSCS at 30% of motor threshold (MT) was applied via a micro-sized in-line quadripolar electrode array positioned epidurally over the L5-L6 dorsal spinal segments. A 4-pronged, 16-contact extracellular recording electrode was plunged into the SDH (depth from cord surface: 300±50um) within 1mm of the active contacts on the SCS array. First, we used brush and innocuous VF (10g) stimuli on the ipsilateral hindpaw to find the receptive-field center, and to characterize the type of responsive SDH neurons by their firing pattern. We then applied brush and VF (1, 2, 6, 10, 15g) to investigate the input-output relationship (I/O) of SDH neurons before (Baseline) and during 10kHzSCS. In 5 rats, a neuropathic pain condition was confirmed by clear expansion of the receptive field compared to normals. Also, brush-evoked responses of SDH neurons in SNL rats were reduced by ~40%. Three different cell types (Adapting, Non-Adapting, and After-discharging) were identified by 10g VF in neuropathic pain rats, whereas only two types (Adapting and Non Adapting) were previously identified in naïve rats. Compared to Baseline, during 10kHzSCS, there was reduction of slope of the I/O relationship in Adapting cells while the increase of Y-intercept was observed in Non-adapting cells with no change of slope.Conclusions: Per previous studies, Adapting and Non-adapting cells might be regarded as excitatory and inhibitory interneurons, respectively. These data suggest an underlying pain signal pathway and functional relationship between neurons in SDH, which is modulated by 10kHzSCS: Activity(excitatory neuron) = Primary Afferent Input / Activity(inhibitory neuron). Thus, any increase in inhibitory interneuron activity (e.g., by 10kHzSCS), will reduce the influence of afferent drive on excitatory interneurons, and hypothetically provide a profound reduction in pain transmission in SDH.

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Poster

748. Somatosensation: Treatments for Persistent Pain

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 748.22/G7

Topic: D.03. Somatosensation – Pain

Support: Dept. of Anesthesiology, UW Hospitals and Clinics

Title: The effect of a $GABA_A$ $alpha_5$ receptor agonist on mechanical sensitivity following nerve injury

Authors: *R. C. LENNERTZ, III[1], G. LI[2], D. KNUTSON[2], J. M. COOK[2], M. BANKS[1];
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Abstract: GABA receptors are targeted by inhibitory interneurons to modulate cortical activity. Peripheral nerve injury diminishes the activity of somatostatin-expressing (SOM) interneurons in somatosensory cortex (S1). Recent studies suggest that SOM neurons suppress dendritic calcium spikes in cortical layer 1 via $GABA_A$ α_5 receptors. Increasing SOM neuron activity in S1 using optogenetics was shown to normalize behavioral mechanical sensitivity following nerve injury. Therefore, we hypothesized that a $GABA_A$ α_5 receptor agonist may augment SOM neuron activity and also decrease mechanical sensitivity following nerve injury. We performed spared nerve injury (SNI) in 7-8 week old C57bl6 mice as a model of neuropathic pain. We assessed paw withdrawal threshold (PWT) as a measure of mechanical sensitivity. Then, we injected the $GABA_A$ α_5 receptor agonist MP-III (1-10 mg/kg) or vehicle in SNI and sham animals 7-10 days following nerve injury. The experimenter was blinded to the content of each injection. We observed a partial improvement in PWT in SNI mice treated with 3 or 10 mg/kg MP-III. There were no changes in PWT in sham mice or in the contralateral paw. There were no differences between male and female mice. Next, we implanted an osmotic pump at the time of the SNI surgery to continuously administer MP-III for 7 days postoperatively. Again, we observed a partial improvement in PWT at POD3 and POD7 that did not persist past the time course of the infusion. We conclude that the $GABA_A$ α_5 receptor agonist MP-III partially improves mechanical sensitivity following nerve injury. Further experiments will need to determine whether MP-III changes cortical activity in S1.

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Poster

748. Somatosensation: Treatments for Persistent Pain

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Program #/Poster #: 748.23/G8

Topic: D.03. Somatosensation – Pain

Support: NRF Grant HI15C3518
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Title: Multi-modal gene theraphy for neuropathic pain

Authors: D. KIM, Y. SIM, H. JI, J. PARK, J. CHO, ***K.-R. KIM**, M. KIM, Y. KWON, M. KIM, H. CHOI, S. KIM;
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Abstract: Neuropathic pain (NP) is chronic pain state syndrome and has complex underlying pathophysiology. Current NP treatment regimens employ anticonvulsants, antidepressants, and opioids. These single target analgesic treatments have limited analgesic efficacy and show low patients' responsiveness. Simultaneous targeting of multiple pathologic elements in NP is required to develop effective NP medicine. KLS-2031 consists of 2 AAV vectors expressing 3 transgenes (AAV-hGAD65 and AAV-hGDNF/hIL-10) to control the major pathological mechanisms of NP, including nerve injury, neuroinflammation, and neuronal hyperactivity. In this study, we evaluated KLS-2031 as a novel therapeutics for NP. The model system utilized in this study was a rat spared nerve injury model. KLS-2031 was administered one time into a lumbar vertebra 4 intervertebral foramen using micro-catheter for targeted delivery of the drug to peri-dorsal root ganglion space. Pain-related behavior was measured with *von Frey* filament (VFF). The effects of KLS-2031 on nerve injury, stress, and neuronal inflammation were assessed by the expression of activated caspase3 and ionized calcium binding adaptor molecule 1 (Iba1). KLS-2031 showed significant analgesic effect in the SNI model. KLS-2031, the three gene combination vectors, significantly reduced mechanical allodynia in the SNI model compared to the single or two gene combination usage. When the long-term analgesic effect was evaluated with the VFF, the effect was maintained for up to 12 weeks in both female and male rats. Furthermore, KLS-2031 showed to be more potent on reducing the expression of activated caspase3 and Iba1. Pathological features of NP were restored to the normal level when the SNI model received transforaminal epidural injection of KLS-2031. KLS-2031 is being developed as combinational gene therapy to treat multiple aspects of pathophysiology involved in NP. Gene combination approach turned out to be more potent than single gene approach in analgesic effect and restoring pathophysiology of NP. Especially, KLS-2031 effectively normalized the peripheral and central sensitization of pain with a single administration. Based on these result, KLS-2031 could be a promising therapeutic option for refractory NP and be a disease-modifying agent.

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Poster

748. Somatosensation: Treatments for Persistent Pain

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 748.24/G9

Topic: D.03. Somatosensation – Pain

Title: Polarization of model superficial dorsal horn (SDH) neurons by kilohertz frequency spinal cord stimulation (KHF-SCS)

Authors: *N. D. TITUS[1], J. E. GILBERT[1], B. J. THIO[1], T. C. ZHANG[2], W. M. GRILL[1]; [1]BME, Duke Univ., Durham, NC; [2]Boston Scientific Corp., Valencia, CA

Abstract: Understanding the mechanisms of action underlying KHF-SCS for chronic pain may lead to improved therapies. Previous single axon recordings in rats showed that extensive activation and block of dorsal column axons by KHF-SCS are unlikely. We hypothesized instead that the oscillating electric field generated during KHF-SCS may directly influence SDH neuron activity; therefore, we modeled the response of a SDH nociceptive-specific cell (NS), GABAergic interneuron (GABA), and vertical neuron to KHF-SCS. The model neurons included realistic biophysical properties determined from both prior literature and particle swarm optimization to match the response of model neurons to published electrophysiological data. In some simulations, we generated baseline activity in the model cells by distributing independent, stochastic synaptic activity across the cells' dendritic arbors. We computed the electric fields generated in the rat spinal cord by a bipolar electrode placed in the epidural space using the finite element method (FEM), applied the FEM calculated potentials to the compartments of morphologically-realistic model neurons, and simulated the effects of 1.2 kHz and 10 kHz SCS on the firing rate (FR) of model neurons. KHF-SCS applied at amplitudes estimated from prior literature to be at or below 40% of motor threshold did not directly activate model neurons; however, KHF-SCS altered patterns of synaptically driven, ongoing activity in the GABA and NS cells in a manner that was dependent on stimulation amplitude, neuron biophysics, and baseline FR. SCS applied at 1.2 kHz or 10 kHz decreased the baseline FR of the NS neuron by up to 30%. Additionally, SCS applied at 1.2 kHz but not 10 kHz increased the baseline FR of the GABA cell by up to 20%. Vertical cell activity was unaffected by KHF-SCS. Finally, we found that the influence of KHF-SCS could be approximated by direct current injections into model neurons, enabling translation of single cell effects determined with biophysically-realistic neurons to a network model of point neurons representing the SDH network. These results suggest the involvement of subthreshold polarization in the analgesic effects provided by KHF-SCS. Acknowledgments: This work was supported by the Boston Scientific Corporation.

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property rights/patent holder, excluding diversified mutual funds); Boston Scientific Corporation. **W.M. Grill:** 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.; Boston Scientific Corporation. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Boston Scientific Corporation. F. Consulting Fees (e.g., advisory boards); Boston Scientific Corporation.

Poster

748. Somatosensation: Treatments for Persistent Pain

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 748.25/G10

Topic: D.03. Somatosensation – Pain

Support: Boston Scientific Corporation

Title: Effects of conventional and kHz frequency spinal cord stimulation (SCS) in a network model of nociceptive processing in the superficial dorsal horn

Authors: *J. E. GILBERT[1], N. D. TITUS[1], T. ZHANG[2], W. M. GRILL[1];
[1]Duke Univ., Durham, NC; [2]Boston Scientific Neuromodulation, Valencia, CA

Abstract: SCS is an effective therapy for neuropathic pain but most animal and computational modeling studies investigating pain and SCS mechanisms focused on the responses of deep dorsal horn wide-dynamic-range (WDR) neurons. Neuropathic pain also involves disinhibition of the superficial dorsal horn (SDH) via loss of glycinergic and GABAergic inhibition and depolarizing shifts in the reversal potential of inhibitory synapses. These changes unmask abnormal feedforward excitation to SDH nociceptive-specific (NS) neurons, and disinhibition may underlie hyperalgesia and allodynia, two features of neuropathic pain. Therefore, we sought to understand how both conventional SCS and novel sub-perception SCS, typically applied at kHz frequencies faster than the refractoriness of dorsal column axons, interacts with the SDH network to reduce pain transmission. We implemented a computational model of SDH neuronal circuitry to characterize the roles of feedforward excitation and different modes of inhibitory control in determining NS neuron activity. We validated the model by comparing network responses to corresponding data from mechanical and electrical stimulation. We modeled conventional SCS as synaptic inputs to the dorsal horn network via activation of dorsal column Aβ afferents and the field effect of kHz frequency SCS as current injections into both NS and GABAergic SDH neurons titrated to produce firing rate effects equivalent to those from direct simulations of kHz frequency SCS. Both conventional SCS applied at 50 Hz and kHz frequency SCS suppressed model NS neuron activity. Furthermore, the combination of field effects due to kHz frequency SCS and SDH network amplification of these effects reduced model NS neuron

activity more than the direct field effects of kHz frequency SCS did alone. The magnitude of the effects from kHz frequency SCS and observed shifts in the optimal frequency of conventional SCS following pain progression were both dependent on the mechanism of disinhibition in the dorsal horn, suggesting a dependence of efficacy on pain etiology. This work synthesizes heterogeneous experimental recordings from superficial dorsal horn neurons into a computational network model that replicates experimental responses and that enabled quantification of SDH neuronal responses to different modes of SCS under diverse neuropathic pain conditions.
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Poster

748. Somatosensation: Treatments for Persistent Pain

Location: Hall A

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Program #/Poster #: 748.26/G11

Topic: D.03. Somatosensation – Pain

Support: DFG grant PL 321/10-2
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Technical University of Munich, School of Medicine, Clinician Scientist Program (KKF)

Title: Longitudinal resting-state electroencephalography correlates of interdisciplinary multimodal treatment of chronic pain patients

Authors: *H. B. HEITMANN[1], S. TA DINH[2], M. M. NICKEL[5], E. S. MAY[3], V. D. HOHN[3], L. TIEMANN[2], T. R. TÖLLE[2], M. PLONER[4];
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Abstract: Chronic pain is a major healthcare issue which poses a large burden on individuals and society. Converging lines of evidence from animals and humans indicate that chronic pain is associated with substantial changes of brain structure and function. However, the functional significance of these changes is only incompletely understood. In particular, it remains unclear how these changes relate to clinical parameters and whether they can be reversed by appropriate therapy. Interdisciplinary multimodal pain therapy (IMPT) is a multimodal treatment provided by an interdisciplinary team collaborating in assessment and treatment using a shared biopsychosocial model and goals. IMPT has been proven effective in the treatment of chronic pain. However, the effects of IMPT on brain function remain to be elucidated. A better understanding of these effects promises insights into the functional significance of brain changes in chronic pain and the brain mechanisms of IMPT. To this end, we analyzed clinical data and resting-state electroencephalography (EEG) recordings of 24 chronic pain patients (age 52.2 ± 17.1 years (mean ± standard deviation), 13 female, predominantly chronic back pain), obtained directly before and six months after IMPT which was provided in a day-clinic setting in a multidisciplinary pain center over a period of 20 days. IMPT was performed according to standards defined by the German Pain Society and included physio- and psychotherapy as well as individual pharmacotherapy. At follow-up six months post IMPT, a significant decrease in average pain intensity (Numerical Rating Scale, 5.3 vs. 4.5, $p = .021$) as well as pain affect (Short-Form McGill Pain Questionnaire affect scale, 5.1 vs. 3.7, $p = .016$) and pain-related disability (Pain Disability Index, 28.6 vs. 23.3, $p = .039$) was found. Moreover, subjective therapeutic benefit from IMPT positively correlated with an increase in the EEG peak frequency from baseline to follow-up ($r = .46$; $p = .029$). Further analyses will relate changes in clinical data to EEG-based connectivity and network measures. Moreover, we will apply a machine learning approach to distinguish between IMPT responders and non-responders. These analyses will advance the understanding of functional plasticity of the brain in chronic pain. Moreover, they might help to identify easily available EEG-based markers and predictors for chronic pain treatment.

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Poster

748. Somatosensation: Treatments for Persistent Pain

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 748.27/G12

Topic: D.03. Somatosensation – Pain

Support: DFG grant PL 321/10-2
DFG grant PL 321/11-2

Title: Dynamics of resting-state electroencephalography in chronic pain patients

Authors: S. TA DINH[1], E. S. MAY[1], C. GIL AVILA[1], H. HEITMANN[1], M. M. NICKEL[1], L. TIEMANN[1], V. D. HOHN[1], T. TOELLE[1], J. GROSS[2], L. LEAL-TAIXÉ[1], ***M. PLONER**[1]; [1]TU Muenchen, Munich, Germany; [2]Univ. of Münster, Münster, Germany

Abstract: Chronic pain is characterized by ongoing pain that persists past normal healing time and lacks the warning function of acute pain. It is associated with significant sensory, cognitive and affective abnormalities, has detrimental effects on quality of life and is a leading cause of disability worldwide. Converging lines of evidence from animals and humans indicate that the brain plays an important role in chronic pain. However, the brain mechanisms of chronic pain are not fully clear yet. We have previously used resting-state electroencephalography (EEG) to define abnormalities of brain function in chronic pain and to establish a brain-based marker of chronic pain. In chronic pain patients and pain-free controls, we systematically analyzed measures of brain activity and brain connectivity. A support vector machine enabled us to differentiate between patients and controls based on frontal connectivity in the theta (4 to 7 Hz) and gamma (60 to 100 Hz) frequency bands. However, classification accuracy was 57 percent, which was significantly above chance level but far from being clinically useful.Here, we aimed to further exploit the potential of resting-state EEG to advance the understanding of the brain pathology of chronic pain and to establish an EEG-based marker of chronic pain. To this end, we assessed the dynamics of brain activity and brain connectivity by analyzing the raw time series EEG data in 101 chronic pain patients (age 58.2 ± 13.5 years (mean ± standard deviation), 69 female)and 84 matched, pain-free controls (age 57.8 ±14.6 years, 55 female). In particular, we aimed to increase the performance of the classification by implementing deep learning on the raw time series data. Moreover, we assessed themoment-to-moment variablity of brain activity by analyzing measures of neuronal variability such as multiscale entropy. Results show that the application of a convolutional neural network architecture to the raw resting-state EEG data yielded an accuracy of 70 percent for the classification of chronic pain patients vs. healthy controls. These findings constitute another step forward towards a brain-based marker of chronic pain. Furthermore, though deep learning networks are generally hard to interpret, the

combination of multivariate pattern analysis and variability analysis might help to understand abnormalities of brain function in chronic pain patients.

Disclosures: S. Ta Dinh: None. **E.S. May:** None. **C. Gil Avila:** None. **H. Heitmann:** None. **M.M. Nickel:** None. **L. Tiemann:** None. **V.D. Hohn:** None. **T. Toelle:** None. **J. Gross:** None. **L. Leal-Taixé:** None. **M. Ploner:** None.

Poster

749. Role of Inflammatory and Immune Responses in Chronic Pain

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 749.01/G13

Topic: D.03. Somatosensation – Pain

Support: NIH NS097880

Title: Dissecting the role of CCL2 in neuropathic pain development

Authors: *J. H. RICHARDS, S. J. CHHAYA, M. R. DETLOFF;
Neurobio. & Anat., Drexel Univ. - Col. of Med., Philadelphia, PA

Abstract: Neuropathic pain is recognized as a neuroimmune disorder, but the mechanisms of this disorder remain unclear. The lack of effective pain relief through current therapies may be due to our limited understanding of the reciprocal relationship between neuronal dysfunction and the immune response to nerve injury in the development and maintenance of pain. The neuronal and immune mechanisms of pain intersect at the dorsal root ganglia (DRG), and we are interested in examining the interaction between macrophages and primary nociceptive neurons of the DRG. We previously showed that spinal cord injury (SCI)-induced neuropathic pain corresponds to a sustained macrophage presence in the DRG. Others report that reducing macrophage chemoattractant molecule CCL2 signaling by knockdown of its receptor can prevent pain development after peripheral nerve injury. Acutely after SCI, CCL2 protein was significantly elevated in the DRG at 24 hours that returned to normal levels by 72h. To better understand the relationship between this transient increase in DRG CCL2 and pain development by recruitment of macrophages, a unilateral injection of recombinant rat CCL2 or vehicle was administered to the C7 and C8 DRG of the uninjured Sprague Dawley rat and assessed the development of neuropathic pain over time. Neuropathic pain was assessed using von Frey and mechanical conflict avoidance paradigm. As expected, all rats exhibited temporary forepaw hypersensitivity due to the surgical procedure. Rats that received CCL2 exhibited persistent forepaw hypersensitivity that did not resolve compared to naïve and vehicle-treated rats ($p<.05$). Rats were sacrificed at 5 and 20 days post injection, and RNA was isolated from C7 and C8 DRGs. Preliminary qPCR analysis revealed that there was a 5 fold increase in CCL2, and concomitant increase in CD68, a macrophage marker at 5 days post SCI. Surprisingly, the

M2/anti-inflammatory macrophage marker Arg1 was significantly elevated and the M1/proinflammatory macrophage marker iNOS was decreased compared to vehicle and naïve animals ($p<.05$). Further qPCR analyses are underway. These data support the hypothesis that CCL2 may be acting to reduce injury-induced inflammation and decrease nociceptor dysfunction.

Disclosures: **J.H. Richards:** None. **S.J. Chhaya:** None. **M.R. Detloff:** None.

Poster

749. Role of Inflammatory and Immune Responses in Chronic Pain

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 749.02/G14

Topic: D.03. Somatosensation – Pain

Support: NIH NS097880 (MRD)

Title: Macrophage recruitment to the dorsal root ganglia modulates pain after spinal cord injury

Authors: *S. J. CHHAYA, J. H. RICHARDS, J. S. DOWLING, M. R. DETLOFF; Neurobio. & Anat., Drexel Univ. Col. of Med., Philadelphia, PA

Abstract: Spinal cord injury (SCI) damages sensory systems and causes chronic, intractable neuropathic pain, which is driven by nociceptor sensitization in the dorsal root ganglia (DRG). Inflammation in the DRG in response to SCI may contribute to nociceptor dysfunction and pain development. Little is known of the immune signaling events that transpire in the DRG after SCI that could induce pathological changes in the nociceptor and drive pain. We have previously shown that an increase in DRG macrophages is associated with pain at chronic timepoints post-SCI. This study aimed to determine whether macrophage recruitment to the DRG after SCI is essential to pain development and if macrophage phenotype and cytokine release can dictate pain. Rats received a moderate, C5 contusion that causes neuropathic pain in a subset of rats as assessed by von Frey and mechanical conflict avoidance tests. We assessed the acute immune response to SCI in the C7-8 DRGs at 12, 24, 48, 72- and 120-hours post-injury (hpi). Macrophage chemoattractant CCL2 levels were assessed using ELISA and qPCR, along with mRNA expression of macrophage phenotype markers and cytokines, and ED1 labeling with immunohistochemistry. A subset of SCI rats received INCB3344, a CCR2 antagonist intravenously acutely after SCI (0-72hpi) to prevent macrophage recruitment to the DRG. Time course experiments revealed a rapid transient increase in CCL2 mRNA in the DRG at 12hpi, followed by recruitment of ED1+ cells. Rats administered INCB3344 from 0-3dpi had fewer macrophages in the DRG at 7 dpi compared to vehicle-treated rats. Surprisingly, this induced transient pain that partially recovered by 28dpi. Macrophages of INCB treated rats were pro-inflammatory by 28dpi; yet, multivariate statistical analysis on early DRG immune environment

revealed that rats were distributed into two distinct clusters acutely after SCI based on mRNA expression- those with a large fold-change in anti-inflammatory markers in the DRG, or with near-normal expression. Our data supports the hypothesis that there is a dichotomy in the peripheral immune response to SCI in the DRG that may influence pain development. While macrophages at 28dpi are pro-inflammatory and associated with pain, early macrophage recruitment may be anti-inflammatory and necessary to prevent pain. Future studies will examine the influence of macrophages on nociceptor electrophysiological dysfunction as a mechanism of DRG neuroimmune interactions contributing to SCI-induced neuropathic pain.

Disclosures: S.J. Chhaya: None. **J.H. Richards:** None. **J.S. Dowling:** None. **M.R. Detloff:** None.

Poster

749. Role of Inflammatory and Immune Responses in Chronic Pain

Location: Hall A

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Program #/Poster #: 749.03/G15

Topic: D.03. Somatosensation – Pain

Support: NIH grants R01NS094664
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Title: Tet1 overexpression mitigates neuropathic pain through rescuing the expression of μ-opioid receptor and Kv1.2 in the primary sensory neurons

Authors: *J. XIAO, Q. WU, G. WEI, Y.-X. TAO;
Rutgers, the State Univ. of New Jersey, Newark, NJ

Abstract: Peripheral nerve injury downregulates the expression of the μ-opioid receptor (MOR) and voltage-gated potassium channel subunit Kv1.2 by increasing their DNA methylation in the dorsal root ganglion (DRG). Ten-eleven translocation methylcytosine dioxygenase 1 (TET1) causes DNA demethylation. Given that DRG MOR and Kv1.2 downregulation contribute to neuropathic pain genesis, this study investigated the effect of DRG TET1 overexpression on neuropathic pain. Overexpression of TET1 in the DRG through microinjection of herpes simplex virus expressing full-length TET1 mRNA into the injured rat DRG significantly alleviated the fifth lumbar spinal nerve ligation (SNL)-induced pain hypersensitivities during the development and maintenance periods, without altering acute pain or locomotor function. This microinjection also restored morphine analgesia and attenuated morphine analgesic tolerance development after SNL. Mechanistically, TET1 microinjection rescued the expression of MOR and Kv1.2 by

reducing the level of 5-methylcytosine and increasing the level of 5-hydroxymethylcytosine in the promoter and 5' untranslated regions of the Oprml1 gene (encoding MOR) and in the promoter region of the Kcna2 gene (encoding Kv1.2) in the DRG ipsilateral to SNL. These findings suggest that DRG TET1 overexpression mitigated neuropathic pain likely through rescue of MOR and Kv1.2 expression in the ipsilateral DRG. Virus-mediated DRG delivery of TET1 may open a new avenue for neuropathic pain management.

Disclosures: J. Xiao: None. **Q. Wu:** None. **G. Wei:** None. **Y. Tao:** None.

Poster

749. Role of Inflammatory and Immune Responses in Chronic Pain

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 749.04/G16

Topic: D.03. Somatosensation – Pain

Support: NIH R01 NS094664

Title: Injectable PLGA coated ropivacaine produces a long lasting analgesic effect on incisional pain and neuropathic pain

Authors: *Y. TAO, X. TIAN, F. LIN, F. JI, A. BEKKER;
New Jersey Med. School, Rutgers, Newark, NJ

Abstract: The management of persistent postsurgical pain and neuropathic pain remains a challenge in clinic. Local anesthetics have been widely used as a simple and effective treatment for these two disorders, but the duration of their analgesic effect is short. We here reported a new poly lactic-co-glycolic acid (PLGA)-coated ropivacaine that was continuously released in vitro for at least 6 days. Peri-sciatic nerve injection of PLGA-coated ropivacaine dose-dependently attenuated paw incision-induced mechanical allodynia and heat hyperalgesia during the incisional pain period and spared nerve injury-induced mechanical and cold allodynia for up to 12 days post-injection. This injection did not produce detectable inflammation, tissue irritation and pathological nerve changes in the sciatic nerve at the injected site, although a mild and transient motor function compromise was observed in the higher dosage-treated groups. Given that PLGA is an FDA-approved medical material and that ropivacaine is used currently in clinical practice, the injectable PLGA-coated ropivacaine represents a new and highly promising avenue in the management of postsurgical pain and neuropathic pain.

Disclosures: Y. Tao: None. **X. Tian:** None. **F. Lin:** None. **F. Ji:** None. **A. Bekker:** None.

Poster

749. Role of Inflammatory and Immune Responses in Chronic Pain

Location: Hall A

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Program #/Poster #: 749.05/G17

Topic: D.03. Somatosensation – Pain

Support: GACR 18-09853S
MSMT LQ1604 BIOCEV-FAR
GAUK 734218

Title: CCL2 attenuates opioid-induced inhibition of nociceptive signaling in the spinal cord in a microglia-dependent manner

Authors: *M. HELEŠ, P. MROZKOVA, D. SULCOVA, P. ADÁMEK, D. SPICAROVA, J. PALECEK;
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Abstract: Opioid therapy, while remaining an effective tool for the treatment of many acute and chronic pain states, is mostly ineffective in neuropathic pain and may even lead to opioid-induced hyperalgesia. Neuropathic pain is often accompanied by neuroinflammation and increased levels of different cytokines and chemokines. Our study focused on the effect of CCL2 (C-C motif chemokine ligand 2) and activation of TRPV1 (transient receptor potential vanilloid 1) on the analgesia induced by activation of MOR (μ-opioid receptor). MOR, TRPV1 and CCL2 receptors (CCR2) are present in presynaptic membranes of nociceptive primary afferent neurons in the spinal cord dorsal horn and modulate synaptic transmission at first nociceptive synapse. To study the modulation of opioid analgesia we used whole-cell patch clamp recordings of miniature (mEPSC) and dorsal root stimulation-evoked excitatory postsynaptic currents (eEPSC) from superficial dorsal horn neurons in rat spinal cord slices. We used the application of MOR agonist DAMGO ((D-Ala2,N-Me-Phe4,Gly-ol5)-enkephalin) (1μM), incubation with CCL2 (10nM) and SB366791 (10 μM) as a TRPV1 antagonist. To evaluate the possible contribution of microglia activation, we applied minocycline (100 μM). In our experiments acute application of DAMGO depressed frequency of mEPSC to 60.8 ± 4.0 % ($P<0.001$, n=16) and amplitudes of eEPSC to 33.0 ± 5.3 % of the control value ($P<0.001$, n=15) while induced increase of eEPSC amplitudes 15 minutes later. Incubation with CCL2 (2 h) partially diminished the DAMGO-induced inhibition of mEPSC (82.4 ± 3.9 %, n=11) and eEPSC (97.4 ± 10.7 %, n = 11). Incubation with minocycline attenuated the CCL2 induced effect. Pretreatment with SB366791 did not change the DAMGO-induced inhibition of eEPSC but prevented the eEPSC amplitudes increase present under control conditions 15 min later. In conclusion, our data suggest that paradoxical hypersensitivity during opioid withdrawal may be at least partially mediated by

TRPV1 receptors and that CCL2 attenuates the inhibitory effect of DAMGO in a microglia activation-dependent manner.

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Poster

749. Role of Inflammatory and Immune Responses in Chronic Pain

Location: Hall A

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Topic: D.03. Somatosensation – Pain

Support: NRF Grant 2017R1A2A2A05001402
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Title: Spinal cytochrome p450c17-induced astrocyte activation is mediated by p38 mitogen-activated protein kinase phosphorylation in a mouse model of neuropathic pain

Authors: S.-R. CHOI[1], A. J. BEITZ[2], *J.-H. LEE[1];
[1]Dept. of Vet. Physiol., BK21 PLUS Program for Creative Vet. Sci. Research, Res. Inst. for Vet. Sci. and Col. of Vet. Medicine, Seoul Natl. Univ., Seoul, Korea, Republic of; [2]Dept Vet & Biomed Sci., Univ. of Minnesota Col. of Vet. Med., Saint Paul, MN

Abstract: It has been suggested that peripheral nerve injury induces spinal astrocyte activation and leads to the development of neuropathic pain. We have recently demonstrated that cytochrome P450c17 is increased in spinal astrocytes and plays a critical role in the development of neuropathic pain following peripheral nerve injury. However, whether or how spinal P450c17 modulates pathological changes in astrocytes remain unclear. Here we investigated whether P450c17 modulates astrocyte activation and whether this process is mediated by p38 mitogen-activated protein kinase (MAPK) and leads to the development of mechanical allodynia in a mouse model of neuropathic pain. Chronic constriction injury (CCI) of the sciatic nerve induced a significant increase in glial fibrillary acidic protein (GFAP) expression in the superficial dorsal horn (SDH, laminae I-II) and nucleus proprius (NP, laminae III-IV) regions of the spinal cord. Repeated daily (from days 0-3 post-surgery) intrathecal (i.t.) administration of the P450c17 inhibitor, ketoconazole significantly inhibited the CCI-induced pathological activation of astrocytes. In addition, i.t. administration of ketoconazole significantly inhibited the CCI-induced increase in p38 MAPK phosphorylation, which is expressed in GFAP-positive astrocytes in the SDH and NP regions. I.t. administration of a sub-effective dose of the p38 MAPK inhibitor, SB203580 potentiated the pharmacological effect of ketoconazole on the development of mechanical allodynia as well as astrocyte activation in the spinal cord of CCI mice. Collectively these results suggest that spinal cytochrome P450c17 activates astrocyte via p38 MAPK

phosphorylation, ultimately leading to the development of mechanical allodynia induced by peripheral nerve injury.
Key Words: MAP kinase; Astrocyte; Neuropathic pain.

Disclosures: S. Choi: None. **A.J. Beitz:** None. **J. Lee:** None.

Poster

749. Role of Inflammatory and Immune Responses in Chronic Pain

Location: Hall A

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Program #/Poster #: 749.07/G19

Topic: D.03. Somatosensation – Pain

Title: Amitriptyline and duloxetine loaded PLGA nanoparticles prolong the analgesic duration through enhanced targeting to microglia

Authors: *S. KIM[1], J. SHIN[2], S. LEE[3], D. KIM[3];
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Abstract: Neuropathic pain caused by functional disorders or pathological changes of the nervous system and various mechanisms has been revealed in previous study but still no treatment has been developed. Both amitriptyline (AMI) and duloxetine (DLX) are potent analgesic agents and are currently used as analgesics in clinical practice. Although AMI and DLX are known as a reuptake inhibitor of serotonin (5-HT) and noradrenaline (NA) from synapse cleft to primary neuron, these drugs have recently been reported to also act on microglia activation. Since microglia activation control is known to be capable of sustaining analgesic action, PLGA nanoparticles were introduced to enhance microglial cell targeting of AMI and duloxetine DLX. Despite AMI and DLX injected group showed analgesic effect on neuropathic pain by spinal nerve ligation (SNL) in rats, the duration time of mitigation was 4 h. We confirmed that AMI and DLX-encapsulated PLGA nanoparticles significantly alleviated mechanical allodynia for 5 days compare to AMI and DLX treatment. Both microglial activation and proinflammatory mediators were notably reduced in spinal dorsal horn with histological and cytokine analysis. Taken together, these data suggest that AMI and DLX encapsulating PLGA nanoparticles can improve for therapeutic duration for neuropathic pain.

Disclosures: S. Kim: None. **J. Shin:** None. **S. Lee:** None. **D. Kim:** None.

Poster

749. Role of Inflammatory and Immune Responses in Chronic Pain

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Topic: D.03. Somatosensation – Pain

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Distinguished Professor Program of Jiangsu

Title: Inhibitory input from the lateral hypothalamus to the ventral tegmental area regulates mesolimbic BDNF signaling to mediate pain sensation

Authors: Y. MA[1,2], *G. ZHANG[1,2], Y. BIAN[1,2], Y. XU[1,2], H. LI[1,2], X. KONG[1,2], Y. NIU[1,2], S. SHA[1,2], A. MANNAN[1,2], J. YANG[1,2], H. ZHANG[1,2], J.-L. CAO[1,2,3];
[1]Jiangsu Province Key Lab. of Anesthesiology, Xuzhou Med. Univ., Xuzhou, China; [2]Jiangsu Province Key Lab. of Anesthesia and Analgesia Application Technology, Xuzhou Med. Univ., Xuzhou, China; [3]Dept. of Anesthesiology, Affiliated Hosp. of Xuzhou Med. Univ., Xuzhou, China

Abstract: The mesolimbic pathway is a collection of dopaminergic (DA) neurons that project from the ventral tegmental area (VTA) to the ventral striatum which include nucleus accumbens (NAc), and this pathway is involved in pain regulation. However, how the mesolimbic pathway is regulated in pain sensation is not clear, especially at a circuit level. VTA receives heavy GABAergic inputs from lateral hypothalamus (LH) which mediates an array of physiological and pathological processes including pain sensation. This study was to detect a possible role for LH-VTA GABAergic circuit in mediating intrinsic analgesia and pain sensation under both physiological and pathological conditions. To determine the role of LH-VTA GABAergic projection in pain regulation under a physiological state, a cocktail of AAV encoding cre-inducible enhanced halorhodopsin 3.0 and channalrhodopsin (AAV-DIO-NpHR and AAV-DIO-ChR2) was injected into the LH of vGAT-Cre mice followed by a bilateral optical fibers implantation in the VTA. Then, paw withdrawal latencies (PWLs) and paw withdrawal thresholds (PWTs) were measured during 5 sessions at a time interval of 2 h: baseline-yellow laser (8 s on - 2 s off) on-laser off-blue laser (20 Hz, 10 ms) on- laser off. Our behavioral tests found that in comparsion with the baseline or laser off timepoints, there is a robust increase in

PWLs and PWTs with yellow laser, which is an intrinsic analgesic property and could be prevented by the treatment of naloxone (2 mg/kg, i.p.) as observed in morphine treated mice. And a significant decrease in PWLs and PWTs was observed when the blue laser was on. Our recent study revealed that the activity of VTA-NAc DA circuit and VTA-generated brain-derived neurotrophic factor (BDNF) expression in the NAc is essential for pain sensation (Zhang et al., *Biol Psychiatry* 2017). Surprisingly but consistently, our molecular study found a robust increase of BDNF in the NAc by repeated photoactivation of the LH-VTA GABAergic projection. Furthermore, photoinhibition of this projection in a persistent inflammatory pain model, mice treated with Completed Freund's Adjuvant, showed similar analgesic effects. The study indicated that the LH-VTA GABAergic projection act as a novel circuit for intrinsic analgesia and pain sensation, and the consistent findings with our own and others (Nieh et al., *Neuron* 2016) prompt us to speculate that excitation of LH-VTA GABAergic neurons might disinhibt VTA-NAc DA neurons via the downstream GABAergic neurons in the VTA to regulate intrinsic analgesia and pain sensation.

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Poster

749. Role of Inflammatory and Immune Responses in Chronic Pain

Location: Hall A

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Topic: D.03. Somatosensation – Pain

Support: Grants-in-Aid for Scientific Research (KAKENHI) from the Japanese Society
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Title: Schwann cell-mediated immune response participates in paclitaxel-induced peripheral neuropathy pathogenesis

Authors: *M. KOYANAGI, S. IMAI, M. MATSUMOTO, Y. IWAMITSU, M. SAIGO, M. NTOGWA, R. HIRAIWA, T. OGIHARA, T. NAKAGAWA, K. MATSUBARA;
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Abstract: Chemotherapy-induced peripheral neuropathy (CIPN) is one of the most common dose-limiting adverse reactions caused by taxanes. Severe CIPN often results in discontinuation of chemotherapy or a drop in quality of life. However, the precise mechanisms underlying CIPN pathogenesis are not fully understood, so that there is no effective way to prevent or treat CIPN. We have previously shown that paclitaxel preferentially impairs myelin-forming Schwann cells,

rather than sensory neurons, and induce dedifferentiation of Schwann cells. Considering the supportive role of Schwann cells in the maintenance of peripheral nervous system, we have assumed that such direct effect of paclitaxel on Schwann cells should be a trigger of CIPN. Here, we found that treatment with paclitaxel (0.01 μM) significantly increased the mRNA expression of an inflammatory factor, X, in dedifferentiated rat primary cultured Schwann cells. Likewise, upregulation of the factor was specifically induced in the mouse sciatic nerve but not in other peripheral organs at the onset of mechanical hypersensitivity after multiple injections of paclitaxel (20 mg/kg, i.p.). The elevation of the factor and significant macrophage infiltration into the sciatic nerve were concurrently observed in paclitaxel injected mice. Furthermore, murine macrophage cell line, RAW264.7, showed a chemotaxis response toward the culture medium containing the inflammatory factor derived from paclitaxel-treated Schwann cells. Consistent with this data, we found that the perineural application of the factor induced infiltration of macrophages into the sciatic nerve and mechanical hypersensitivity in mice. In conclusion, we propose here that the inflammatory factor derived from dedifferentiated Schwann cells chemoattracts macrophages into the peripheral nerve after paclitaxel treatment. These Schwann cell-dependent peripheral immune responses should play a crucial role in the development of paclitaxel-induced CIPN.

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Poster

749. Role of Inflammatory and Immune Responses in Chronic Pain

Location: Hall A

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Program #/Poster #: 749.10/G22

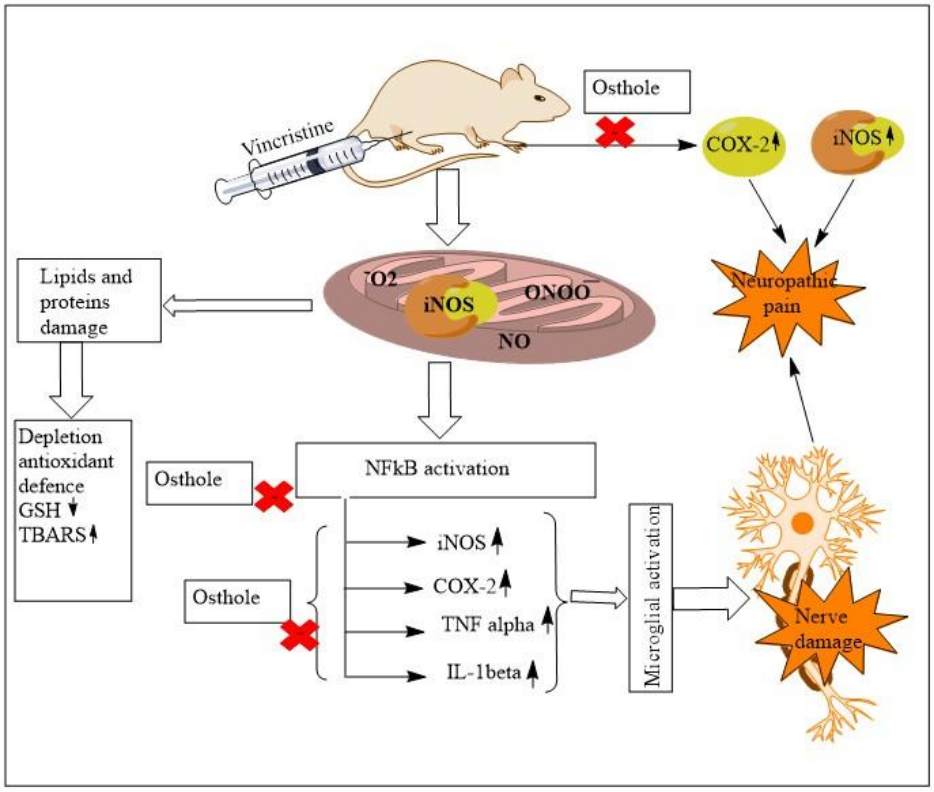
Topic: D.03. Somatosensation – Pain

Title: Modulation the NFκB mediated inflammatory cytokines and oxidative stress contribute to ameliorative effect of osthole in painful peripheral neuropathy

Authors: *G. SINGH, Jr, P. SINGH, R. BHATTI;
Guru Nanak Dev Univ., Amritsar, India

Abstract: Background Chemotherapy-induced peripheral neuropathy is a common adverse effect of several commonly used cancer treatments, including vinca alkaloids, taxanes and platinum agents. NFκB is an important transcription factor, which regulates a diverse array of cellular process, includings immunological response, inflammation and apoptosis. Increased expression of NFκB plays a vital role in the pathogenesis of several inflammatory diseases including neuropathy. **Aim** Current investigation has been design to explore the effect of osthole on vincristine induced neuropathic pain in rats. **Method** Rats were divided into four groups, each

group containing six animals. The first group was normal control that was treated with vehicle daily for a period of 14 days. The second group was vincristine control and received vincristine (100 µg/kg, i.p.) in two 5 days cycle with 2 day break between cycle. The third and fourth groups received gabapentin (60 mg/kg, i.p.) and osthole (10 mg/kg i.p.) respectively daily for 14 days starting from day 1. At the end of 14 days, blood and tissue were harvested for biochemical and histological examination. **Results** Osthole was found to produce significant reduction in pain perception as compared to vincristine group. Osthole significantly ameliorated vincristine induced inflammatory changes including NFκB, iNOS, COX-2 and inflammatory cytokines. **Conclusion** Osthole could provide a useful lead in developing new drugs in investigation of painful neuropathy.



Disclosures: **G. Singh:** None. **P. Singh:** None. **R. Bhatti:** None.

Poster

749. Role of Inflammatory and Immune Responses in Chronic Pain

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 749.11/G23

Topic: D.03. Somatosensation – Pain

Support: NIH Grant R01DE17794
NIH Grant R01NS87988

Title: IL-23 induces persistent mechanical pain hypersensitivity via macrophage-neuron interaction in female mice

Authors: *X. LUO, Q. HE, S. BANG, R.-R. JI;
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Abstract: 2016 National Health Interview Survey (NHIS) data indicates that an estimated 20.4% (50.0 million) of U.S. adults had chronic pain, with higher prevalence of chronic pain reported among females. However, female-dominant pain pathways remain less studied and unknown. Recently, we discovered that male and female macrophages equally contribute to chemotherapy-induced peripheral neuropathy (CIPN) but macrophage toll-like receptor 9 (TLR9) signaling is only required by males, implicating the sexual polymodality of macrophages in chronic pain. Interleukin-23 (IL-23) is released by pro-inflammatory macrophages, but the contribution of IL-23 and IL-23 receptor (IL-23R) signaling to chronic pain remains unclear. We found that intraplantar administration of IL-23 induced mechanical allodynia only in female but not male mice. IL-23-evoked mechanical allodynia in females was prevented by intraplantar treatment of IL-23R antagonist or *Il-23r* siRNA. Of note, C-fiber ablation by resiniferatoxin or deletion of *Trpv1* abolished IL-23-induced mechancial allodynia in females, suggesting a requirement of C-fibers and TRPV1. Additionally, IL-23 induced mechanical allodynia in female nude mice and female *Rag1* knockout mice, implicating that IL-23-mediated pain may not require T cells or B cells signaling. We also examined the role of IL-23/IL-23R in CIPN, induced by four injections of paclitaxel (PTX) in both sexes. In dorsal root ganglia (DRG), F4/80-positive macrophages expressed IL-23 in both sexes. PTX caused a great increase in IL-23 mRNA levels in female DRG than male DRG. FACS analysis further indicated that PTX-treated females exhibited a larger population of IL-23/F4/80-positive macrophages than males in DRG. Interestingly, IL-23R was expressed by TRPV1-positive neurons. IL-23R antagonist or *Il-23r* siRNA reduced mechanical allodynia only in females, but IL-23R antagonist had no effect in female CIPN mice lacking *Tprv1*. Finally, IL-23 was also capable of inducing mechanical allodynia in male mice primed with estrogen, suggesting that estrogen may contribute to IL-23/IL-23R-mediated pain in females. Together, our findings establish the IL-23/IL-23R signaling axis as a novel female-dominant signaling pathway in chronic pain via macrophage-neuron interaction. Our study constitutes a critical step forward in our understanding of sexual dimorphism in chronic pain.

Disclosures: X. Luo: None. **Q. He:** None. **S. Bang:** None. **R. Ji:** None.

Poster

749. Role of Inflammatory and Immune Responses in Chronic Pain

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 749.12/G24

Topic: D.03. Somatosensation – Pain

Support: Thompson Family Foundation Initiative at Columbia University (TFFI)

Title: Axon-glia interactions are disrupted in chemotherapy-induced peripheral neuropathy

Authors: *A. JOSHI[1], A. K. SINGH[2], A. KAVELAARS[2], C. J. HEIJNEN[2], M. RASBAND[1]; [1]Baylor Col. of Med., Houston, TX; [2]Symptom Res., Univ. of Texas MD Anderson Cancer Ctr., Houston, TX

Abstract: Chemotherapy induced peripheral neuropathy (CIPN) is a severe, dose-limiting side effect of chemotherapy treatment. Several mechanisms have been proposed for the development of CIPN with major attention on axonal dysfunction. However, whether axon-glia interactions are altered in CIPN remains unknown. The spectrin cytoskeleton is crucial for the formation and maintenance of paranodal axon-glia junctions flanking nodes of Ranvier. Importantly, the spectrin cytoskeleton is susceptible to proteolysis by calpain, which is activated in CIPN. Thus we hypothesize that paranodal junctions are disrupted in CIPN. To induce the peripheral neuropathy, we injected Cisplatin (CIS, cumulative 23mg/kg) or Paclitaxel (PTX, 12mg/kg) intraperitoneally in mice. After 4 weeks of the treatment, both CIS and PTX induced significant mechanical allodynia. The intraepidermal nerve fiber density in the paw skin was significantly reduced in treated mice. To examine the membrane domain organization, we performed immunohistochemistry of sural and saphenous nerves using nodal and paranodal markers. Notably, CIS and PTX both disrupted paranodes as shown by abnormal localization and distribution of nodal and paranodal proteins. The phenotype of paranodal disruption was comparable when we used another high dosage regimen for PTX (cumulative 200mg/kg). Taken together, our results suggest that paranodal axon-glia interactions are disrupted in CIPN, which may contribute to the pathogenesis of CIPN.

Disclosures: A. Joshi: None. **A.K. Singh:** None. **A. Kavelaars:** None. **C.J. Heijnen:** None. **M. Rasband:** None.

Poster

749. Role of Inflammatory and Immune Responses in Chronic Pain

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 749.13/G25

Topic: D.03. Somatosensation – Pain

Support: Duke University funding

Title: Further characterization of TLR5 expression in mouse dorsal root ganglion and spinal cord: Implications in mechanical allodynia and chronic itch

Authors: *M. MATSUDA[1,4,5], Z. WANG[1], C. JIANG[1], Z.-Z. XU[1], Q. HAN[1], R.-R. JI[1,2,3]; [1]Dept. of Anesthesiol., [2]Dept. of Neurobio., [3]Dept. of Cell Biol., Duke Univ. Med. Ctr., Durham, NC; [4]Dept. of Anesthesiol., Kyoto Okamoto Mem. Hosp., Kyoto, Japan; [5]Dept. of Anesthesiol., Kyoto Prefectural Univ. of Med., Kyoto, Japan

Abstract: Mechanical allodynia, induced by normally innocuous low-threshold mechanical stimulation, represents a cardinal feature of neuropathic pain. Although large, myelinated group A fibers, in particular A beta fibers, have previously been implicated in mechanical allodynia, an A-fiber-selective pharmacological blocker is still lacking. Recently, we reported a new method for targeted silencing of A-fibers in neuropathic pain. We found that Toll-like receptor 5 (TLR5) is co-expressed with neurofilament-200 in large-diameter A-fiber neurons in the dorsal root ganglion (DRG). Activation of TLR5 with its ligand flagellin, together with QX-314, leading to TLR5-dependent blockade of A-fiber neurons of mouse DRGs and inhibition of mechanical allodynia after nerve injury and chemotherapy (Xu et al., 2015). To further characterize TLR5 expression in DRG and spinal cord, we generated *Tlr5*-GFP reporter mice. Surprisingly, GFP-TLR5 only labels a very small portion of DRG neurons (<0.1%), with an average diameter of 29.82 ± 6.95 μm (18.57 - 38.11) and an average area of 482.7 ± 202.4 sq. μm (223.3 - 693.9). In contrast, RNAscope analysis of *Tlr5* mRNA expression reveals a larger population of 10-30% DRG neurons that are co-localized with NF200, and the percentage of TLR5-positive neurons varies based on the number of the mRNA-positive puncta in each neuron. Strikingly, in the spinal cord dorsal horn, GFP-TLR5 labels axonal arborization in ventral lamina II and lamina III, (lamina vIIi-dIII), indicating a subset of A beta fibers. In a mouse model of chronic itch, induced by implantation of cutaneous T cell lymphoma (CTCL) cells, flagellin/QX-314 co-application effectively suppressed spontaneous chronic itch, suggesting a possible role of TLR5-expressing A fibers in chronic itch. In summary, TLR5 labels different types of DRG neurons, depending on how the TLR5-positive neurons are defined. It is likely the majority of TLR5-expressing DRG neurons are A-fiber neurons especially Aβ-fiber neurons. Importantly, targeting TLR5-expressing afferents may provide new therapeutics for treating mechanical allodynia and chronic itch.

Disclosures: **M. Matsuda:** None. **Z. Wang:** None. **C. Jiang:** None. **Z. Xu:** None. **Q. Han:** None. **R. Ji:** None.

Poster

749. Role of Inflammatory and Immune Responses in Chronic Pain

Location: Hall A

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Program #/Poster #: 749.14/G26

Topic: D.03. Somatosensation – Pain

Support: NIH R01 CA200263
H.E.B. Endowment
Thompson Family Fundation Initiative

Title: Macrophage infiltration is associated with the sensitization of dorsal root ganglion neurons through the release of oncostatin M

Authors: Y. LI[1], M. L. UHELSKI[2], R. Y. NORTH[3], T. J. ABERCROMBIE[4], T. MARRI[4], H. R. RHODES[5], K. N. SHEFFIELD[5], S. I. GALANG[6], ***P. M. DOUGHERTY**[1];
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Abstract: Macrophage activation and recruitment to sites of injury or infection is a vital component of immune function following tissue insult. M1 macrophages stimulate the immune system and release pro-inflammatory cytokines, while M2 macrophages reduce inflammation and promote tissue growth and repair. M1 macrophages secrete high levels of IL-12, a pro-inflammatory cytokine, and oncostatin-M (OSM). OSM is a member of the IL-6 cytokine family that is pro-inflammatory in endothelial tissues but also promotes cancer cell plasticity and metastasis through a STAT3-dependent pathway. The function of OSM and its receptors in the peripheral nervous system has not yet been established. Expression of OSM receptor is upregulated in dorsal root ganglia (DRG) of cancer patients with neuropathic pain associated with compression of tissue by the growth of bone metastases, suggesting involvement in nociception. The current study explored the effects of OSM on cultured human and rat DRG neurons and also determined its effect on the behavioral responses of adult rats to mechanical and thermal stimuli. Immunohistochemistry in tissue excised from a cancer patient with radiculopathy showed macrophage infiltration into the DRG co-localized with the expression of OSM. These results support evidence from analyses of mRNA expression suggesting increased OSM activity in patients with neuropathic pain. *In vitro* studies of dissociated human DRG neurons showed that OSM (10 ng/ml) treatment induced spontaneous discharges and abnormal membrane oscillations. Intrathecal OSM (10 ng) produced long-lasting mechanical hyperalgesia in adult rats but did not alter withdrawal latencies to heat stimuli. Immunohistochemistry in rat

DRG tissue showed co-localization of the OSM receptor (OSMR) with mostly IB4-positive neurons and a few CGRP-positive neurons. Further, OSMR expression did not co-localize with TRPV1 expression, indicating that the sensitization induced by OSM does not impact neurons involved in processing noxious heat. Rat DRG neurons also exhibited spontaneous activity and abnormal membrane oscillations following OSM (10 ng/ml) treatment. Further studies confirmed that this effect was limited to capsaicin-insensitive neurons. Calcium imaging also showed that cells responding to OSM (10 ng/ml) did not respond to capsaicin (1 μM), and vice versa. These results suggest that increased levels of OSM following macrophage infiltration into the DRG contribute directly to the sensitization of the subpopulation of nociceptors expressing OSMR, and this mechanism could provide a novel target for the treatment of neuropathic pain in cancer patients. (2,284 of 2,300 characters)

Disclosures: Y. Li: None. **M.L. Uhelski:** None. **R.Y. North:** None. **T.J. Abercrombie:** None. **T. Marri:** None. **H.R. Rhodes:** None. **K.N. Sheffield:** None. **S.I. Galang:** None. **P.M. Dougherty:** None.

Poster

749. Role of Inflammatory and Immune Responses in Chronic Pain

Location: Hall A

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Program #/Poster #: 749.15/G27

Topic: D.03. Somatosensation – Pain

Support: NCI 1R41CA210857
NINDS R01NS098772
NIDA R01DA042852

Title: Lessons from autoimmunity: Unraveling the role of CRMP5 in neuropathic pain

Authors: *A. MOUTAL[1], R. BESANÇON[2], S. LUO[1], I. KANAZAWA[1], C. WATRIN[2], J. HONNORAT[2], R. KHANNA[1];
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Abstract: Neuroimmune interactions contribute to abnormal pain states and one relatively understudied aspect of this is through the action of human autoantibodies. One such rare neurological condition is Paraneoplastic Syndrome where a peripheral tumor can trigger an immune response against a neuronal auto-antigen. In this syndrome, anti-CV2 autoantibodies targeting collapsin response mediator protein 5 (CRMP5) are associated with a painful axonal asymmetric polyradiculoneuropathy in ~80% of patients. The anti-CV2 autoantibodies targeting collapsin response mediator protein 5 (CRMP5) are associated with neuropathic pain in patients. CRMP5 is an understudied onconeural protein highly expressed in the developing brain. In

adults, CRMP5 expression is lost in the brain but retained in sensory neurons, nerves and synapses present in the spinal cord. Using patients' autoantibodies and transgenic mice, we tested the hypotheses that (i) CRMP5 is anti-nociceptive and (ii) disruption of CRMP5 functions contributes to neuropathic pain. After identifying the epitope on CRMP5 targeted by the anti-CV2 antibodies, we found that anti-CV2 autoantibodies induced mechanical allodynia through a spinal mechanism. This could be recapitulated by triggering auto-immunity against CRMP5 in rats, thus providing us with a novel model of auto-immune CRMP5 neuropathy. We further established that auto-immunity targeting CRMP5 was sufficient to elicit allodynia. In investigating the mechanism(s) in a rat model of neuropathic pain, we found that CRMP5 expression was lost at post-synaptic sites in the dorsal horn of the spinal cord. Restoring CRMP5 expression reversed mechanical allodynia in rats with neuropathic pain. On the contrary, knockdown of CRMP5 expression in the spinal cord induced mechanical allodynia. These results show that CRMP5 expression levels contribute to mechanical allodynia. We are now exploring the physiological role of CRMP5 in pain sensations using CRMP5 knockout transgenic mice. Together, these data shows that CRMP5 antagonism in anti-CV2 autoimmune neuropathy or CRMP5 loss of expression in neuropathic pain, underlies mechanical allodynia. Regulating CRMP5 anti-nociceptive functions could be a novel therapeutic target for chronic pain.

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Poster

749. Role of Inflammatory and Immune Responses in Chronic Pain

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 749.16/G28

Topic: D.03. Somatosensation – Pain

Title: Arginase II attenuates neuroinflammation & pain behaviors after nerve injury in mice

Authors: *L. T. PHAM, Y. JIN, N. SHIN, D. KIM;
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Abstract: Microglia phenotypes have been divided into two groups: M1 & M2 microglia based upon their promotion to inflammatory pathogenesis. Arginase-ll (Arg-II) is an enzyme involved in arginine metabolism & expressed in microglia in central nervous system. In this study, we attempted to determine whether the presentation of Arg-II is in M1 or M2 microglia phenotype & its regulation on neuroinflammatory process. Finally we investigated loss of Arg-ll exaggerates microglia activation & pain behaviors after nerve injury-induced neuropathic pain. Spinal nerve transection (SNT) experimental model was used in this study to induce neuropathic

pain in mice. As a result of peripheral nerve injury, SNT induced microgliosis, astrogliosis in spinal cord, & upregulation of inflammatory signals in both WT & Arg-ll KO mice. Notably, these inflammatory implications were significantly increased in Arg-ll KO group compared to WT group. We also observed the more robust microgliosis, & lower pain threshold in ArG-ll KO group than those in WT group. Furthermore, our data revealed the higher upregulations of M1 pro-inflammatory cytokines, such as IL1β, IL6, NO & the lower downregulations of M2 anti-inflammatory cytokines, including Arginase-l, IL10, IL4, in Arg-ll KO mice. Additionally, the stronger expression of iNOS, ROS, & the decrease in the expression of CD206, YM1, Foxp3 in Arg-ll KO Group were found compared to WT group. These results suggested that Arg-II promote contribution to inflammatory resolution. The reduction or loss of Arg-ll results in the stronger development of neuroinflammation in spinal dorsal horn, & then pain behaviors after nerve injury-induced neuropathic pain.

AUTHORS:Yuhua Yin[1,2,#], Thuỳ Linh Phạm[1,2,#], Juhee Shin[1,2], Nara Shin[1,2], Dong-Wook Kang[1,3], Sun Yeul Lee[4], Won-hyung Lee[4], Cuk-Seong Kim[1,3], Jinpyo Hong[2], Dong Woon Kim[1,2]

Disclosures: **L.T. Pham:** None. **Y. Jin:** None. **N. Shin:** None. **D. Kim:** None.

Poster

749. Role of Inflammatory and Immune Responses in Chronic Pain

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 749.17/G29

Topic: D.03. Somatosensation – Pain

Support: VA merit I01RX001940

Title: Pain pathology-dependent differential alteration of sensory ganglia Tmem100 in inflammatory pain and neuropathic pain

Authors: *H. YU[1], **S. SHIN**[1], F. WANG[2], H. XU[2], H. XIANG[2], B. ITSON-ZOSLE[2], Q. H. HOGAN[3];
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Abstract: Transmembrane protein 100 (Tmem100) is expressedin dorsal root ganglia (DRG) neurons and plays a role in modulating interactions between transient receptor potential ankyrin type 1 (TRPA1) and vanilloid type 1 (TRPV1) ion channels, both of which are crucial for nociception. However, it is not defined whether peripheral nerve injury induces changes in Tm100 expression. This study shows that Tmem100 is expressed in both neurons and perineuronal glial cells in the rat DRG. The plasma membrane and intracellular localization of Tmem100 are identified in 83±6.6% of IB4-positive and 48±6 % of calcitonin gene-related

peptide-positive neurons, as well as in medium- and large-sized neurons, with its immunopositivity colocalized to TRPV1 (94±5%) and TRPA1 (96±3%). Tmem100 is also detected in the perineuronal satellite glial cells and in some microglia. Tmem100 protein is significantly increased in the lumbar DRGs in the complete Freund adjuvant inflammatory pain. By contrast, ligation of the rat L5 spinal nerve diminishes Tmem100 expression in the associated DRG, with immunoblot and immunohistochemistry showing reduced Tmem100 protein levels in both neurons and satellite glial cells, whereas Tmem100 is unchanged in the adjacent L4 DRG. The spared nerve injury model also reduces Tmem100 protein in the DRGs. Our data demonstrate a pain pathology-dependent alteration of DRG Tmem100 protein expression, upregulated during CFA inflammatory pain but downregulated during neuropathic pain. Additionally, viral-mediated overexpression of Tmem100 in astrocyte and microglia cell lines and in SGCs isolated from rat DRG significantly blunt their proliferation in culture, suggesting that Tmem100 likely plays a role in control SGC proliferation.

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Poster

749. Role of Inflammatory and Immune Responses in Chronic Pain

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 749.18/G30

Topic: D.03. Somatosensation – Pain

Support: European Union

Title: Detailed characterization of myeloid cell number and phenotype after nerve injury

Authors: *Z. LIANG, Z. HORE, P. HARLEY, F. DENK, S. B. MCMAHON;
King's Col. London, London, United Kingdom

Abstract: Objective and Rationale: Chronic pain is a major public health problem affecting more individuals in the United States than cancer, heart disease and diabetes combined. Millions of suffers are unable to work or are pushed into devastating opioid addiction as a result of medication overuse. Neuropathic pain, arising from damage or disease of nerves themselves, is particularly intractable. In part, it is caused by immune and inflammatory cells driving the development of hypersensitivity in peripheral sensory neurons. The detailed kinetics and phenotype of this inflammatory response are still relatively poorly understood. Here we set out to generate a detailed time-course of immune cell responses in sciatic nerve and its dorsal root ganglia (DRG) in a mouse model of neuropathic pain.
Methods: We induced partial sciatic nerve ligation (PSNL) in adult C57BL/6J male and female mice (n = 6) and extracted immune cells from lumbar DRG (L3-L5) and sciatic nerve, 0.5cm

either side of the suture. We then performed flow cytometry and fluorescence-activated cell sorting (FACS) at various time points after the surgery, including day 1, day 3, day 7, day 15 and day 28. Different myeloid cell populations were selected for FACS (20 cells each), amplified using the SMARTer protocol and sent for RNA sequencing.
Results: The number of immune cells (as measured by CD45) dramatically increased and remained elevated in ipsilateral nerve until day 28. In detail, we observed early infiltration of neutrophils (Ly6G+) and monocytes (Ly6C+), accompanied by a gradual increase in the number of resident (CD11b+, MHCII-, Ly6C-) and activated (CD11b+, MHCII+, Ly6C-, CD11c-) macrophages. In contrast to nerve, differences in immune cell numbers were much less stark in the DRG. Several previously undescribed populations could be observed in both tissues, such as a permanent CD11b+/Ly6G+ population in DRG and a Ly6C+/MHCII+ in nerve after injury. Our results also pointed towards sexually dimorphic responses in aspects of this immune response. However, the precise size of this effect remains unclear, since variability between biological replicates was inherently large, despite our best efforts to standardize protocols.
Conclusions: Detailed description of inflammatory cell responses to traumatic nerve injury in male and female mice may help reveal the contribution of different immune cell populations to peripheral sensitization at different time-points. Our results will aid to define the immunological phenotype of several distinct populations and may help reveal potential opportunities for novel analgesic drug development.

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Poster

749. Role of Inflammatory and Immune Responses in Chronic Pain

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 749.19/DP07/G31

ControlExtraData.DynamicPosterDisplay:
Dynamic Poster
Topic: D.03. Somatosensation – Pain

Support: NS065926

Title: Real time imaging of mitochondrial dynamics in the dorsal root ganglion following nerve injury

Authors: *J. M. MWIRIGI[1], C. PAIGE[2], V. PRAKASH[3], S. SHIERS[2], T. J. PRICE[4];
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Abstract: Mitochondria are dynamic and motile organelles that respond rapidly to oxidative stress and cellular energy demands. Their morphological changes, as determined by fission and fusion, have been linked to the progression of neuropathic pain as well as neurodegenerative disorders like Parkinson's, Alzheimer's and Huntington's. However, little is known about specific pathology underlying mitochondrial dysfunction after peripheral nerve injury or how pharmacological interventions affect these changes. Our goal was to evaluate mitochondrial dynamics following peripheral nerve injury by characterizing axonal mitochondrial density, movement in axons and fusion-fission events, as determined by mitochondrial length, using spinning disc confocal imaging with mitochondrial dyes. To do this, we dissociated dorsal root ganglia (DRG) from mice with spare nerve injury (SNI), a model of neuropathic pain. We then stained mitochondria with mitotracker green and used spinning disk microscope to capture time lapse videos. We observed a significant increase in axonal mitochondrial density in DRG cultures obtained from SNI mice when compared to naïve cultures. Representative kymograph images depict a larger proportion of mitochondria moving anterogradely in axons of DRG neurons from SNI mice. Interestingly, we found that the SNI-mitochondria are trafficked at lower velocities. Previous studies have shown that calcium overload in damaged mitochondria may contribute to decreased mitochondrial motility. Additionally, mitochondrial length varied considerably within the SNI group but was generally greater than naïve group indicating either that a significant percentage remained in the fused state or that there is a failure of fission in DRG neurons after injury. Collectively, our findings highlight the benefit of real time imaging of DRG neurons to gain greater insight into specific mitochondrial dysfunction after nerve injury. Our findings likely have important implications for therapeutic approaches to neuropathic pain.

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Poster

749. Role of Inflammatory and Immune Responses in Chronic Pain

Location: Hall A

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Program #/Poster #: 749.20/G32

Topic: D.03. Somatosensation – Pain

Support: MOST grant 106-2320-B-008-004-MY3

Title: Proton sensing receptor OGR1 in peripheral afferents modulates neuron activities and immune cell infiltration to maintain chronic pain state

Authors: Y. CHIN, Y.-H. LU, *W.-H. SUN;
Natl. Central Univ., Taoyuan, Taiwan

Abstract: Neuropathic pain is a complex, chronic pain state that is usually accompanied by a lesion or disease of the nervous system, causing severe disturbance to the quality of life. Chronic excessive inflammatory response after injury may contribute to the maintenance of persistent pain. Although the role of immune cells and cytokines in mediating allodynia and hyperalgesia has been extensively studied, it has not been completely elucidated how chronic pain state is maintained. According to hyperalgesic priming hypothesis, the maintenance of chronic pain state requires protein kinase Cε activation. Ovarian Cancer G Protein-Coupled Receptor 1 (OGR1), a proton-sensing receptor expressed in small-diameter dorsal root ganglion (DRG) neurons, macrophages and neutrophils, is fully activated at pH6.8 and mediates Gq protein-protein kinase C pathway. However, it remains unclear which role OGR1 plays in neuropathic pain. To address this question, I used shRNA specific to OGR1 gene to suppress OGR1 gene expression in peripheral afferents to explore OGR1 function in the model of chronic constriction injury (CCI) of the sciatic nerve. CCI induced long-term hyperalgesia at least 14 weeks. Suppression of OGR1 gene expression reversed mechanical hyperalgesia from week 4 after CCI surgery. OGR1 knockdown also reduced granulocyte infiltration at week 2 and 4, and decreased intracellular calcium increase at week 4. Therefore, hyperalgesia shortening in OGR1 knockdown mice could be attributed to a decrease in calcium signals in DRG neurons and a reduction of granulocyte infiltration in the sciatic nerve. Accordingly, these results suggested that OGR1 may regulate neuron activities to modulate immune cell infiltration, further regulating the maintenance of chronic pain.

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Poster

749. Role of Inflammatory and Immune Responses in Chronic Pain

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Topic: D.03. Somatosensation – Pain

Support: NIH Grant K08NS094547
Foundation for Anesthesia Education and Research (FAER) Mentored Research Training Grant

Title: Whole system immune phenotyping of male and female mice reveals striking sex differences and similarities in the immune response to injury

Authors: V. L. TAWFIK[1], Q. J. BACA[1], ***N. A. HUCK**[1], E. S. HAIGHT[1], E. A. GANIO[1], H. SHEN[1,2], A. CULOS[1], M. S. GHAEMI[1], J. CLARK[1], N. AGHAEEPOUR[1], B. GAUDILLIERE[1]; [1]Anesthesia Dept., Stanford Univ., Stanford, CA; [2]Dept. of Orthopedic Surgery, The First Affiliated Hosp. of Soochow Univ., Suzhou, China

Abstract: Impaired recovery after surgery is characterized by chronic post-surgical pain and affects 30% of patients. Enhanced Recovery After Surgery (ERAS) pathways highlight the significance of protracted surgical recovery; however, the elements of these protocols that may improve recovery are uncertain. We undertook the current study to determine the whole system immune response to surgery in a tibial fracture mouse model of orthopedic trauma in order to identify key pathologic responses that could be targets for ERAS protocols. One week after injury, both male and female mice demonstrated a profound decrease in mechanical threshold and weight bearing, which returned to baseline by 7 weeks. In parallel, we collected serial blood samples for whole system immune phenotyping by mass cytometry at baseline, 12 hours, 1 week and 7 weeks after injury. This revealed similar immune cell frequencies at baseline between the sexes, with 11 of 13 cell type frequencies unchanged. We next evaluated intracellular signaling pathways within each cellular population and found several with near identical intracellular signaling responses in both sexes (ex. neutrophils) and others with sexually dimorphic intracellular signaling responses (ex. myeloid dendritic cells). Strikingly, at all time points after injury the number of significantly different features between sexes was increased and a majority were in the adaptive immune response. To reveal whole system dynamics of the response to injury we used a recently developed elastic net (EN) model approach to complex mass cytometry datasets. The EN revealed that at 12 hrs and 1 week the sex-specific response to injury was divergent. This study provides, for the first time, a whole system immune profile of male and female mice at baseline and after orthopedic surgery. Our data suggest that differences in the adaptive immune response to surgery underlie sex differences, a finding that implies the need for sex-specific personalized ERAS protocols.

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Poster

749. Role of Inflammatory and Immune Responses in Chronic Pain

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Topic: D.03. Somatosensation – Pain

Support: NIH K08NS094547
FAER MRTG-BS
Department of Anesthesiology, Stanford
Department of Orthopedic Surgery, First Affiliated Hospital of Soochow University, Soochow, China

Title: Identification of unique spinal cord microglial subpopulations in a mouse model of complex regional pain syndrome

Authors: T. FORMAN[1], E. HAIGHT[1], Y. TAKEMURA[2], S. CORDONNIER[1], ***H. SHEN**[1,3], F. DALE-HUANG[1], V. TAWFIK[1];
[1]Dept. of Anesthesiology, Perioperative and Pain Med., Stanford Univ., Stanford, CA; [2]Dept. of Anesthesiol., Univ. of Toyama, Toyama, Japan; [3]Dept. of Orthopedic Surgery, Dept. of Orthopedic Surgery, First Affiliated Hosp. of Soochow Univ., Suzhou, China

Abstract: Chronic pain is a common and often debilitating problem that affects 100 million Americans. A better understanding of pain's molecular mechanisms is necessary for developing safe and effective therapeutics. Microglial activation has been implicated as a mediator of chronic pain in numerous preclinical studies, however, the heterogeneity of microglia has thus far been underappreciated. In order to unveil the time and sex-dependent contributions of microglia to chronic pain in males and females, we utilized a clinically-informed mouse model of complex regional pain syndrome (CRPS) and monitored microglia throughout disease progression using the novel microglial marker, Tmem119. Mice developed the cardinal signs of CRPS after tibial fracture-casting (allodynia, unweighting, warmth and edema). In a mechanical-conflict avoidance paradigm this injury resulted in mice taking longer to cross from a non-noxious aversive brightly lit chamber through a chamber with noxious aversive floor probes compared to baseline. Evaluation of spinal cord sections from these mice demonstrated that both males and females exhibited microglial activation as evidenced by increases in CD11b; however, activation was attenuated and delayed in females. Expression of Tmem119 also varied between sexes with increases only noted in male microglia after injury. Most interestingly, two distinct subpopulations of microglia were observed based on their relative expression of Tmem119, size and granularity, and the relative abundance of these Tmem119-defined subsets changed after injury in a sex-specific fashion. Our findings suggest that the response of microglia to injury is not "one size fits all" but rather may vary depending on individual cell phenotype, timing after injury and sex of the subject.

Disclosures: T. Forman: None. **E. Haight:** None. **Y. Takemura:** None. **S. Cordonnier:** None. **H. Shen:** None. **F. Dale-Huang:** None. **V. Tawfik:** None.

Poster

749. Role of Inflammatory and Immune Responses in Chronic Pain

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 749.23/G35

Topic: D.03. Somatosensation – Pain

Support: NIH Grant K08NS094547
FAER Mentored Research Training Grant

Department of Anesthesiology, Perioperative & Pain Medicine at Stanford University

Title: Transcriptome analysis of repopulated spinal cord microglia identifies potential targets to block the acute-to-chronic transition in a mouse model of pain

Authors: *S. WU, E. S. HAIGHT, T. E. FORMAN, D. J. CLARK, V. L. TAWFIK;
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Abstract: Acute pain after injury or surgery is common and treatable, importantly, however, an estimated 5-30% of patients transition from acute to chronic pain with the mechanisms underlying this transition representing a major knowledge gap. Microglial activation in the spinal cord dorsal horn contributes to the acute to chronic pain transition, however, their exact contribution remains unknown. We used *Cx3CR1*^{CreER};*R26*^{iDTR} mice to transiently deplete microglia in the clinically-informed tibial fracture/casting mouse model of complex regional pain syndrome (CRPS). We found that microglial depletion during the acute phase decreased allodynia and abrogated the chronic phase of CRPS. Microglia repopulated after 3 days in the context of ongoing injury, suggesting they exhibited a “pro-resolution” phenotype. We isolated these microglia from the spinal cord and performed transcriptome analysis to comprehensively identify differentially expressed genes in repopulated microglia that may explain their contribution to pain resolution. The top expressed genes defined a microglia-specific signature confirming our FACS-based isolation technique. A wide range of genes were dysregulated in spinal cord microglia of CRPS mice, which included 12 out of 17 significantly upregulated genes reported in a nerve injury pain model. The CRPS-induced changes of all identified genes were attenuated in repopulated microglia. Our transcriptome analysis of repopulated microglia identified a number of candidate genes that may contribute to the resolution of pain. Further functional studies focusing on each gene need to be rigorously performed to validate their potential in the treatment of pain.

Disclosures: S. Wu: None. **E.S. Haight:** None. **T.E. Forman:** None. **D.J. Clark:** None. **V.L. Tawfik:** None.

Poster

750. Somatosensation: Pain, Imaging, and Perception

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 750.01/G36

Topic: D.03. Somatosensation – Pain

Support: University of Toronto Faculty of Dentistry
Bertha Rosenstadt Endowment Fund

Title: A new model of pain-cognition interactions

Authors: *A. Y. LIN[1], M. MCANDREWS[3], A. YU[2], D. A. SEMINOWICZ[4], M. MOAYEDI[2]; [1]Dent., [2]Fac. of Dent., Univ. of Toronto, Toronto, ON, Canada; [3]Krembil Neurosci. Ctr., Univ. Hlth. Network, Toronto, ON, Canada; [4]Dept of Neural & Pain Sci., Univ. of Maryland, Baltimore, Baltimore, MD

Abstract: Background: Pain poses a large health and economic burden on society. It is a complex experience with sensory, motor, affective and cognitive dimensions. Little is known about the underlying mechanisms of the interaction between pain and cognitive function in healthy people[1]. A prevalent model of pain-cognition interactions is that pain distracts from a task, resulting in slower task performance or reduced accuracy[2]. Here, we propose a different model: that pain itself is perceived as a task by the brain - and thus competes for limited cognitive resources dependent on its assigned value[3].
Objective/Hypothesis: The objective of this study is to determine whether pain poses a cognitive load. Specifically, we aim to test whether competing tasks are negatively affected by pain because of increased cognitive load. We hypothesize that participants' performance on a cognitive task will be slower and less accurate when they experience pain.
Methods: Twenty-six right-handed healthy participants (13 women) performed a computerized version of the cognitive-branching task designed to utilize the brain's working memory and multitasking system (1). Each participant completed the task with (3) no stimulus (baseline), (2) tonic heat pain, and (1) a salience-matched non-painful somatosensory stimulus (tonic electrical stimulus). Reaction times and error rates on the task were recorded for each condition and analysed using a two-way, repeated measures ANOVA.
Results: Salience and intensity ratings were matched between pain and electrical stimuli. In the pain condition, participants demonstrated slower reaction times ($p<0.05$), but no difference in error rates ($p>0.05$), compared to baseline. No differences were observed between electric and baseline conditions ($p>0.05$).
Conclusions: Pain affects task performance by potentially posing a cognitive load rather than simple distracting from a competing task. This was demonstrated by the differences in task performance between the pain condition and salience matched, non-painful electric condition.
Significance: This study provided insight into a different model of pain in which individuals perceive pain as a task and prioritize it based on its assigned value.
References: [1]Koechlin, E. Nature 1999; 399:148-51; 108:129-36; [2]Legrain V., Pain 2009; 144:230-2; [3]Akarian, A.V., Pain 2004

Disclosures: A.Y. Lin: None. **M. McAndrews:** None. **A. Yu:** None. **D.A. Seminowicz:** None. **M. Moayedi:** None.

Poster

750. Somatosensation: Pain, Imaging, and Perception

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 750.02/G37

Topic: D.03. Somatosensation – Pain

Title: The coil orientation dependency of pain sensation induced by transcranial magnetic stimulation

Authors: *K. TANI[1], S. TANAKA[2];
[1]Lab. of Psychology, [2]Hamamatsu Univ. Sch. of Med., Hamamatsu, Japan

Abstract: Background and aims: Transcranial magnetic stimulation (TMS), one of cortical stimulation methods, is widely used to evaluate the neurophysiological or neuropsychological function in healthy and stroke patients. However, TMS often accompanies an uncomfortable pain sensation on stimulation spot as a side effect (Rossi et al., 2009). Considering that this pain sensation seems to be derived mainly from the muscle, it is possible that the pain sensation may depend on the direction of electric current induced by TMS relative to the muscle fiber. In this study, we assessed whether pain threshold was different between TMS coil orientations. **Methods:** Seven healthy subjects (2 females and 6 males, aged 21-23 years) participated in this study with written informed consent. This study was approved by the ethical committee of Hamamatsu University School of Medicine. The position and orientation of TMS coil on subjects' head were monitored with a neuro-navigation system. Single-pulse TMS was applied over the scalp just above the left Broca's area (BA), and coil orientation was changed ranged from 0° to 180° relative to inferior-superior direction in steps of 30°. Subjects were asked to report weather they felt pain after each TMS. The pain threshold was defined as the minimum stimulation intensity (%) that induced the pain sensation more than five out of ten stimulations. Significance was set at $p < 0.05$. **Results:** Mean (±SE) pain threshold was 33.9(±4.3) % for 0°, 29.8(±3.2) % for 30°, 29.4(±3.9) % for 60°, 31.4(±5.7) % for 90°, 33.4(±5.3) % for 120°, 36.1(±5.8) % for 150°, and 35.1(±4.4) % for 180°, respectively. One-way repeated-measure ANOVA revealed a significant main effect of the coil orientation [$p = 0.04$]. Post-hoc tests showed that the pain threshold in 60°condition were significantly lower than from that in 150° condition [$p = 0.04$]. **Conclusion:** Results showed that the pain threshold with the electric current in the anterosuperior direction tended to be lower than with that with electric current in the anteroinferior direction. The direction-specific pain threshold may be related to the directional specificity in the temporalis muscle fibers. This research was supported by Committee to Promote Research on the Possible Biological Effects of Electromagnetic Fields of the Ministry of Internal Affairs and Communications, Japan.

Disclosures: K. Tani: None. **S. Tanaka:** None.

Poster

750. Somatosensation: Pain, Imaging, and Perception

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 750.03/G38

Topic: D.03. Somatosensation – Pain

Support: R33AT009310

Title: Real and imagined acupuncture modulate opioidergic and dopaminergic networks in analgesic process

Authors: *J. CAO, Y. TU, S. ORR, G. WILSON, J. PARK, J. LIU, R. L. GOLLUB, J. KONG; Dept. of Psychiatry, Massachusetts Gen. Hosp., Charlestown, MA

Abstract: Introduction: Acupuncture and guided imagery have proven to be effective in treating pain. Our previous study introduced a novel intervention for pain relief called video-guided acupuncture imagery treatment (VGAIT), which integrates acupuncture with imagery and has demonstrated its potential clinical value for pain management. Much less is known about the intrinsic brain functional connectivity responsible for this analgesia processing. **Methods:** 27 healthy subjects were recruited for a crossover-design study that included five sessions (a training and familiarity session and four intervention sessions administered in a randomized order). We investigated changes in pain threshold and resting state functional connectivity (rsFC) modulated by real acupuncture on the right leg, sham acupuncture, VGAIT, and VGAIT control. Accumulating evidence has shown that the brain activity and functional connectivity (FC) in the opioidergic descending pain modulatory system (DPMS) and dopaminergic reward system play indispensable and interactive roles in relieving pain. Thus, periaqueductal gray (PAG) and ventral tegmental area (VTA), key regions of these two systems, respectively, were chosen as seed regions to perform rsFC analysis. **Results:** We found that real acupuncture and VGAIT can significantly increase subjects' pain thresholds, while sham acupuncture and VGAIT control did not significantly modulate subjects' pain thresholds. The fMRI rsFC results revealed that compared with sham acupuncture, real acupuncture produced significant PAG-precuneus (Pcu) rsFC decreases and greater VTA-amygdala (AMY)/hippocampus (HIP) rsFC increases. The decreased PAG-Pcu and increased VTA-HIP rsFCs were significantly associated with subjects' heat pain threshold changes applied on the contralateral forearm. VGAIT induced significant decreases of PAG rsFC with precentral (PreCG)/posterior cingulate cortex (PCC)/Pcu, middle cingulate cortex (MCC), and medial prefrontal cortex (mPFC), as well as VTA rsFC decreases with caudate (CAU) and MCC, compared to VGAIT control. Direct comparison between real acupuncture and VGAIT showed that VGAIT significantly decreased functional connectivity between PAG-PreCG/Pcu, VTA-CAU/anterior cingulate cortex (ACC)/nucleus accumbens (NAc), and VTA-MCC rsFCs compared to real acupuncture. **Conclusions:** Our findings

demonstrate the important roles of the DMPS and reward system in acupuncture and VGAIT analgesia, and they shed light on the development of new pain treatment methods.

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Poster

750. Somatosensation: Pain, Imaging, and Perception

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 750.04/G39

Topic: D.03. Somatosensation – Pain

Support: Mitacs Accelerate

Title: Investigating the neural basis of pain sensitivity in fibromyalgia syndrome using functional magnetic resonance imaging

Authors: *H. WARREN[1], G. IOACHIM[2], J. M. POWERS[3], P. W. STROMAN[4];
[1]Ctr. for Neurosci. Studies, [3]Dept. of Biomed. Sci., [4]Ctr. for Neurosci Studies, [2]Queen's Univ., Kingston, ON, Canada

Abstract: Chronic pain affects roughly 20% of the population, negatively impacting both the economy and patients' quality of life. In most chronic pain conditions, the underlying cause of the pain is difficult to diagnose, and the efficacy of treatments for these conditions are highly subjective and often only marginally effective. To improve diagnostic and treatment quality, a better understanding of the underlying neural mechanisms involved in chronic pain conditions is required.

Many chronic pain conditions appear to involve abnormalities within the central nervous system, including altered descending pain modulation. Recent imaging studies have found evidence that the net effect of descending pain modulation is the sum of both 'reactive' and 'continuous' modulation components such that the state before the experience of a noxious stimulus can influence how pain is perceived. We therefore hypothesized that the continuous component of descending pain modulation is altered in chronic pain conditions.

To test our hypothesis, we used functional magnetic resonance imaging (fMRI) to compare the neural responses to pain in two participant groups: female participants with fibromyalgia syndrome (FM), a chronic pain condition that affects 2-4% of the population, and age-matched (within two years) female participants without a chronic pain condition, which we defined as healthy controls. This study was limited to females because FM is up to 9 times more prevalent in women than in men.

Each participant underwent two fMRI sessions. One session involved fMRI of the brainstems and cervical spinal cords, the other session involved brain fMRI, in order to investigate neural

responses to pain throughout the central nervous system. During the imaging sessions, the participants underwent a 'threat-safety' paradigm. In the 'threat' portion of the paradigm, a thermal stimulus was administered to the palm of each participant's right hand to elicit a calibrated pain response. In the 'safety' portion of the paradigm, participants were not given the painful heat stimulus. The 'threat' and 'safety' runs were interleaved in a randomized order, and in each run the participants were notified one minute into the run whether they were going to experience the 'threat' or not.
Analyses of connectivity and temporal properties of BOLD responses across regions of the CNS known to be involved in pain processing demonstrate differences in the continuous component of descending pain modulation between controls and participants with FM. The results further our understanding of how descending pain modulation is altered in FM.

Disclosures: H. Warren: None. **G. Ioachim:** None. **J.M. Powers:** None. **P.W. Stroman:** None.

Poster

750. Somatosensation: Pain, Imaging, and Perception

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 750.05/G40

Topic: D.03. Somatosensation – Pain

Support: K24 AT007323
R01 AT008563

Title: Altered resting state functional connectivity of the hypothalamus in fibromyalgia and the modulation effect of mind-body intervention

Authors: *J. KONG[1], Y. HUANG[1], S. YU[1], M. CHENG[1], J. LIU[1], J. PARK[1], G. WISON[1], C. WANG[2];
[1]Massachusetts Gen. Hosp., Boston, MA; [2]Tufts Med. Ctr., Boston, MA

Abstract: Background: Fibromyalgia (FM) is a multidimensional, complex disorder with devastating effects on quality of life with decreased productivity and increased healthcare costs. The hypothalamus is a functionally diverse region of the brain that regulates vital bodily functions, such as stress, immune response, autonomic and endocrine functions, sleep, and fluid homeostasis. This study aims to investigate the functional connectivity changes of the hypothalamus in fibromyalgia patients and the modulation effect of mind-body intervention.
Method Fibromyalgia patients and matched healthy control subjects (HC) were recruited. Resting state fMRI scans were applied in fibromyalgia patients before and after 12-week Tai Chi intervention and once in HCs. The bilateral medial hypothalamus (MH) and lateral hypothalamus (LH) were used as regions of interest. Data analysis was conducted on 20 patients and 19 HCs

using CONN. **Results** Fibromyalgia patients showed significant symptom reduction as measured by Revised Fibromyalgia Impact Questionnaire scores after Tai Chi intervention. Resting state functional connectivity (rsFC) analysis using the MH as seed showed that fibromyalgia patients significantly increased rsFC with the bilateral subcallosal cingulate cortex and decreased rsFC with the amygdala, thalamus, cerebellum, and PAG compared to HCs at baseline. After Tai Chi intervention, fibromyalgia patients showed increased (normalized) rsFC with the left amygdala, thalamus, PAG, and cerebellum. Functional connectivity analysis using the LH as seed found that fibromyalgia patients are associated with increased rsFC with the right temporal pole and decreased rsFC with the right occipital inferior gyrus/cerebellum. After the intervention, fibromyalgia patients showed greater rsFC with the bilateral rACC and MPFC, left PCC, and right MTG/STG. **Conclusion**: Elucidating the role of the hypothalamus in fibromyalgia and the modulation effect of Tai Chi may deepen our understanding of the pathophysiology of fibromyalgia as well as the mechanisms underlying mind-body intervention and facilitate, development of new pain management methods.

Disclosures: J. Kong: None. **Y. Huang:** None. **S. Yu:** None. **M. Cheng:** None. **J. Liu:** None. **J. Park:** None. **G. Wison:** None. **C. Wang:** None.

Poster

750. Somatosensation: Pain, Imaging, and Perception

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 750.06/G41

Topic: D.03. Somatosensation – Pain

Support: Charles D. and Mary Bauer Foundation
NIH R01DK110669

Title: Sensorimotor functional connectivity to the salience network is spatially heterogeneous in healthy humans

Authors: A. K. HEGARTY, M. S. YANI, A. M. ALBISHI, L. A. MICHENER, *J. J. KUTCH; Biokinesiology and Physical Therapy, USC, Los Angeles, CA

Abstract: Resting-state functional connectivity analyses typically group sensorimotor body regions as a homogenous network. We have recently shown that patients with chronic pain exhibit reproducible changes in resting-state functional connectivity between specific sensorimotor regions and the salience network, a network known to be important in pain processing. Therefore, we wanted to determine if inconsistencies in functional connectivity between the salience network and various sensorimotor regions would emerge even in healthy individuals, which may provide important insights about which body regions may be particularly prone to chronic pain development. Using electromyography and tasked-based functional

magnetic resonance imaging (fMRI) in 20 participants, we first localized distinct regions-of-interest spanning a large range of sensorimotor cortex, ranging from medial (gluteal) to intermediate (shoulder) to lateral (hand). Then, using an age and sex-matched set of 154 participants from a repository dataset of resting-state fMRI, we found that the medial, intermediate, and lateral sensorimotor areas exhibited significant heterogeneity in functional connectivity to the salience network. We further examined these inconsistencies by plotting the continuous functional connectivity to the salience network. On a flattened map of sensorimotor cortex, we also observed heterogeneity with relatively high functional connectivity to the salience network for trunk and face regions, and low functional connectivity for extremities including the hands and feet. We conclude that sensorimotor cortex can not be considered spatially homogeneous in its interaction with other large-scale brain networks. Different sensorimotor regions on the body surface may be prioritized differently for pain and threat assessment by the salience network.

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Poster

750. Somatosensation: Pain, Imaging, and Perception

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 750.07/G42

Topic: D.03. Somatosensation – Pain

Support: DoC PT160162

Title: Photosensitivity thresholds are associated with chronic pain levels in TBI and PTSD

Authors: *N. M. BALBA[1], A. MCBRIDE[5], S. D. MIST[2], K. D. JONES[6], B. NARDOS[1], R. J. OLSON[5], S. C. HARDMAN[5], M. L. CALLAHAN[5], M. P. BUTLER[3], M. M. LIM[4], M. M. HEINRICHER[4];
[1]Behavioral Neurosci., [2]Anesthesiol. and Perioperative Med., [3]Oregon Inst. of Occup. Hlth. Sci., [4]Neurol., Oregon Hlth. & Sci. Univ., Portland, OR; [5]VA Portland Hlth. Care Syst., Portland, OR; [6]Sch. of Nursing, Linfield Col., Portland, OR

Abstract: Chronic pain is in part driven by sensitization of pain-processing circuits in the central nervous system. Traumatic brain injury (TBI) and post-traumatic stress disorder (PTSD) are neurobiological conditions which are independently linked to an increased risk of chronic pain and self-reported photosensitivity. Individuals with comorbid TBI+PTSD have an even higher risk of developing these symptoms. However, the relationship between chronic pain and photosensitivity within these disorders remains unclear. The purpose of this study was to examine differences in chronic pain and photosensitivity in individuals with a history of TBI

and/or PTSD. Subjects completed a battery of self-report surveys relating to chronic pain, neurological functioning, and TBI/PTSD symptomology before being tested for pressure pain thresholds (using pressure algometry) and visual photosensitivity thresholds (VPT). Participants were then categorized into one of three groups based on a semi-structured, validated diagnostic interview for TBI and criteria from the PTSD Checklist for DSM 5 (PCL-5) survey for diagnosis of PTSD. Groups included: 1) Controls: subjects with no TBI or PTSD (n=31); 2) TBI: subjects with TBI, but no PTSD (n=76); and 3) TBI+PTSD: subjects with both TBI and PTSD (n=45). Only 5 subjects in this sample were classified as PTSD without TBI, and are not reported here. Using the Symptom Impact Questionnaire (SIQR) as a measure of chronic pain severity, we found that subjects suffering from comorbid TBI+PTSD had significantly higher levels of chronic pain and lower VPTs compared to Controls (P <0.01) and TBI subjects (P <0.01). VPTs were significantly correlated with chronic pain severity in the Control (R = -0.37, P = 0.05) and TBI groups (R = -0.32, P <0.01), but this correlation was strongest in the TBI+PTSD group (R = -0.40, P = 0.01). VPTs were also significantly correlated with pressure pain thresholds in the TBI+PTSD group (R = 0.41, P <0.01), but not in the Control (R = 0.21, P =0.29) or the TBI groups (R = 0.20, P = 0.10). Using a multiple linear regression model, we found that VPTs were a better predictor of chronic pain complaints (β = -0.16, P = 0.01) than other diagnostic measures including pressure pain thresholds (β = 0.001, P = 0.98). Taken together, these results suggest that photosensitivity levels could be used as a marker for individuals in whom central sensitization drives chronic pain, and could be applied to other populations that suffer from chronic pain. Future studies will use functional magnetic resonance imaging (fMRI) to see if these behavioral results relate to differences in cortical activity between groups in response to pressure pain and light stimuli.

Disclosures: **N.M. Balba:** None. **A. McBride:** None. **S.D. Mist:** None. **K.D. Jones:** None. **B. Nardos:** None. **R.J. Olson:** None. **S.C. Hardman:** None. **M.L. Callahan:** None. **M.P. Butler:** None. **M.M. Lim:** None. **M.M. Heinricher:** None.

Poster

750. Somatosensation: Pain, Imaging, and Perception

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 750.08/G43

Topic: D.03. Somatosensation – Pain

Title: Functional ultrasound and fMRI neuroimaging in somatosensory processing studies, acute and neuropathic pain models for preclinical drug discovery

Authors: A. SHATILLO, *A.-M. KÄRKKÄINEN, T. MIETTINEN, J. KOPONEN, K. KUPTSOVA, D. MISZCZUK;
Charles River Discovery, Kuopio, Finland

Abstract: Advancements in development of effective pain-relief therapies in acute and chronic pain conditions are of utmost importance to alleviate the suffering of the patients and lift the socio-economic burden of the disorders that involve nociceptive system. In turn, these advancements are impossible without implementing of the new testing paradigms, objective assays and models to evaluate pain and efficacy of new compounds in preclinical setting.
In this work we used functional neuroimaging to setup and characterize several models of acute (electrical and chemical stimulation) and neuropathic (oxaliplatin-induced) pain in rats and mice. We applied state-of-the-art imaging techniques that measure local changes in brain perfusion in response to painful stimuli - functional ultrasound (fUS) and functional magnetic resonance imaging (fMRI).
Functional ultrasound is a novel, non-invasive imaging technique based on ultrafast plane-wave acquisition of the doppler ultrasound signal with real-time data processing, which enables high-sensitivity imaging of relative cerebral blood volume (rCBV) changes with high resolution. The fUS readout is based on the same physiological mechanisms as functional MRI (fMRI).
Functional MRI experiments were performed in 7T Bruker PharmaScan MRI scanner in anesthetized rats (Wistar, males) with T2*-weighted gradient echo sequence for blood-oxygen level dependent (BOLD) contrast. Two different noxious stimulation paradigms for acute pain fMRI experiments were used - electrical forepaw stimulation (10 Hz, 1-1.5 mA, 4x30s blocks) and injection of pain-inducing compounds (5% formalin or allyl isothiocyanate, AITC) into the plantar surface of the hind paw.
Chemotherapy-induced peripheral neuropathy (CIPN) was induced in mice (C57BL/6J, males) by oxaliplatin (4.5 mg/kg; i.p.) or vehicle treatment every 3 - 4 days for a period of 21 days. At the end of oxaliplatin challenge, mice were tested for cool allodynia followed by fUS imaging (fUS prototype, Iconeus, Paris, France) with unilateral hind paw and whiskers stimulation (4x30s intervals with 1 min of rest in between).
Both fUS and fMRI data were preprocessed and analyzed in a similar fashion, by extracting the signal time series from corresponding brain areas for the response profile analysis and statistical mapping by correlating it to the stimulation model. Various extent of the sensory and pain networks activation was detected, correlating with stimulation intensity.
Provided data and methodology established in this study, demonstrates the utility and benefits of the functional neuroimaging for drug testing in therapeutic area of pain and in sensory processing disorders.

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Poster

750. Somatosensation: Pain, Imaging, and Perception

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 750.09/G44

Topic: D.03. Somatosensation – Pain

Support: German Research Foundation

Title: Appetitive and aversive learning and brain plasticity in the development of chronic back pain

Authors: *H. FLOR, K. USAI, M. LÖFFLER, F. NEES;
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Abstract: We sought to determine if the previously reported shift from nociceptive to emotional processing in the pain chronicity process might be related to maladaptive emotional learning and related brain plasticity. In a still ongoing combined cross-sectional and longitudinal study we examined 40 patients with subacute back pain, 40 chronic back pain patients and 40 healthy controls in an aversive and appetitive pavlovian conditioning paradigm as well as an instrumental monetary reward versus pain relief task during functional magnetic resonance imaging. Ratings of valence and arousal and skin conductance responses were also recorded. In comparison to controls, the chronic back pain group showed enhanced aversive and reduced appetitive learning with a stronger activation of limbic areas during aversive and sensorimotor in contrast to striatal areas during appetitive conditioning. In addition, the response to the unconditioned appetitive stimulus (pleasant touch) was dampened in the chronic back pain patients. We also found divergent subregion-specific response patterns in the insula for appetitive versus aversive learning within and between groups. For the chronic pain patients, we also found a stronger response to pain relief than monetary reward with a shift of the striatal response. The development of chronic pain has been predicted by limbic-prefrontal connectivity during learning and moderated by stress and anxiety. Our data suggest that emotional pavlovian and instrumental conditioning may be an important mediator of the shift of nociceptive to emotional/motivational brain circuits in the chronicity process and supports treatment interventions that reverse aversive and enhance appetitive pain-related memories. Supported by the Deutsche Forschungsgemeinschaft (Collaborative Research Center 1158 (Heidelberg Pain Consortium)).

Disclosures: H. Flor: None. **K. Usai:** None. **M. Löffler:** None. **F. Nees:** None.

Poster

750. Somatosensation: Pain, Imaging, and Perception

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 750.10/H1

Topic: D.03. Somatosensation – Pain

Support: Funded by the Max Planck Society

Title: Somatosensory evoked potentials in the human spinal cord

Authors: *B. NIERULA[1], T. STEPHANI[1], M. KAPTAN[1], A. MOURAUX[2], B. MAESS[1], G. CURIO[3], V. V. NIKULIN[1,4], F. EIPPERT[1];
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Abstract: Neuroscientific research on human somatosensation has largely focused on cortical processes. However, before somatosensory stimuli reach the brain, some processing already occurs in the dorsal horn of the spinal cord. Since a detailed understanding of spinal somatosensory processing is still lacking, we carried out a study in which we non-invasively recorded somatosensory evoked potentials (SEPs) from the human spinal cord - as well as the peripheral nervous system and the brain - in order provide a comprehensive picture of human somatosensation.
In 40 healthy participants (10 measured so far) we separately stimulated the median and tibial nerve with non-painful electrical impulses and recorded the resulting SEPs from target areas in the cervical and lumbar spinal cord (as well as the peripheral nerves and the brain) with surface electrodes - 64 on the scalp and 36 electrodes organized in rectangular patches around the 6th cervical (SC6) and the 1st lumbar vertebra (L1). We aimed to extend the findings of earlier studies on spinal SEPs by making use of an adequately powered sample-size, a much higher spinal electrode density, state-of-the-art recording equipment, and artefact removal methods (e.g. addressing prominent cardiac influences).
Initial data showed clear spinal cord potentials with the expected mean amplitude and latency for both median (N13 over SC6: -1.2 μV, 13.1 ms) and tibial nerve stimulation (N22 over L1: -0.5 μV, 22.7 ms). These potentials were reproducible as evidenced by an odd-even split of the epochs in the data. We also recorded clear peripheral and cortical potentials for both types of stimulation (i) median nerve: N6 at biceps: -3.5 μV, 5.9 ms; N9 at Erb's point: -1.1 μV, 9.6 ms; N20 at primary somatosensory cortex: -1.0 μV, 18.4 ms; ii) tibial nerve: N8 at knee: -2.2 μV, 8.8 ms; P38 at primary somatosensory cortex: 1.9 μV, 41.5 ms). All reported potentials are grand averages over 10 participants.
Future analyses of the whole sample will address the spinal responses in more detail and will also investigate how the amplitude of spinal responses is related to responses in peripheral nerves and the brain. We hope that this study will provide a comprehensive understanding of somatosensory stimulus processing at all levels of the neuraxis.

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Poster

750. Somatosensation: Pain, Imaging, and Perception

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 750.11/H2

Topic: D.03. Somatosensation – Pain

Support: NSERC Grant RGPIN/06221-2015

Title: Placebo modulation of pain networks in the human brainstem and spinal cord investigated by means of fMRI

Authors: *P. W. STROMAN, J. M. POWERS, G. IOACHIM, H. WARREN;
Ctr. for Neurosci. Studies, Queen's Univ., Kingston, ON, Canada

Abstract: The placebo effect is a positive cognitive modulation of behaviors, and in terms of pain refers to the experience of reduced pain as a result of expecting lower pain. This effect is important because it reveals cognitive and affective influences on human pain perception, and can confound investigations of the effectiveness of pain therapies, or contribute beneficially to pain relief. Although it is expected that descending pain regulation in the brainstem (BS) and spinal cord (SC) may play a role in the placebo effect, these neural mechanisms have rarely been studied. In the present study we used functional magnetic resonance imaging (fMRI) of the human BS/SC to investigate the neural basis of the placebo effect in studies involving noxious heat stimuli applied to the hand, with the expectation of lower pain in some trials.Twenty healthy people completed questionnaires to characterize personality traits, and participated in quantitative sensory testing, sham MRI training, and then fMRI studies. The placebo effect was investigated by informing participants 1 minute into each trial whether the “Base” temperature would be applied, which was calibrated to evoke moderate pain, or a temperature 1 °C lower would be applied (the “Placebo” temperature). The 30-second duration noxious heat stimulus was applied to the hand one minute later (at the 2-minute mark), allowing time for participants to anticipate the stimulus. After each trial (4.5 minutes total) the participants were asked to rate the peak pain intensity and unpleasantness experienced during the stimulation period. Unbeknownst to the participants, the same temperature was actually applied in each trial.Behavioral results confirmed that participants experienced lower pain when the lower temperature stimulus was expected. Pain intensity ratings (0-100 scale) decreased from an average of 49 ± 10 (mean ± sd) for the “Base” state to 43 ± 12 for the “Placebo” state ($p < 10^{-3}$, paired t-test). FMRI results were analyzed by means of structural equation modeling and demonstrated significant connectivity between SC, BS, and thalamus regions. Connections were also identified with significant correlations across participants between the change in connectivity values between states, and the change in unpleasantness ratings between states. BOLD responses and connectivity between regions were observed to depend significantly on both pain sensitivity and on the study state

(Base vs Placebo). Overall, the results demonstrate that the placebo effect is modulated by a network of regions that are known to be involved with descending pain regulation, autonomic regulation, and integration of sensory and autonomic functions.

Disclosures: P.W. Stroman: None. **J.M. Powers:** None. **G. Ioachim:** None. **H. Warren:** None.

Poster

750. Somatosensation: Pain, Imaging, and Perception

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Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 750.12/H3

Topic: D.03. Somatosensation – Pain

Support: NSERC Grant RGPIN/06221-2015

Title: Brainstem and spinal fMRI during the expectation of pain: Exploring coordinated networks

Authors: *G. IOACHIM[1], J. M. POWERS[1], P. W. STROMAN[2];
[2]Ctr. for Neurosci Studies, [1]Queen's Univ., Kingston, ON, Canada

Abstract: Spontaneous variations in activity of brainstem (BS) and spinal cord (SC) regions may arise from a number of functions such as autonomic regulation, sensory, and motor functions. Recent evidence suggests that changes in a person's cognitive/emotional state are linked to changes in identified BS and SC resting-state networks, indicating that these networks likely play a role in the integration of homeostatic autonomic functions. Several studies have also shown that placebo and nocebo effects can involve brainstem regions, which could be of particular interest for research involving predictable painful stimuli. The aim of this study was to investigate how these BS and SC resting-state networks change when participants are specifically expecting pain. Previously, data were obtained from the cervical SC and brainstem in 17 healthy participants during a stimulation paradigm that involved a predictable noxious heat stimulus. Participants experienced both trials with (expect-pain condition) and without the heat stimulus (expect-no-pain condition), in a random order, but were informed 1 minute into each trial whether to expect heat or not. Blood oxygenation-level dependent (BOLD) fMRI data were obtained at 3 tesla, with T2-weighted single-shot fast spin-echo imaging. For the current study we investigated functional connectivity in the entire 3D region with structural equation modelling (SEM) during each run (baseline period, after participants were told whether to expect a painful stimulus, while feeling pain/no pain, and after pain). SEM results showed extensive connectivity within and across BS and SC regions both when participants were expecting pain, and when they were expecting no pain. Furthermore, significant differences in connectivity between regions of the BS and SC were also identified between the two conditions. Importantly,

a large proportion of identified connections in the expect-no-pain condition were also present in previously described resting-state BS/SC networks. In contrast, there were a number of unique connections identified in the expect-pain condition, including in the period of time when participants knew to expect pain (but had not felt the painful stimulus yet).These results indicate that connectivity across BS/SC networks is influenced by the expectation of pain in ways distinct from other cognitive tasks. The known functions of the regions involved in the connections unique to the expect-pain condition support the conclusion that the BS/SC networks identified during the expectation of pain likely serve to integrate autonomic regulation functions with pain processing.

Disclosures: G. Ioachim: None. **J.M. Powers:** None. **P.W. Stroman:** None.

Poster

750. Somatosensation: Pain, Imaging, and Perception

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 750.13/H4

Topic: D.03. Somatosensation – Pain

Support: Canadian Institutes of Health Research
Mayday Fund

Title: Sex-differences in brain modular organization in chronic pain

Authors: *C. FAUCHON[1], D. MEUNIER[2], K. S. HEMINGTON[1,3], J. CHENG[1,3], R. BOSMA[1,3], N. OSBORNE[1,3], A. ROGACHOV[1,3], A. KIM[1,3], R. INMAN[1,4], K. D. DAVIS[1,3,5]; [1]Krembil Res. Inst, Univ. Hlth. Network, Toronto, ON, Canada; [2]Inst. Neurosci Timone, Aix Marseille Univ., Marseille, France; [3]Inst. of Med. Science, Univ. of Toronto, Toronto, ON, Canada; [4]Dept. Of Medicine, Univ. of Toronto, Toronto, ON, Canada; [5]Dept. Surgery, Univ. of Toronto, Toronto, ON, Canada

Abstract: Objective and rationale:
Some chronic pain conditions show a sex-specific prevalence. There are also sex differences in antinociceptive brain circuitry in patients with chronic pain and in healthy individuals. Patients with chronic pain exhibit brain abnormalities of inter- and intra-network functional connectivity (FC) within the dynamic pain connectome. Brain network topology can provide further insight into these sex differences. Here, we modeled the brain as a modular network using graph analysis based on resting-state fMRI (rsfMRI) data in males and females with chronic pain.
Methods:
We acquired rsfMRI data from males (n=45) and females (n=20) with chronic low back pain (cLBP) associated with ankylosing spondylitis, and age/sex-matched healthy controls (HC). Data were preprocessed and parcellated based on the human connectome project atlas using Nipype to

create 360 anatomical regions (nodes). For each subject, timeseries data were extracted and thresholded, and FC matrices were generated by computing Pearson correlations between every node, using the neuropypcon package. The modular analyses were run on the average Z-correlation matrix for each group to segregate the brain network into modules of regions with high FC. Inter- and intra-modular connectivity and other global and nodal networks metrics were computed. Permutation tests were applied between groups.

Results:

Males with cLBP and HCs had the same modular structure with 6 modules, whereas females with cLBP had an 8 module topology. Networks common to both sexes were 1) frontoparietal, 2) occipital, 3) sensorimotor and salience, 4) parietal superior, 5) temporal and subcortical regions, and 6) ventro-medial prefrontal cortex (vmPFC). In both healthy and cLBP females groups, the frontoparietal module was split in two modules and females with cLBP had an extra module in the mid cingulate cortex (MCC). Both males and females with cLBP had more inter-modular connections and less intra-modular connections compared to HCs. These findings were more pronounced in females with cLBP who had a significant increase of connections in MCC, vmPFC, anterior insula and parietal regions and a decrease of connections in the operculo-insular region, SMA and PCC compared to HCs. In contrast, in the males with cLBP, inter-modular connectivity was greater in the subcortical, prefrontal and parietal cortices and decreased in premotor and cingulate motors regions compared to HC.

Conclusions:

Brain network organization in patients with chronic pain show sex differences. Therefore, a framework to assess the efficacy and side effects associated with pain treatment targets should consider sex differences.

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Poster

750. Somatosensation: Pain, Imaging, and Perception

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 750.14/H5

Topic: D.03. Somatosensation – Pain

Title: Age related changes in autonomic nervous response to different levels of painful stimulation

Authors: M. MIYAMAE[1], *A. NAKAE[2], K. NOMURA[2], C. KISHIMOTO[2], Y. MINEGISHI[1], R. URABE[1], K. NAKAI[1], T. YANAGIDA[2];

[1]Univ. of Fukui Hosp., Eiheiji-cho, Japan; [2]Osaka Univ. Grad. Sch. of Frontier Biosci., Suita-shi, Japan

Abstract: Background: To prescribe an appropriate amount of analgesics is often challenging for doctors because pain is a subjective symptom. To avoid the misuse of prescription opioids, objective evaluation of pain is necessary. The autonomic nerve response to pain is useful for evaluating pain objectively, but it is a fact that autonomic nerve response is affected by age. This study aimed to clarify age-related changes in autonomic responses to painful stimulation. Methods: After receiving the approval of the ethical committee of Osaka University, we recruited 157 healthy subjects and obtained written informed consent. The subjects were divided into three groups namely; young group (20-29 years old), middle-aged group (30-59 years old), and elderly group (60- years old). After checking the sensitivity to pain using Pathway(Medoc, Israel), participants were applied 30 seconds stimulation of 36℃, 48℃ and two more temperatures between 36℃ and 48℃. During stimulation, subjects evaluated their amount of pain using CoVAS (Medoc, Israel). Using pulse oximeter, information regarding PR (Pulse Rate), PWA (Pulse Wave Amplitude), and PI (Perfusion Index) were obtained. SCR (Skin Conductance Response) data was also obtained. In analyzing these data, Tukey's HSD test was performed to find the differences between groups. Results & Discussions: Through VAS analyses, it was confirmed that stimulation temperature was appropriately set for each participant. AT 48℃ stimulation PR significantly increased among the young and middle-aged groups ($p<0.001$), but not among the elderly group.The AUC at the 48 ℃ was significantly higher among the young group than in the middle-aged and elderly groups ($p<0.014$). PWA has decreased significantly among all levels stimulation in the young group ($p<0.024$), but only at the 48 ℃ stimulation in the middle-aged and elderly groups ($p<0.034$). The AUC was significantly lower in young group compared to the middle-aged group at lower temperature that we set by between 36℃ and 48℃, and in middle-aged and elderly groups at higher temperature we set between 36℃ and 48℃ ($p<0.023$). SCR increased significantly between almost all temperatures among young group ($p<0.002$), and we couldn't find the same differences among middle-aged and elderly groups. Conclusions: Only among younger generation, autonomic response to various amounts of pain is useful for monitor pain objectively. Only strong pain may be detected by autonomic responses from middle-aged generation to elderly.

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Poster

750. Somatosensation: Pain, Imaging, and Perception

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 750.15/H6

Topic: D.03. Somatosensation – Pain

Title: An investigation of PGE2-mediated pain relief following virtual reality

Authors: C. J. RINCONES, H. RHODES, B. G. GARCIA-GONZALEZ, ***J. A. BOYETTE-DAVIS**;
St. Edward's Univ., Austin, TX

Abstract: Virtual reality (VR) has received increasing attention in neuroscience research for its potential therapeutic applications. Recent literature has investigated its use in physical therapy, surgery, therapy, and most recently physicians have been using it as a type of distraction therapy for minor painful procedures. Little has been done to investigate the mechanistic ways VR might reduce pain; however, there is a plethora of evidence to support that prostaglandins, chemicals found to increase inflammation, play a role in pain. It was postulated that VR could potentially mediate the release of these inflammatory mediators and therefore decrease pain. The current study explored the relationship between prostaglandins, specifically PGE2, and calming VR. Seventy-nine participants (average age: 20) experienced the cold pressor test (CPT), an experimentally induced painful stimulus, while simultaneously viewing a calming VR scene (7 males, 33 females). This group was compared to a control group who did not experience VR (7 males, 32 females). Time and ratings of pain were collected for both participant threshold and tolerance during the CPT. Additional data was collected regarding pain catastrophizing (PCS) and retroactive pain levels. No differences were found for pain threshold ($p = .417$), pain tolerance ($p = .403$), or PCS total scores ($p = .197$) between the two groups. However, males took significantly longer to reach pain tolerance than females ($p = .002$) indicating a higher pain tolerance. Tolerance ratings were positively correlated with PCS total scores ($r = .293$, $p = .009$), and PCS was also positively correlated to both retroactive pain ratings ($r = .223$, $p = .048$) and pain frequency ($r = .355$, $p = .001$). These results confirm previous findings regarding gender differences in pain, and add to the literature on PCS as an important mediator of pain perception. Moreover, ELISA immunoassays were used to quantify pain-induced PGE2 release. Analyses revealed that PGE2 modulates these effects. This study establishes the necessity of further exploring the parameters of VR efficacy before a wide spread implementation of VR in the clinical field and further underscores the importance of considering pain catastrophizing in investigations of therapeutic outcomes for pain.

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Poster

750. Somatosensation: Pain, Imaging, and Perception

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Program #/Poster #: 750.16/H7

Topic: D.03. Somatosensation – Pain

Support: NSERC Grant RGPIN/06221-2015

Title: The neural basis for music analgesia in the human brain and brainstem

Authors: *J. M. POWERS, G. IOACHIM, P. W. STROMAN;
Ctr. for Neurosci. Studies, Queen's Univ., Kingston, ON, Canada

Abstract: Music has been used to treat pain for thousands of years, and its effect has been characterized in behavioural studies and with functional magnetic resonance imaging (fMRI). It is hypothesized that music exerts an analgesic effect through descending modulation within the periaqueductal gray-rostral ventromedial medulla (PAG-RVM) opioidergic pathway. The aim of this study was to investigate the neural basis of music analgesia. Specifically, we hypothesize that the amygdala and other limbic structures contribute to analgesia produced by listening to music, because of the involvement of these regions with the affective component of pain. FMRI was carried out at 3 tesla with data spanning the brain and brainstem, in order to investigate the effects of music on a network of pain-related regions. Twenty healthy participants (23 ± 3 years of age) each underwent a 1-hour stimulus training session in a sham MRI lab followed by a 1.5-hour session of repeated fMRI acquisitions. During all fMRI acquisitions, noxious stimulation was applied to the hand with an MRI-compatible robotic contact thermal heat stimulator (RTS-2, SpinalMap Inc.). Participants were instructed to bring in 6 selections of their favourite music, which they would describe as being highly pleasant, stimulating, happy, and familiar. During 6 of the fMRI runs participants listened to music, and in 6 runs there was no music; this was done in a randomized order. Behavioural results confirmed that participants experienced a significant decrease in pain unpleasantness scores from 27 ± 15 (mean ± s.d.) during the “No-Music” condition to 23 ± 14 during the “Music” condition ($p < 0.006$, paired t-test). Pain intensity was not found to be significantly different ($p < 0.14$). Structural equation modeling (SEM) demonstrated networks of brain/brainstem regions with significant connectivity and revealed differences between runs with and without music as well as across periods of the stimulation paradigm. The results indicate that music influences pain perception within a network including the amygdala, anterior cingulate cortex, PAG, hippocampus and thalamus. This work contributes to a new view of how human pain is regulated in healthy people, and aids our understanding of the continuous modulation of pain. Moreover, it provides a critical baseline of research for future studies into how pain processing is altered in chronic pain conditions.

Disclosures: J.M. Powers: None. **G. Ioachim:** None. **P.W. Stroman:** None.

Poster

750. Somatosensation: Pain, Imaging, and Perception

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Topic: D.03. Somatosensation – Pain

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Center for Cognitive Aging & Memory
OAIC

Title: Insular and hippocampal resting state functional connectivity is associated with chronic pain duration in community dwelling older adults

Authors: *Y. CRUZ-ALMEIDA, P. VALDÉS-HERNÁNDEZ, N. EBNER, P. LYSNE, D. RAMIREZ;
Pain Res. & Intervention Ctr. of Excellence, Univ. of Florida, Gainesville, FL

Abstract: Chronic pain is common in older adults negatively impacting quality of life. Emerging evidence suggests that longer pain duration may modify brain structure in persons with chronic musculoskeletal pain, but little is known about its potential impact on brain function. We investigated such effects in chronic pain elders (60-82, M=72±6, n=38) enrolled in the Neuromodulatory Examination of Pain and Mobility Across the Lifespan (NEPAL) study with a large variability in self-reported chronic pain duration (PDUR, Mean=10±13 years, <1—56). They underwent a resting state functional MRI (fMRI) connectivity (FC) scan as a neurobiological proxy of the brain's repeated encoding of the pain experience. Whole brain 3T fMRIs were preprocessed with SPM12 and normalized with DARTEL to account for our sample's large morphometric variability. Using CONN, fMRIs signals were denoised and averaged within region-of-interest (ROIs), to calculate all-to-all ROI-to-ROI z-transformed correlations (FCs). ROIs were defined from the atlases Brainnetome (A246), AAL116 and 32 empirical resting state network (RSN) nodes. GLM was fitted for each FC as dependent variable, PDUR as independent variable of interest and age, sex as nuisance regressors. PDUR and age were not correlated (r=0.20, p=0.100), justifying age as a covariate. Significance of PDUR effect was evaluated with a T-contrast thresholded using False Discovery Rate $q<0.05$ (FDR) across 77,000 connections. Results indicated that FC between the left dorsal dysgranular insula and the left caudal hippocampus (cHipp-L) positively correlated with PDUR ($p_{FDR}<0.03$). To loosen the conservative threshold criterion that such amount of connections yields, we excluded atlas246 resulting in 10,000 connections. This time, PDUR positively correlated with FC between left hippocampus and "salience" RSN frontal-lateral node, $p_{FDR}<0.02$ (left) and $p_{FDR}<0.03$ (right). These nodes mostly contain the frontal operculum, the dorsal agranular insula and the opercular inferior frontal gyrus, related to pain somesthesis/monitoring/discrimination. In general, the salience network is involved in detecting salient stimuli and self-awareness through sensory/emotional/cognitive integration, while the hippocampus is crucial for memory. Thus, enduring pain across the lifespan may gradually shape the way cognition and pain perception interact with memory systems to eventually imprint its chronic effects on human behavior.

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Poster

750. Somatosensation: Pain, Imaging, and Perception

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Korean Institute of Oriental Medicine (C18210)
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Title: Reduced tactile acuity in chronic low back pain is linked with structural neuroplasticity in primary somatosensory cortex and is modulated by acupuncture therapy

Authors: H. KIM[1], I. MAWLA[2], J. LEE[2], J. GERBER[2], K. WALKER[2], J. KIM[1], A. WASAN[3], R. R. EDWARDS[4], J. KONG[2], T. KAPTCHUK[5], R. GOLLUB[2], B. R. ROSEN[2], ***V. NAPADOW**[2];
[1]KIOM, Daejeon, Korea, Republic of; [2]Massachusetts Gen. Hosp., Boston, MA; [3]Univ. of Pittsburgh, Pittsburgh, PA; [4]Brigham and Women's Hosp., Boston, MA; [5]Beth Israel Deaconess Med. Ctr., Boston, MA

Abstract: Patients suffering from chronic Low Back Pain (cLBP) show impaired somatosensory processing and reduced tactile acuity, i.e.reduced ability to resolve fine spatial details with the perception of touch. The mechanism(s) underlying this reduced tactile acuity are unknown but may include changes in peripheral mechanoreceptors or central circuits (e.g. neuroplasticity in primary somatosensory cortex, S1). Further, little is known about the linkage between changes in tactile acuity and amelioration of cLBP by somatically-directed therapeutic interventions, such as acupuncture. In this longitudinal neuroimaging study, we evaluated healthy control (HC, N=50) adults and cLBP patients (N=102) with structural brain imaging (T1 for Voxel Based Morphometry, VBM; Diffusion Tensor Imaging, DTI) and tactile acuity testing using two-point discrimination threshold (2PDT) over the lower back (site of pain) and finger (control) locations. Patients were evaluated at baseline and following a 4-week course of acupuncture, with patients randomized to either verum (genuine) acupuncture, sham acupuncture (with or without somatosensory afference), or no-intervention usual care control. Compared to HC, cLBP patients demonstrated reduced acuity (greater 2PDT, p=0.01) over the low back, but not on the finger (p=0.29), suggesting that chronic pain affects tactile acuity specifically at body regions encoding the experience of clinical pain. Gray matter volume in the S1-back representation region was elevated in cLBP and correlated with greater 2PDT-back scores (r=0.27, p=0.02). DTI

assessment of Fractional Anisotropy (FA) in S1-adjacent white matter revealed that, compared to HC, cLBP patients demonstrate reduced FA in S1-back regions (p=0.01). Following verum acupuncture therapy, tactile acuity over the back was improved (reduced 2PDT) and greater improvements were associated with reduced S1-back gray matter volume (r=0.52, p=0.03) and increased S1-back adjacent white matter FA (r=-0.56, p=0.01). These changes and associations were not seen for non-verum control interventions. While low back pain reduction was greater following verum compared to control interventions (repeated measures ANOVA, Group x Time interaction on LBP bothersomeness, F[1,67]=3.99, P=0.0498), neuroanatomical and tactile acuity changes were not linked with clinical outcomes after 4-weeks of therapy. Thus, S1 neuroplasticity in cLBP may represent early mechanistic changes in somatosensory processing that are linked with improved tactile acuity and predict longer-term improvements in clinical pain severity following successful therapy.

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Poster

750. Somatosensation: Pain, Imaging, and Perception

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 750.19/H10

Topic: D.03. Somatosensation – Pain

Title: Developed implantable needle-type sensor devices for use in the simultaneous *in vivo* visualization of brain centers involved in nociception

Authors: *R. B. REBUSI, Jr[1], M. C. GUINTO[1], J. OLOROCISIMO[2], Y. OHTA[1], M. HARUTA[1], K. SASAGAWA[1], J. OHTA[1];
[1]Material Sci., [2]Biol. Sci., Nara Inst. of Sci. and Technol., Ikoma, Japan

Abstract: The lateral capsular subdivision of the central nucleus of the amygdala (CeLC), known as its nociceptive center, receives and relays nociceptive signals and is responsible for the sensation and emotional response to pain. This amygdalar region receives serotonergic input from a portion of the dorsal raphe nucleus of the midbrain (DRN) which secretes Substance P, a neuropeptide important for pain perception. It is currently uncertain as to what role the DRN has in nociception and its processing in relation to its downstream amygdalar counterparts.
In this study, we aim to elucidate the direct nociception neural pathway bridging the DRN to the CeLC by the use of implantable needle-type devices developed by our laboratory. This device is composed of a CMOS-based image sensor chip embedded on a flexible substrate with a μ-LED light source. It has a width of 0.7 mm, a thickness of 0.2 mm, and an insertable length of 3 mm. These dimensions allow for minimally injurious implantations, even simultaneous ones, that only

affects brain regions by the implantation path and target. The use of a CMOS-based image sensor gives useful visual data, even if limited. All of these allows for high output *in vivo* studies not limited by a weight burden or extensive injury.
For the methodology, two devices are to be simultaneously implanted adjacent to the CeLC and the DRN of GCaMP6 mice. These transgenic mice have neurons that express Ca^{2+}-calmodulin-binding GFP constructs that will fluoresce with appropriate light stimulation during neuronal actional potentials. The implantation method for these two nuclei has been refined with the proper sterotaxic coordinates and implantation paths finalized. Complications arising from straightforward implantation methods, such as overlying blood vessels and ventricles, have been addressed with the use of angled implantations and stricter animal maintenance. Bi-phasic pain induction will be via the subcutaneous injection of 2% formaldehyde in the upper arm, opposite to the implanted brain hemisphere. Nociception will be confirmed by the devices recording neuronal activity and the observation of animal behavior.
We have already acquired separate recordings of the target brain regions in mice that underwent the formalin test and the results have shown neuronal activity in both regions concurrent with pain perception, as interpreted from behavioral observations. The next steps are to confirm the reproducibility of the separate recordings, and then to apply the optimized methodologies on double implantations to procure simultaneous nociception-linked neural recordings.

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Poster

750. Somatosensation: Pain, Imaging, and Perception

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Title: Dynamic reconfiguration of functional brain network during sustained pain

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Abstract: Pain is not just a simple reflex to nociceptive input, but it is rather constructed through complex interactions among multiple brain systems over time. However, it remains poorly understood how the patterns of brain activity and connectivity dynamically change over the period of experiencing sustained pain. Here, we used functional magnetic resonance imaging to investigate the dynamic changes in functional brain network architecture during 20 minutes of experiencing capsaicin-induced tonic pain in 48 participants. The network-level analysis results showed that the network transitivity and assortativity were significantly decreased in the tonic pain condition compared to the control condition ($p < .05$ for both), whereas the characteristic path, global efficiency, and network-level modularity were not changed ($p = .09$, .10, and .57). When we examined the temporal dynamics in these network attributes from the initiation to the remission of pain, the assortativity, modularity, and global efficiency increased over time, while transitivity and characteristic path decreased. Furthermore, we developed machine-learning models designed to track the changes in pain ratings within each individual based on some node-level network measures, including eigenvector centrality. These models showed the high levels of predictive performance (average $r = 0.66$), providing a promising network-based neuroimaging biomarker for tonic pain. The brain regions with high positive predictive weights included primary somatosensory cortex, dorsal anterior cingulate cortex, dorsomedial and dorsolateral prefrontal cortex, right dorsoparietal insula, and right inferior parietal lobule. We further characterized the mesoscale network dynamics over the time-course of the experimental tonic pain using a temporal community detection method. This study provides a new insight into how dynamic interactions among multiple brain systems construct and process pain experience over time, which could potentially advance our mechanistic understanding of sustained (e.g., chronic) pain.

Disclosures: **J. Lee:** None. **C. Woo:** None.

Poster

750. Somatosensation: Pain, Imaging, and Perception

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 750.21/H12

Topic: D.03. Somatosensation – Pain

Support: Wellcome Trust PhD scholarship S122871-101

Title: Imaging pain modulation from cortex to spinal cord

Authors: *V. OLIVA[1], A. WILSON[2], R. HARTLEY-DAVIES[2], R. MORAN[3], A. E. PICKERING[1], J. BROOKS[2];
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Abstract: Distraction from pain is a robust strategy to transiently decrease pain perception. Previous studies have shown this process to involve pain modulatory nuclei in the brainstem (Brooks et al, J Neurosci 2017) and the spinal cord (Sprenger et al., Curr Biol 2012) but this has never been achieved with supratentorial structures to define the actions of the entire descending pain modulatory system.
The challenges of imaging spinal cord are numerous: tissue heterogeneity adjacent to the cord causes spatial fluctuations in the magnetic field, cardiac and respiratory processes cause physiological noise and movement in the cord which is complicated by the challenge of obtaining a sufficiently uniform magnetic field over the large field of view. Using approaches similar to those adopted by Islam et al. (Magn Reson Med, 2019) and Finsterbusch et al. (Neuroimage, 2013) we sought to simultaneously obtain fMRI data from brain, brainstem and spinal cord during an attentional analgesia paradigm.
We recruited 22 healthy volunteers who received thermal stimuli on their left forearm (C6 dermatome) at two temperatures (painful/warm), whilst simultaneously performing a rapid serial visual presentation task with two levels of difficulty (Brooks et al 2017).
Whole CNS functional images were acquired with a 3T Siemens Skyra MRI scanner and slice specific z-shim offsets, which were chosen for the spinal cord and low medulla, and had an in-plane resolution of 1.77mm and 4mm slice thickness. In addition, we recorded cardiac and respiratory waveforms during imaging to regress physiological noise from functional data. Imaging data were pre-processed as per Brooks et al. (2017) and analysed in FEAT (FSL). A group analysis for brain was performed in FEAT and for brainstem in RANDOMISE.
A main effect of temperature contrast showed brain activation in pain related areas (e.g. insular cortex, $Z > 2.3$, cluster corrected $p < .05$). In the brainstem we found activation in the RVM (TFCE corrected, $p < .05$). In the spinal cord we observed activity in the C6 segment of the spinal cord ($Z > 2.3$, uncorrected, n=13).
The use of a large field of view in the z-direction poses challenges for image acquisition, but it allows us to build a complete map of pain perception and its cognitive modulation: from spinal cord detection of a nociceptive stimulus, through brainstem relays modulating its intensity, to the cortical/cognitive representation of pain in higher brain regions.

Disclosures: V. Oliva: None. **A. Wilson:** None. **R. Hartley-Davies:** None. **R. Moran:** None. **A.E. Pickering:** None. **J. Brooks:** None.

Poster

750. Somatosensation: Pain, Imaging, and Perception

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 750.22/H13

Topic: D.03. Somatosensation – Pain

Support: ERC StG 758974

Title: A role for predictive coding in pain perception?

Authors: *U. HORN, F. EIPPERT;
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Abstract: Pain is a useful and important warning signal of impending or actual tissue damage, but knowledge of the factors that determine how the experience of pain derives from nociceptive input is still rather coarse. Here we used the framework of predictive coding in order to ask whether the experience of pain might be best characterized not just as passively arising from nociceptive stimulation, but as an active inferential process, in which the central nervous system constantly generates predictions about the sensory inputs it receives and adjusts these predictions in light of new sensory input. We acquired data from 40 healthy participants (6 obtained so far) using a probabilistic heat-pain paradigm that allows for i) varying predictive information and nociceptive input across trials, ii) a temporal dissociation of prediction and prediction error signals and iii) a characterization of prediction and prediction error influences on the subjective perception of pain. In each participant, we recorded trial-wise cue- and outcome-induced skin conductance, pupil dilation, and cardiac responses as well as ratings of perceived pain on a VAS (converted to values from 0 to 100). An analysis of the first 6 participants' (skin conductance, pupil dilation, rating) data revealed that cue-based physiological responses before the onset of heat-stimulation followed the predicted probability of receiving pain. Outcome-based responses showed that painful heat resulted in larger responses than non-painful heat (averaged standardized logarithmic skin conductance amplitudes following stimulation: 0.42 and 0.15, averaged standardized logarithmic pupil dilation amplitudes: 0.26 and 0.19 (a.u.)) consistent with average pain ratings of 73.8 and 19.5. Due to the small sample size, we were not able to reliably quantify prediction error signals in the data - this issue will be revisited with the full sample. In the future, we will i) extend these analyses to the whole sample of participants, ii) use a model-based approach in order to distinguish between different explanatory models (e.g. an intensity coding model vs different predictive coding models), and iii) use this paradigm in combination with functional magnetic resonance imaging (fMRI) of spinal cord responses. Together, this should allow us to ascertain whether predictive signals significantly contribute to the various components of pain processing - from the level of dorsal horn responses to subjective perception.

Disclosures: U. Horn: None. **F. Eippert:** None.

Poster

750. Somatosensation: Pain, Imaging, and Perception

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 750.23/H14

Topic: D.03. Somatosensation – Pain

Support: NCCIH Grant 4R33AT009306-03

Korea Institute of Oriental Medicine

Title: Hyperscanning the patient-clinician interaction: Brain-to-brain concordancesupports therapeutic alliance, facial mirroring, and placebo analgesia

Authors: D.-M. ELLINGSEN[1], *K. ISENBURG[2], C. JUNG[2], J. LEE[2], J. GERBER[2], I. MAWLA[3], R. SCLOCCO[2], K. JENSEN[4], M. L. LOGGIA[2], R. R. EDWARDS[5], J. KELLEY[2], I. KIRSCH[6], T. KAPTCHUK[6], **V. NAPADOW**[2];
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Abstract: The patient-clinician relationship can powerfully shape pain and placebo response, but the brain mechanisms are unknown. We simultaneously recorded functional MRI (i.e. hyperscanning) in patient-clinician dyads, who interacted via on-line video, while clinicians (acupuncturists) treated evoked pain in patients (fibromyalgia). We hypothesized that placebo analgesia and non-verbal communication would be supported by concordant fMRI response in ventrolateral Prefrontal Cortex (vlPFC), anterior Insula (aINS), and Temporoparietal Junction (TPJ), which are implicated in social mirroring, empathy, and theory-of-mind. Each patient was matched with a clinician (n=37 dyads). Each dyad was unique and scanned under one of two conditions: 1) after having established therapeutic alliance through a clinical intake by the clinician (Social interaction, n=19), or 2) no such intake (No interaction control, n=18). During block-design fMRI, patients received 12 moderately painful cuff pressures to the left leg while the clinician applied (real sub-sensory threshold microcurrent / sham, double-blind) electro-acupuncture stimulation (EA) to reduce cuff pain. Facial expression was assessed via Affectiva software. While cuff pressure was identical for all stimuli, patients' pain was significantly decreased during both real ($p=0.01$) and sham ($p=0.01$) EA treatment compared to overt no-treatment. Correspondingly, clinicians rated vicarious pain as decreased with treatment (real/sham combined), relative to no-treatment ($p<0.0001$). Therapeutic alliance was higher for Social interaction relative to No interaction control ($p<0.0001$). Further, higher facial mirroring was associated with higher therapeutic alliance and stronger placebo analgesia ($r=-0.52$, $p=0.03$). A conjunction analysis of patients' and clinicians' brain response during anticipation of pain/treatment demonstrated consistent activation of vlPFC, aINS, and TPJ. Furthermore, patients' right TPJ activity showed higher dynamic (trial-to-trial) concordance with clinicians' social mirroring circuitry (vlPFC, aINS, TPJ) for Social Interaction relative to No-Interaction dyads. Finally, placebo-related increase in vlPFC activity during evoked pain (Treat-NoTreat) mediated the relationship between patient-clinician concordance in right TPJ during anticipation and placebo analgesia (Total effect (a*b): -1.799**, $p=0.006$). TPJ is a key node in social mirroring and theory-of-mind processing, and brain-to-brain coupling of TPJ activity between interacting patients and clinicians may support therapeutic alliance and psychosocially facilitated analgesia.

Disclosures: D. Ellingsen: None. **K. Isenburg:** None. **C. Jung:** None. **J. Lee:** None. **J. Gerber:** None. **I. Mawla:** None. **R. Sclocco:** None. **K. Jensen:** None. **M.L. Loggia:** None. **R.R. Edwards:** None. **J. Kelley:** None. **I. Kirsch:** None. **T. Kaptchuk:** None. **V. Napadow:** None.

Poster

750. Somatosensation: Pain, Imaging, and Perception

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 750.24/H15

Topic: D.03. Somatosensation – Pain

Support: Natural Science and Engineering Research Council of Canada, Grant number 06659
Fonds de Recherche du Québec en Santé

Title: Spinal and cerebral integration of bilateral nociceptive inputs in left-handed individuals

Authors: *S. NORTHON, N. RUSTAMOV, M. PICHE;
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Abstract: It has been suggested that some pain-related information is processed preferentially in the right cerebral hemisphere. Considering that functional lateralization can be affected by handedness, spinal and cerebral pain-related responses may be different between right- and left-handed individuals. This has critical implications for brain imaging and neuromodulation studies on pain and pain modulation mechanisms. A recent study in right-handed individuals showed that the spinal nociceptive flexion reflex (RIII-reflex) and pain-related gamma oscillations in prefrontal, cingulate and sensorimotor regions are increased by concurrent nociceptive inputs from the contralateral limb. Moreover, this study indicates that RIII-reflex facilitation is due to descending motor pathways. The objective of the present study was to examine whether these processes are affected by handedness. The RIII-reflex as well as pain-related evoked potentials (ERP) and spectral perturbations (ERSP) were compared between ten right-handed (5F, age: 24.4 ± 3.5) and ten left-handed (6F, age: 24.4 ± 6.8) participants. The RIII-reflex, ERP, ERSP and pain perception were induced by painful transcutaneous electrical stimulation of the sural nerves and left hypothenar area. Stimulation intensity was adjusted individually at 120% of RIII-reflex threshold for the lower limbs and 120% of pain threshold for the left hypothenar area, in five conditions of 21 stimuli each: three unilateral conditions (right and left sural nerve and left hypothenar area) and two bilateral conditions (both sural nerves; right sural nerve with left hypothenar area). The amplitude of the RIII-reflex, ERP, ERSP as well as pain ratings were compared between groups and conditions using a mixed ANOVA. A significant difference was observed between conditions (main effect of condition) for RIII-reflex amplitude ($p<0.001$), the N100 ($p<0.001$), theta oscillations ($p<0.001$) and gamma oscillations ($p=0.005$). Planned comparisons revealed that these responses were increased in bilateral compared with unilateral conditions. However, these effects were not significantly different between right- and left-handed individuals. These results suggest that spinal and cerebral integration of bilateral nociceptive inputs is similar between right- and left-handed individuals. They also imply that

pain responses measured in this study may be examined independently of handedness. However, it remains to be clarified whether cortical sources of pain responses are lateralized differently between right- and left-handed individuals.

Disclosures: S. Northon: None. **N. Rustamov:** None. **M. Piche:** None.

Poster

750. Somatosensation: Pain, Imaging, and Perception

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 750.25/H16

Topic: D.03. Somatosensation – Pain

Support: Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks (ACTTION) Grant

Title: Convergent neural representations of pain in healthy volunteers: A large-scale fMRI meta-analysis

Authors: A. XU[1], B. LARSEN[1], E. B. BALLER[1], J. SCOTT[1], V. SHARMA[1], A. ADEBIMPE[1], R. H. DWORKIN[2], R. R. EDWARDS[3], S. B. EICKHOFF[4,5], C. R. EICKHOFF[5,6], *T. D. SATTERTHWAITE[1];
[1]Dept. of Psychiatry, Univ. of Pennsylvania, Philadelphia, PA; [2]Dept. of Anesthesiol. and Perioperative Med., Univ. of Rochester Sch. of Med. and Dent., Rochester, NY; [3]Dept. of Anesthesiology, Perioperative and Pain Med., Brigham and Women's Hospital, Harvard Med. Sch., Boston, MA; [4]Inst. for Systems Neurosci., Heinrich-Heine Univ., Düsseldorf, Germany; [5]Inst. of Neurosci. and Med. (INM-7), Res. Ctr. Jülich, Jülich, Germany; [6]Inst. of Clin. Neurosci. and Med. Psychology, Heinrich-Heine-University, Düsseldorf, Germany

Abstract: Characterizing a reliable neural signature of pain is critical for translational applications. Many prior fMRI studies have examined circuits recruited by induced pain in healthy participants. However, synthesizing these data to identify convergent patterns of pain-related brain activation can be challenging due to the heterogeneity of experimental designs and samples. Here, we address this challenge by conducting a comprehensive meta-analysis of fMRI studies of induced pain in healthy participants. Following pre-registration, two independent reviewers evaluated 4,927 abstracts returned from a broad search of 8 databases, with 222 fMRI experiments meeting inclusion criteria. We analyzed these experiments using Activation Likelihood Estimation with rigorous type I error control (voxel height $p<0.001$, cluster FWE $p<0.05$). Our results reveal a convergent pattern of pain-related activation in the secondary somatosensory cortex, anterior and posterior insula, anterior cingulate cortex, and thalamus. Notably, this network was consistently recruited despite variation in experimental design and sample composition, including stimulation technique, location of pain induction, and participant

sex. Taken together, these findings suggest that pain induction in healthy volunteers consistently recruits a core brain network, encouraging translational applications in drug development and clinical trials using fMRI.

Disclosures: A. Xu: None. **B. Larsen:** None. **E.B. Baller:** None. **J. Scott:** None. **V. Sharma:** None. **A. Adebimpe:** None. **R.H. Dworkin:** None. **R.R. Edwards:** None. **S.B. Eickhoff:** None. **C.R. Eickhoff:** None. **T.D. Satterthwaite:** None.

Poster

750. Somatosensation: Pain, Imaging, and Perception

Location: Hall A

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Topic: D.03. Somatosensation – Pain

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UF MBI Career Enhancement Award

Title: Experiences of discrimination are differentially associated with pain-related brain structure in male and female individuals from different race groups with or at risk for knee osteoarthritis

Authors: *E. L. TERRY[1], J. J. TANNER[1], J. S. CARDOSO[1], K. T. SIBILLE[1], S. LAI[1], H. DESHPANDE[2], G. DEUTSCH[2], B. R. GOODIN[2], L. A. BRADLEY[2], C. C. PRICE[2], R. B. FILLINGIM[1];
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Abstract: Non-Hispanic Black (NHB) individuals report higher rates of discrimination compared to their non-Hispanic White (NHW) counterparts. Further, NHB males report the highest rates of discrimination. Exposure to discrimination that is perceived as stressful might result in dysregulation of biopsychosocial and physiological processes and contribute to poorer pain-related outcomes in NHBs. Functional neuroimaging studies of discrimination and psychosocial stress suggest higher perceived discrimination associates with anterior cingulate cortex (ACC) activity and functional connectivity between the amygdala and pain-related cortical regions (e.g., insula, prefrontal cortex). The associations between brain structure and experiences of discrimination, however, remain largely unexplored. Moreover, no neuroimaging studies have investigated relationships between experiences of discrimination and pain-related brain region structure by ethnicity and sex. The current project is a sub-study of an ongoing

multi-site (University of Florida and University of Alabama at Birmingham) observational cohort investigation. Participants were 143 older adults with knee pain, including 27 NHB males, 23 NHW males, 41 NHB females, and 52 NHW females. All participants completed the Experiences of Discrimination questionnaire and Magnetic Resonance Imaging (MRI). High resolution three dimensional (3D) T1-weighted images were processed using FreeSurfer 6.0. Pre-selected cortical thickness (insula, ACC, primary somatosensory (S1), dorsolateral prefrontal (DLPFC), and medial prefrontal (MPFC) cortex) and volumes (amygdala, thalamus, hippocampus) were exported to SPSS for analyses. Partial correlation analyses were stratified by race and sex and adjusted for age, education, body mass index, study site, and pain intensity. Results revealed higher experiences of discrimination were associated with thicker S1 ($r = .55$, $p = .01$), DLPFC ($r = .48$, $p = .02$), insula ($r = .41$, $p = .06$), and rostral ACC ($r = .35$, $p = .11$) in NHB males, while higher experiences of discrimination were associated with thinner insula ($r = -.55$, $p = .02$), S1 ($r = -.47$, $p = .05$), MPFC ($r = -.62$, $p = .01$), and caudal ACC ($r = -.42$, $p = .08$) in NHW males. In NHB females, higher experiences of discrimination were associated with smaller amygdala ($r = -.39$, $p = .02$) and thicker DLPFC ($r = .33$, $p = .05$), while higher experiences of discrimination were associated with thicker caudal ACC ($r = .27$, $p = .07$) in NHW females. These results suggest experiences of discrimination might affect different structural brain components based on both race/ethnicity and sex in individuals with or at risk for knee osteoarthritis.

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Poster

750. Somatosensation: Pain, Imaging, and Perception

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 750.27/H18

Topic: D.03. Somatosensation – Pain

Support: R37AG033906
R01AG054370
UL1TR001427
UL1TR001417
1K22NS102334
1P30AG059297

Title: Differences in the association of neuropathic pain with S1 and caudal ACC thickness in individuals from different ethnic/race groups with or at risk for knee osteoarthritis

Authors: *J. CARDOSO[1], J. TANNER[2], E. L. TERRY[1], K. T. SIBILLE[3], S. LAI[4], H. DESHPANDE[5], G. DEUTSCH[5], B. R. GOODIN[6], L. A. BRADLEY[7], C. PRICE[2], R. B. FILLINGIM[1];
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Abstract: Research provides extensive evidence that neuropathic pain leads to reorganization of the somatosensory cortex. Moreover, non-Hispanic Blacks (NHB) with chronic pain experience greater pain intensity and disability compared to their Non-Hispanic White (NHW) counterparts. Despite this, limited research has examined racial and ethnic differences in neuropathic pain and its association with brain structures previously shown to be relevant to various chronic pain conditions. The current project is a sub-study of an ongoing prospective study being conducted at the University of Florida and the University of Alabama at Birmingham. The study recruited community-dwelling adults with chronic knee pain, between the ages of 45 and 85 years. Sixty seven participants self-identified as NHB and 74 as NHW. High-resolution anatomical MRI (T1-weighted MP-RAGE, $1mm^3$ resolution) data were acquired at both sites on a 3 Tesla Philips Achieva. Images were processed using FreeSurfer 6.0 (Fischl, 2012). All subjects completed the PainDETECT questionnaire to assess neuropathic pain features. Grey matter volumes and thickness for pre-selected brain structures (i.e. ACC, S1, amygdala) were exported to SAS software, version 9.4 (SAS Institute Inc., Cary, NC) for analysis. Partial correlations and analysis of covariance were performed to assess the relationship between grey matter and neuropathic pain. For the ANCOVA portion of the analysis, groups of varying levels of neuropathic pain were set according to past publications. Analyses were stratified by ethnicity/race and all models were adjusted for: age, sex, body mass index, income, study site, pain catastrophizing, clinical pain intensity, and cognitive function. For NHBs, analysis revealed an association between having more neuropathic pain features and greater cortical thickness in S1 ($r=.35$, $p < .01$ and $F=3.8$, $p <0.5$). For NHWs, more neuropathic pain features were marginally associated with greater cortical thickness in the caudal ACC ($r= 0.2$, $p < 0.11$ and $F=2.86$, $p=0.06$). Taken together, our study suggests that there are ethnic/race differences in the associations between neuropathic pain symptoms and cortical thickness in pain-related brain sites.

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Poster

750. Somatosensation: Pain, Imaging, and Perception

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 750.28/H19

Topic: D.03. Somatosensation – Pain

Support: Ben and Catherine Ivy Foundation

Title: Effects of common anesthetic regimens on sigma-1 receptor PET imaging

Authors: S. T. REYES[1], A. ROMERO[1], B. VAN DER WILDT[1], J. CASTILLO[1], C. R. MCCURDY[3], S. BISWAL[1], C. PACHARINSAK[2], J. DEMARTINI[1], ***F. T. CHIN**[1]; [1]Radiology, [2]Comparative Med., Stanford Univ. Sch. of Med., Stanford, CA; [3]Medicinal Chem., Univ. of Florida, Gainesville, FL

Abstract: Background: Sigma-1 receptors (S1Rs) are a unique class of receptors that have been linked to a variety of neurological conditions such as obsessive-compulsive disorder, addiction, and pain. We previously reported a correlation of increased S1R expression at sites of neuropathic pain utilizing positron emission tomography (PET) imaging using ^{18}F-FTC-146, a S1R antagonist. The versatility of applications for ^{18}F-FTC-146 across species brought forth a range of anesthetic drugs that can be used for non-human species and questioned how these drugs may affect S1R binding. In this pilot study, we studied mice under different commonly used anesthetic cocktails (AC) to evaluate how ^{18}F-FTC-146 PET may be affected.
Methods: 6-Week-old wild type mice were anesthetized with the following ACs (N=4/group) and subsequent 60-min dynamic PET scan after tracer injection (106 ± 29 µCi): 1) Isoflurane (IF) induction at 5% and maintenance at 1.5% 2) intraperitoneal injection (IP) of Ketamine (90 mg/kg) and Dexmedetomidine (1.8 mg/kg) 3) IF induction 5%, maintenance 1% with IP of Midazolam (5 mg/kg), Xylazine (10 mg/kg) and Ketamine (100 mg/kg) 4) Induction with IF 5% maintenance 2% to place catheters, turn off IF and maintain with 5% Guaifenesin (loading dose 1 ml/kg then 2 mL/kg/h CRI) and Propofol (150 mg/kg/h CRI) with oxygen mask. Mice were perfused post-scan and harvested organs were counted for biodistribution analysis. Standard uptake values (SUV) for whole brain were calculated using Pmod3.7.
Results & Discussion: Image analysis of whole brain showed AC 1, 2, and 3 gave average SUV curve peaks from 3.16-3.55 in brain and mice given AC 1 and 2 exhibited no difference in washout rate. Since Ketamine is a known S1R antagonist, it was interesting to find that it had no effect on ^{18}F-FTC-146 uptake when compared to mice given IF only. AC 3 afforded more rapid washout in the brain prompting follow-up studies to examine whether the presence of xylazine or midazolam contributes to this phenomenon. Additionally, mice given AC 3 showed 5-fold higher bone uptake of injected dose indicating possible metabolic effect promoting radiodefluorination of ^{18}F-FTC-146. AC 4 showed an average peak on the SUV curve of 2.39 and demonstrated a

shallow slope to indicate slow washout. One-way ANOVA test showed that when comparing the 30-40 min timeframe for each AC to IF, AC 2 and 4 were not significantly different unlike AC 3. In order to assess IF as a control anesthesia for ^{18}F-FTC-146, follow-up studies with varying IF mass doses will be performed.
Conclusion: In this study, we found that AC 3 used in rodents and horses does significantly decrease ^{18}F-FTC-146 binding with the S1R and would affect the PET imaging data.

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Poster

750. Somatosensation: Pain, Imaging, and Perception

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Program #/Poster #: 750.29/H20

Topic: D.03. Somatosensation – Pain

Support: NIH Grant DA044121
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Title: Performance based traits and their reorganization in chronic pain

Authors: *D. RECKZIEGEL, R. JABAKHANJI, B. YIP, T. J. SCHNITZER, A. APKARIAN; Northwestern Univ. Feinberg Sch. of Med., Chicago, IL

Abstract: Heterogeneity of patients, even within a specific chronic pain condition, is a commonly accepted clinical concept. Identifying measurable phenotypic characteristics of patients that are most predictive of individual variability in treatment outcomes remains a challenge in the field of chronic pain, largely due to the lack of standardization, and long duration of assessments. The recently developed NIH Toolbox is a comprehensive set of neuro-behavior tools allowing quick assessment of multiple areas of neurological functioning. It was validated based on a nationally representative sample, enabling comparison of individual outcomes to age-, sex- and education-adjusted normative data. Here we used the toolbox to characterize neuro-behavior traits in healthy and chronic back pain individuals (CBP). We hypothesize that measures can be divided into meaningful principal domains (traits), some of which are reorganized with chronic pain, and others may be predictors of treatment outcomes. Data included in the analyses were from N=1047 individuals: N=994 were from a publicly available dataset of healthy subjects, N=53 were from individuals with CBP (ongoing clinical trial). Participants were tested in a range of abilities (NIH Toolbox): 6 cognitive (assessing episodic memory, attention, working memory, language, executive function, and processing speed), 17 emotional (regarding negative affect, well-being, and social relations.), 5 motor

(including dexterity, strength, balance, endurance, and locomotion), 1 odor, and 2 taste. We first analyzed the scores of N=994 individuals in all 31 items using factor analysis. Next, we analyzed demographic-adjusted standardized T-scores from each latent variable in CBP relative to normative data, and tested for associations between traits and pain.
We find that the battery measurements can be divided into five meaningful principle domains: positive emotion, cognition, negative emotion, motor and taste. CBP participants displayed means that were one or more standard deviation below that of the normative data in three of these domains: cognition, motor, and taste, but not emotion. Taste, and especially perceived bitter taste intensity, was associated with pain severity (Pearson's $r = 0.45$, $p < 0.01$).
We demonstrate five performance-based traits, with three being disrupted in chronic pain. Importantly, both negative and positive emotion traits remain unperturbed. These findings are surprising as we would expect both coping and suffering to impact emotional traits. Whether the identified traits are predictive of treatment outcomes remains to be tested.

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Poster

751. Vision: Populations and Networks

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Topic: D.07. Vision

Support: DFG: FOR-1847
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Title: Neural correlates of perceptual echoes in marmoset primary visual cortex

Authors: *J. SCHWENK[1,2], E. ZAVITZ[3], R. VANRULLEN[4], N. S. PRICE[3], F. BREMMER[1,2]; [1]Neurophysics Dept., Univ. of Marburg, Marburg, Germany; [2]Ctr. for Mind, Brain and Behavior, Universities of Marburg and Gießen, Germany; [3]Physiology, Monash Univ., Clayton, Australia; [4]CNRS, CerCo, Toulouse, France

Abstract: Recently it has been demonstrated that the steady-state response to random luminance input is dominated by a large oscillatory component at late temporal lags, the perceptual echo (VanRullen & MacDonald, 2012). This component has been studied in detail in humans using EEG recordings, and shown to predict perceptual performance over time. It has been proposed that the oscillations originate in V1, travelling in waves across the cortex as a mechanism to coordinate temporal and spatial processing (rhythmic sampling) (Lozano-Soldevilla & VanRullen, 2019). However, the direct neural correlates of the echo response have not been

identified so far.
Here, we aimed to investigate the perceptual echo response in areas V1 and V2 of the common marmoset (Callithrix jacchus). Extracellular recordings were performed so far in one adult monkey under anesthesia (sufentanil + nitrous oxide), while the animal was stimulated with random luminance sequences of 10 s duration. Signals were recorded from 96-channel arrays positioned on the border between V1 and V2, either in the left or the right hemisphere. Position and extent of the stimulation patch were chosen to match the summed receptive field covered by all units in the array.
The presented sequences were cross-correlated with the LFP to obtain the field impulse response function (IRF) at each electrode. The preliminary results reveal a brief oscillatory component in the IRF starting after the large initial response (~50 ms). This component was in the theta range (5 Hz), and exhibited phase propagation across the array, consistent with the behavior of a travelling wave. Correlation of the stimulus sequences and spike trains shows a similar oscillatory component in the response of a subset of neurons. The oscillations in LFP and single-unit IRFs were tightly linked at individual electrode locations.
With these findings we present first evidence at a cortical level of late oscillatory components in the visual impulse response function. The observed properties of the oscillations suggest that they represent a mechanism similar to the perceptual echoes previously described in the EEG. Thus, our results provide an important first step to understanding the neural basis of this phenomenon.

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Poster

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Title: Action potentials representing visual motion direction are phase-locked to the LFP in area MT in anaesthetised marmosets

Authors: *B. H. OAKLEY[1,3], E. ZAVITZ[1,3], M. A. HAGAN[1,3], Y. T. WONG[1,2], N. S. C. PRICE[1,3];
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Abstract: Visual perception relies on communication between distinct cortical areas, each of which serves a distinct role in visual processing. This communication depends primarily on action potentials or "spikes", but the role of the local field potential (LFP) in influencing or co-ordinating this spiking remains unclear. In awake primate area V1, action potentials are phase-locked to the LFP and orientation selectivity is modulated by the phase of the gamma-band oscillations. This is consistent with the theory that communicating areas may rely on transient increases in coherence between these oscillations, to ensure the propagation of signals from one area to another. In this paradigm, the sending area entrains the oscillatory activity in the receiver, such that information arrives during the receiving area's excitatory period. In awake macaques, attention has been shown to determine which of two visually stimulated V1 populations entrains a downstream area, though it is not known whether this entrainment occurs in the absence of attentional modulation. Here, we test this by recording simultaneously from neurons in two connected visual areas, V1 and MT, in four sufentanil-anaesthetised marmosets. We implanted a 96-channel Utah array in V1, followed by a 32-channel laminar array in MT, ensuring we were recording from overlapping receptive fields. As previously seen in V1, we found that MT spiking is phase-locked to the LFP, and the spikes occurring in the spike-preferred phase contain more information about the direction of motion of the presented stimulus. This phase-dependence persists even when controlling for spike-count differences between phases by using phase-bins with varying widths, to ensure any increases in tuning strength are not due to higher numbers of spikes. Surprisingly, this phase-locking is in the alpha/beta bands, rather than gamma as previously shown. However, we also observe increases in gamma-band power during stimulus presentation, as well as increases in local spike-field coherence in the gamma-band LFP. These results suggest phase-locked stimulus information is present even in the absence of attentional modulation, and therefore represents a fundamental characteristic of inter-area communication.

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Poster

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Title: Cortical electrocorticogram (ECoG) has high information content

Authors: *S. KANTH, S. RAY;
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Abstract: Neural activity in the brain can be recorded at several levels of resolution by using different electrodes. Microelectrode arrays record spiking activity of nearby neurons as well as provide a signal called local field potentials (LFP) that is thought to index population synaptic activity. Though arrays are quite invasive, these signals have good spatial resolution. On the other hand, electroencephalography (EEG) records activity at the scalp and is non-invasive, but has low spatial resolution and poor signal-to-noise ratio. Between these extremes lies the electrocorticogram (ECoG), which uses subdural disc electrodes placed on the cortical surface. ECoG is less invasive than intracranial electrodes but has better resolution than EEG and has been used to localize epileptic seizures. These electrophysiological signals have also been used in Brain Machine Interfaces (BMIs). Knowing which of them is the most informative can help make better choices for BMI implants. However, a fair comparison of these signals has been difficult due to variations in recording set ups, tasks, species etc. To address this issue, we designed a custom array that had both ECoG (3x3 array, 2.3 mm diameter separated by 1 cm, AdTech Inc) and microelectrodes (9x9 array, 400-micron separation, Blackrock Microsystems), allowing simultaneous recording of spikes, LFP and ECoG. We recorded signals from the primary visual cortex (V1) of 2 macaques. On some sessions, we also recorded simultaneous EEG. To ensure that the results were not biased towards any one type of signal based on receptive field size or other properties, we presented a large set of full screen natural images (5 categories, 16 images in each) and their grayscale and scrambled versions, while the monkey fixated at the center. This mimics a “natural” situation of decoding the external world using popular electrode arrays of different types. For performing the comparison, we used both information theoretic and decoding approaches. Surprisingly, we found that ECoG signals were the most informative, outperforming LFP and spikes in decoding image identity, and vastly superior to EEG. For all signals, gamma frequencies (30-80 Hz) had high information, and other frequencies supplied non-redundant information. Using more electrodes led to increased accuracy, as did using spikes and LFP together. Combining a few ECoGs had better accuracy than combining LFP and spikes from a much larger number of electrodes. High ECoG performance was due to the responses having more variability across images, as measured by signal coefficient of variance. These results have strong implications for BMIs, where ECoGs are finding increased application.

Disclosures: S. Kanth: None. **S. Ray:** None.

Poster

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Support: Wellcome Trust/DBT India Alliance 500145/Z/09/Z

Title: Evidence for interaction between steady-state visually evoked potential tags at nearby flicker frequencies

Authors: *S. SALELKAR, S. RAY;
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Abstract: The steady-state visually evoked potential (SSVEP) is an oscillatory response to periodic visual stimulation, detectable in the electroencephalogram (EEG) recorded over the posterior scalp. Due to its high signal-to-noise ratio, relative immunity to artifacts and modulation by cognitive processes, the SSVEP has been the workhorse in frequency tagging studies, which involve the simultaneous presentation of two temporally modulated stimuli. In visual attention studies using frequency tagging, it has been seen that paying attention to one stimulus increases the SSVEP amplitude at the tagging frequency of that stimulus and simultaneously decreases the SSVEP amplitude at the unattended frequency. This has been explained using a “push-pull” or “spotlight” mechanism of attention. However, could the change in SSVEP amplitude be merely due to the presence of competing temporal frequencies, without any top-down cognitive modulation? If so, does it depend on the separation between the tagging frequencies or stimulus properties (such as orientations)? To address this question, we recorded spiking activity and local field potential (LFP) from the primary visual cortex (V1) as well as EEG from two awake macaque monkeys while they passively fixated sinusoidal counterphase gratings or plaids. Consistent with previous results, stimulus frequencies in and around the alpha range (8-16 Hz) produced the largest SSVEP responses. We, therefore, analyzed the modulation of SSVEP responses at 8 Hz and 16 Hz (“target” frequencies) as a function of stimulus frequencies in the lower delta (2 Hz) to high beta (30 Hz) range (“mask” frequencies) around the target frequency. We found that the target SSVEP response was reliably suppressed by the mask counterphasing at a different temporal frequency. We also found that target SSVEP suppression was generally asymmetric along the temporal frequency axis, with greater suppression at lower temporal frequencies of the mask than at higher temporal frequencies. Further, the strength of this asymmetry depended on the relative orientation difference between the target and the mask, with similar orientations causing significant suppression and orthogonal orientations causing little or no suppression. To explain the results, we adapted the well-known normalization model to SSVEP responses and characterized the suppression as a function of the difference in temporal

frequencies and orientations of the target and mask components. Our results provide evidence for interaction between temporal frequencies independent of effects of cognitive modulation, and suggest exercising caution in the interpretation of frequency tagging studies.

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Poster

751. Vision: Populations and Networks

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Title: Stimulus information, and correlated trial-to-trial variability, are distributed widely throughout interlaminar subpopulations in v1

Authors: *D. J. DENMAN[1,2], C. REID[1];
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Abstract: All sensory stimuli are represented by large populations of single neurons. Recently developed electrophysiology technologies have enabled simultaneous observation of spike times from large numbers of neurons. In spite of the shift to population recording, the extent to which spike count and/or spike timing (and their variability) contribute to population coding has mostly remained in the domain of model-based approaches. Here we assess, empirically, response variability and the stimulus information across several timescales in populations of up to 200 simultaneously recorded neurons. We first describe the statistics of responses to repeated stimuli at several temporal scales (20 - 3 Hz), recorded in awake mice across dorsal lateral geniculate (dLGN) and primary visual cortex (V1) using high-density electrophysiology (Neuropixels). We use a linear support vector decoder as probe for stimulus information in populations selected from these recordings. By varying the temporal resolution used for decoding we found that, despite considerable trial-to-trial variability, populations contain additional stimulus information in relative spike times (< 40 msec). Notably, optimal decoding populations were always distributed widely across V1 layers, whether using spike counts, times, or both. To assess how trial-to-trial variability impacts the population representation, we compared optimal decoding populations to the shared variability across layers in V1 and dLGN, including both shared variability in spike count and spike timing (jitter). We found strong layer- and structure-dependent correlations in rate variability and jitter within subpopulations. Layer- and structure-specific trial shuffling allow us to reveal the impact - on population representation accuracy and

its structure - of shared variability across sets of laminae. In summary, we find stimulus identity is best represented by the concurrent activity of overlapping subpopulations across all layers of V1, suggesting that the brain utilizes spike times distributed across at least all V1 layers, and likely across visual areas, to represent visual stimuli.

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Poster

751. Vision: Populations and Networks

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Topic: D.07. Vision

Title: On the relationship between gamma amplitude and frequency in awake macaque V1

Authors: *G. SPYROPOULOS[1], J. R. DOWDALL[1], M. L. SCHOLVINCK[1], C. A. BOSMAN[3], B. R. LIMA[4], A. PETER[1], I. ONORATO[1], J. KLON-LIPOK[1], R. ROESE[1], S. NEUENSCHWANDER[5], W. SINGER[2], M. VINCK[1], P. FRIES[1];
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Abstract: In cortex, excitation and inhibition are tightly balanced. This E-I balance is directly involved in the generation of the gamma rhythm. Some models implementing E-I balance predict that the amplitude of a gamma cycle is positively correlated with its duration. A previous study concluded that this prediction holds for gamma rhythms in rodent hippocampus. We investigated, whether it also holds for another important system showing strong gamma oscillations, namely the primary visual cortex of the awake primate. The previous study derived gamma amplitude and frequency from the peaks and troughs of the gamma (20-100 Hz) filtered local field potential (LFP). We found that this approach leads to positive amplitude-duration correlations for synthetic noise, i.e. in the absence of a rhythm. Therefore, we used the Hilbert transform of the unfiltered LFP to define periods with strong and pure gamma (i.e. linearly unfolding gamma phase) and then derived local peaks and troughs and thereby gamma-cycle amplitudes and durations. Gamma amplitudes and durations calculated in this way showed a positive correlation. This held, when we removed effects of extrinsic factors, like perturbations after stimulus onset or after microsaccades. Note that the conventional power spectrum in the gamma band also relates gamma amplitude to its frequency, which is the inverse of its duration. We found that the power spectrum is not a good representation of the distribution of cycle-wise ("instantaneous") amplitudes. The distribution of durations aligned with the power-spectral peak, whereas the distribution of amplitudes was shifted to lower frequencies. Furthermore, durations correlated negatively with firing rates and positively with spike-LFP phase locking, with longer

cycles entailing stronger firing rate modulations. Thus, in awake macaque V1, long gamma cycles have higher amplitudes and lower rates, suggesting that slower gamma is due to a stronger inhibition that prolongs the cycle and leads to weaker overall firing. The power spectrum in the gamma range does not primarily reflect the amplitudes of the underlying cycles, but rather the likelihood of the corresponding cycle durations.

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Poster

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Title: Detecting information-limiting noise correlations in early visual cortex

Authors: J. S. MONTIJN[1], R. G. LIU[1], A. ASCHNER[3], A. KOHN[4], *P. E. LATHAM[5], .. IBL COLLABORATION[6], A. POUGET[2];
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Abstract: If the brain processes incoming data efficiently, information in the relevant neural circuits should match behavioral performance. For instance, if there is enough information in a visual cortical area to determine the orientation of a grating to within 1°, and the code is simple enough to be read out by downstream circuits, then animals should be able to achieve that performance behaviorally. Despite over 30 years of research, it is still not known how efficient the brain is. For tasks involving a large number of neurons, the amount of encoded information is limited by differential correlations, so determining the amount of encoded information requires quantifying the strength of differential correlations. Detecting them, however, is difficult; current methods require recording spikes from thousands of neurons simultaneously, which is not yet

feasible. We report here a new method, which requires on the order of 100s of neurons and trials, a regime which can be attained by current experimental methods. This method relies on computing the alignment of the neural stimulus encoding direction, $\mathbf{f}'$, with the principal components (PCs) of the noise covariance matrix, $\mathbf{\Sigma}$. It can be shown that the presence of differential correlations implies that fluctuations along $\mathbf{f}'$ are proportional to the square root of the number of neurons, N. For large N, this implies that $\mathbf{f}'$ is one of the noisiest directions of $\mathbf{\Sigma}$, and is therefore be spanned by a small number of its largest PCs. Our method compares the alignment between $\mathbf{f}'$ and the PCs of $\mathbf{\Sigma}$ against that expected if correlations were removed by shuffling the data. Using simulations with a leaky-integrate-and-fire neuron model of the LGN-V1 circuit, we confirmed that this method can indeed detect even small levels of differential correlations, consistent with those that would limit orientation discrimination thresholds to ~0.1°. We applied this technique to V1 recordings in awake monkeys. This revealed differential correlations consistent with a discrimination threshold of 0.5°-3°, which is not far from typical discrimination thresholds. These results suggest that V1 contains about as much information as is seen in behaviour, which would imply that downstream circuits are efficient at extracting the information available in V1.

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Poster

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Vision for Tomorrow

Title: Aberrant interactions of opposite hemifield inputs to visual cortex in albinism

Authors: *E. J. DUWELL[1], E. N. WOERTZ[2], J. MATHIS[3], J. CARROLL[4], E. A. DEYOE[5]; [1]Biophysics, [2]Cell Biology, Neurobiology, and Anat., [3]Neurol., [4]Ophthalmology & Visual Sci., [5]Radiology, Med. Col. of Wisconsin, Milwaukee, WI

Abstract: Albinism is an inherited disorder characterized by disrupted melanin synthesis in the eye, and often in the skin and hair. This retinal hypopigmentation is accompanied by pathological decussation of temporal retinal afferents at the optic chiasm during development, ultimately resulting in overlapping representations of opposite hemifields in visual cortex of each hemisphere. We reported at SFN 2018 that this aberrant overlap results in fMRI imaging voxels with bilateral dual pRFs. How such conflicting inputs might interact to determine a dual-pRF

voxel's BOLD response is unknown. To test this, we used a paradigm in which the right and left hemifields were stimulated simultaneously with separate sinusoidal gratings, each having a variety of contrasts (0, 8, 20, 45, 100%). We then measured the BOLD response of individual 2.5mm cubic voxels to each contrast combination. Each fMRI run consisted of 5 blocks. Within each block, a given hemifield was stimulated sequentially with each contrast while the grating presented to the opposite hemifield was fixed at one of the 5 contrasts. The latter contrast was then incremented sequentially across blocks. We examined the responses of approximately 2300 voxels in one subject with albinism. Most visually responsive voxels, both single and dual-pRF, exhibited BOLD responses that increased within a block as a function of contrast presented to the primary pRF component. However, for approximately 20% of dual-pRF voxels, the gain of this function increased dramatically across blocks in response to the contrast presented to the opposite hemifield pRF component. This phenomenon was often observed in clusters dual pRF voxels, but was not observed in single-pRF voxels. These results demonstrate for the first time that aberrant retino-cortical projections in albinism may produce cortical voxels with dual inputs from opposite hemifields that interact in a multiplicative or otherwise nonlinear fashion. The consequences of such unique cortical physiology remain unclear but may provide a substrate for as-yet undocumented perceptual aberrations.

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Poster

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Title: Change in avalanches and visual tuning during optogenetic drive of interneurons in mouse visual cortex

Authors: *T. L. RIBEIRO, M. VICTOR, A. VAKILI, D. PLENZ;
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Abstract: Neuronal avalanches are spatiotemporal clusters of activity that reflect balanced neuronal propagation in the brain. Avalanches are power-law distributed and therefore scale-free, which is in line with expectations from so-called critical dynamics. Criticality has been suggested to optimize information processing. Yet, the link between avalanches, the balance in excitatory-inhibitory (E-I) and information processing is poorly understood. Here we study this

relationship in the visual cortex of awake mice subject to visual stimuli.We employed two-photon imaging of head-fixed mice positioned on a running wheel to infer spiking activity in neurons. Retinotopic mapping was performed to discriminate areas of the visual cortex. Viral-injection into cortical layer 2/3 resulted in robust expression of the genetically encoded calcium indicator (GECI) GCaMP7s. In order to measure effects of changes in the E-I balance, we also injected transgenic mice (PV-Cre, SST-Cre and VIP-Cre) with Cre-dependent opsins C1V1 or Chrimson allowing us to optically drive those interneurons. A chronic cranial window was centered over the primary visual cortex (V1) and mice were subjected to passive viewing of drifting bars at different angles (2 s each, randomly chosen) at maximum contrast interspaced by 2 s of gray screen. During the experiment, for randomly selected trials, optogenetic drive of the opsin-expressing cells was achieved by either wide-field stimulation with a LED or individual-cell stimulation through a spatial-light modulator (SLM). At any point, mice could self-initiate locomotion. Pupil diameter was assessed continuously to measure the animal's state of arousal. More than ~150 neurons were recorded consistently in a ~500 x 500 μm area at a frame rate of ~30 Hz.Spiking increased during locomotion and sub populations of neurons were identified to have preferred orientations. We analyzed neuronal avalanche statistics in those populations with and without visual stimulus present as well as with and without optogenetic drive, separating periods of locomotion from quiet resting. Power law statistics was found to be robustly maintained during visual stimulation independent of orientation. However, avalanche dynamics as well as tuning properties changed during stimulation of interneurons. We conclude that visual cortex maintains critical state dynamics and a particular E-I balance during visual processing.

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Poster

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Title: The structure of population activity in area MT of awake marmosets studied using two-photon microscopy

Authors: *J. J. PATTADKAL[1], B. ZEMELMAN[1], N. J. PRIEBE[2];
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Abstract: Area MT neurons in primates are motion-sensitive signaling the direction and speed of objects and integrating multiple motion components to yield complex representations of object movement. Because MT neurons are selective for specific motion components, population level

measurements are required to access object motion representation. To study these population level representations we used marmosets *C. jacchus*, whose lissencephalic brains allow us to monitor the activity of a large population of neurons at single cell resolution using the calcium indicator GCaMP. We expressed GCaMP6f using an AAV fitted with the inhibitory neuron-specific h56D promoter (Mehta et al, 2019). Marmoset MT inhibitory neurons are directionally selective and were organized in space according to their direction preference. We recorded from a large number of neurons responding to random dots motion stimuli and then used unsupervised dimensionality reduction techniques to examine the low dimensional trajectories of the population activity. Population trajectories in this low dimensional space formed segregated paths where population responses to proximate directions are mapped to nearby locations. The trajectories were markedly different from those during spontaneous activity. These data are consistent with a model for motion processing in which population responses are dominated by a single attractor, instead of multiple attractors. Our observations were corroborated by changes in the average correlation of neurons between stimulus-driven and spontaneous network activity. On average, pairwise residual correlation between cells during stimulus periods were lower than correlations between cells during spontaneous activity (medians: 0.05±0.001 versus 0.08±0.001 s.e.m., respectively). We also found that the correlations had only a small dependence on the difference in preferred directions between cells. The correlations, however, did rely on the distance between the two cells, decreasing as the distance between cells increased. The falloff with distance was faster for stimulus period correlations than for the spontaneous correlations (exponential space constants: 117 versus 248 microns, respectively). These population measurements provide direct insight into the dynamics of sensory networks in awake primates.

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Poster

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Title: The information asymptote in large cortical neural populations

Authors: *M. KAFASHAN[1], R. NOGUEIRA[2], S. CHETTIH[1], A. JAFFE[1], C. HARVEY[1], R. MORENO-BOTE[3], J. DRUGOWITSCH[1];
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Abstract: How much information does neural population activity encode about the world? Such information has been estimated in small neural populations, but little is known about how it scales when moving to populations of sizes relevant to mammals. To characterize this scaling, we simultaneously recorded the activity of hundreds of neurons from area V1 of mice stimulated with drifting gratings. We found that information about drift direction initially increased with larger population sizes, but later leveled off, suggesting a finite asymptotic limit of information available to the animal. As comparisons to trial-shuffled recordings revealed, this limitation was induced by noise correlations. Information scaling was quantitatively well-matched by an information scaling model endowed with information-limiting, differential correlations. We used this match to obtain a Bayesian estimate of the information asymptote. This estimate was consistent across different drift direction discriminations, and with known mouse direction discrimination performance. Furthermore, we found asymptotic information to increase for higher grating contrast, and higher mouse running speeds, consistent with previously reported analyses using smaller populations. Our information scaling model allowed us to estimate the population size required to reach some fraction of the asymptotic information, which suggested a widely distributed population code whose "distributedness" is only weakly modulated by the amount of encoded information, as controlled by contrast and running speed. Furthermore, we did not find any evidence for the existence of a most informative sparse subpopulation that could substitute for the whole population. Our work thus provides, to our knowledge, the first characterization of the structure and scaling of information in mammalian neural population codes that extrapolates beyond population sizes recorded in the experimental setup.

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Poster

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Location: Hall A

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Program #/Poster #: 751.12/H32

Topic: D.07. Vision

Title: Characterization of network activity changes during repeated natural movie stimuli in mice

Authors: *R. IYER, J. SHANG, B. HU, I. MAGRANS DE ABRIL, S. MIHALAS;
Allen Inst. For Brain Sci., Seattle, WA

Abstract: The mammalian central nervous system has a vast complexity with hundreds of cell types (Tasic et al. 2018) and intricate patterns of mesoscopic (Harris et al. 2018) and microscopic (Seeman et al. 2018) organization. At the same time the details of this organization are plastic. The gold standard for measurements of plastic changes involves patch-clamp methods (Bi and Poo, 1998). However such experiments are difficult to do at scale. Changes in activity distributions of IT neurons between novel and familiar stimuli have been previously observed and used to infer plasticity rules using rate based models (Lim et al. 2015).
Recent advancements in extracellular recordings allow simultaneous recording of up to tens of thousands of neurons in the central nervous system using the Neuropixels system (Jun et al. 2017). In this study we extend the characterization of plastic changes in the network to higher order terms by making use of simultaneous recordings of large numbers of neurons across multiple visual areas in response to a short natural movie which was presented a hundred times. Consistent with previous studies, we observe changes in selectivity of individual neurons to a particular frame of the movie. We observe subsets of neuron pairs which show significant and consistent changes in their covariance through the repetition of the the movie, and the change is positively correlated to the signal correlation of the neuron pairs. As an additional control, we plan to explore if the observed changes can be attributable to changes in network states arising due to behavioral covariates such as locomotion, pupil size etc.
The recorded network is expected to be at a dynamic equilibrium, in which inputs from the environment sculpt the network, and the connectivity is expected to be defined by covariance of features in natural scenes (Iyer and Mihalas, 2017). However, the repeated presentation of a movie which is short enough to not cover well the set of covariances observed in natural scene statistics, can potentially push the network towards a new equilibrium that could account for the observed changes.
Simulations using simple networks of leaky integrate and fire (LIF) neurons with spike time dependent plasticity (STDP) together with a fast homeostatic mechanism show qualitatively similar changes in single neuron selectivity. We plan to use different machine learning approaches to analyse the neural responses, to infer the evolution of STDP rules from neural activity and other biophysical parameters.

Disclosures: R. Iyer: None. **J. Shang:** None. **B. Hu:** None. **I. Magrans De Abril:** None. **S. Mihalas:** None.

Poster

751. Vision: Populations and Networks

Location: Hall A

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Program #/Poster #: 751.13/H33

Topic: D.07. Vision

Support: NIH Grant R35NS097287

Title: Synaptic mechanisms of state-dependent neural activity in mouse primary visual vortex

Authors: *D. B. NESTVOGEL, D. A. MCCORMICK;
Inst. of Neurosci., Univ. of Oregon, Eugene, OR

Abstract: Sensory processing in the neocortex is strongly modulated by spontaneous synaptic membrane fluctuations. The dynamics of these fluctuations are directly linked to the behavioural state of the animal. At low levels of arousal, the pupil of the animal is constricted and large, low frequency fluctuations dominate the membrane potential of cortical neurons. When the animal is aroused, the pupil is dilated, the animal oftentimes engages in running and the membrane potential exhibits high-frequency fluctuations. Results from recent studies employing imaging and extracellular recording techniques indicate that facial movements such as whisking predict state-dependent action potential firing more accurately in visual cortex than other measures previously used for this sake such as pupil diameter and locomotion. In the present study, we made use of in-vivo whole cell recordings in the visual cortex of awake mice to address this issue on the synaptic level. By monitoring spontaneous animal behaviour with a high speed camera, we find that whisker pad movements explain the variability and timing of spontaneous synaptic fluctuations more accurately than other behavioural measures such as pupil diameter and locomotion. Specifically, our results show that the coupling of whisker pad movements to membrane depolarization in excitatory V1 cells occurs on a rapid time scale of tens of miliseconds, which indicates that a fast transmitter system may mechanistically account for these state-dependent changes. In an additional set of experiments, we study the occurrence of the previously described 3-6 Hz oscillation in visual cortex in relation to facial movements. Previous studies have shown that this oscillation is the dominant LFP pattern at rest, but that it may also occur at periods when the animal is aroused. To further dissect the circuit mechanism on how this oscillation is generated, we simultaneously record in the thalamus and visual cortex. Preliminary results indicate that the 3-6 Hz oscillation is indeed state-dependent and that it relies on thalamocortical connections in order to occur. In summary, our results provide new insights into the exact timing and relationship between facial movements of mice and spontaneous patterns of synaptic activity in the visual cortex.

Disclosures: D.B. Nestvogel: None. **D.A. McCormick:** None.

Poster

751. Vision: Populations and Networks

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Topic: D.07. Vision

Support: RIKEN CBS institutional funding
RIKEN BSI institutional funding
JSPS grant in aid 26290011
JSPS grant in aid 17H06037
Fujitsu collaborative grant

Title: Network interactions in the mouse visual cortex are predictive of perceptual decisions

Authors: *J. G. ORLANDI[1], S. GRZELKOWSKI[2,1], M. ABDOLRAHMANI[1], R. AOKI[1], D. LYAMZIN[1], A. BENUCCI[1];
[1]Lab. for Neural Circuits and Behavior, RIKEN Ctr. for Brain Sci., Wakoshi, Japan; [2]FNWI, Univ. van Amsterdam, Amsterdam, Netherlands

Abstract: Decision making involves the processing of neural signals through feedforward and recurrent networks in cortical and subcortical brain regions. These networks are concurrently being driven by a multiplicity of other cognitive signals related to the animal interactions with the environment. Hence, isolating features of the neural dynamics that are causally related to the decision making process has proved to be challenging.
Here we focused on perceptual decisions in mice trained in a two-alternative forced choice orientation discrimination task. We analyzed GCaMP signals recorded during the behavioral task from mice (n=8, Thy1-GCaMP6f) implanted with a cranial window over occipital-parietal areas, providing access to the widefield activations of 10-12 cortical areas. We reasoned that a necessary property - although not sufficient - for neural activations to be causal in the decision-making process is to carry predictive information on the animal choices or task outcome. Standard dimensionality reduction analysis of the simultaneously recorded areas could only differentiate trial-averaged activations for left-right choices, with large variability across animals. Importantly, choices or outcomes (correct, incorrect, time-out response) could not be decoded from individual trials. We next trained a family of non-linear supervised classifiers using the pairwise interactions between responses, thus relying on a measure of inter-area functional connectivity. The classifiers successfully decoded choices and outcomes from individual trials, more robustly for choices than for outcomes.
To isolate the contribution of motion-execution signals (needed to select the target stimulus, see Abdolrahmani et al, bioRxiv 2019), we further trained the classifiers on the recorded body movements, including saccadic ones. As expected, the classifiers could decode choices from body movements when considering time windows proximal to the choice execution, but performed at chance level at preceding times. On the contrary, neural activity and connectivity features carried predictive power significantly before motor execution, possibly reflecting pre-motor or choice-related signals. The analysis of the internal structure of the classifiers will allow us to identify the dynamical signatures of the cortical interactions carrying most weight for the classification performance. In conclusion, the observed predictive components in the large-scale activations of occipital-parietal visual areas suggest a causal involvement of the inter-area interactions for the decision-making process.

Disclosures: **J.G. Orlandi:** None. **S. Grzelkowski:** None. **M. Abdolrahmani:** None. **R. Aoki:** None. **D. Lyamzin:** None. **A. Benucci:** None.

Poster

752. Active Vision and Context Modulation

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Support: R01 EY021827
P30 EY019005
NARSAD Young Investigator Award
E. Matilda Ziegler Foundation
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P30 EY026878

Title: Cortical mechanisms underlying saccadic suppression

Authors: *S. DENAGAMAGE[1], M. P. MORTON[1], J. H. REYNOLDS[3], M. P. JADI[2], A. S. NANDY[1];
[1]Neurosci., [2]Psychiatry, Yale Univ., New Haven, CT; [3]SNL-R, Salk Inst., La Jolla, CA

Abstract: Primates use ballistic eye movements called saccades to shift their field of view and bring objects of interest to the center of the retina for detailed examination. To maintain perceptual stability during rapid retinal motion, the visual system actively anticipates upcoming saccades and suppresses visual processing accordingly. This phenomenon, termed saccadic suppression, results in well characterized decreases in visual sensitivity during peri-saccadic stimulus detection tasks. Correspondingly, the firing rates of cells in the visual cortex drops during saccades. The mechanisms underlying the changes in neural activity that accompany saccadic eye movements remain poorly understood. We hypothesize that the laminar architecture of the sensory neocortex, which is strongly conserved across visual cortical areas, plays a key role in mediating saccadic suppression. To investigate this possibility, we recorded spontaneous extracellular activity across cortical layers using linear array probes in area V4. Our findings indicate that spiking units in different cortical layers vary in the timing and degree of peri-saccadic firing rate modulation. Notably, a significant proportion of narrow-spiking (putative inhibitory) input layer units increase their firing rates in response to a saccade, and may play a significant role in suppressing the firing of other units. We also find that saccade onset increases low-frequency local field potential (LFP) power and may generate a low-frequency LFP phase reset, inducing increased phase-locking of spikes during and immediately after a saccade. Overall, our results suggest that inter- and intra- laminar interactions between distinct neural populations regulate the effects of saccadic suppression in the visual cortex.

Disclosures: **S. Denagamage:** None. **M.P. Morton:** None. **J.H. Reynolds:** None. **M.P. Jadi:** None. **A.S. Nandy:** None.

Poster

752. Active Vision and Context Modulation

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NIH Grant P30 EY026878 (Yale Vision Core)
Gruber Foundation (MPM)

Title: Physiological correlates of perceptual threshold

Authors: ***M. P. MORTON**[1], S. DENAGAMAGE[1], J. H. REYNOLDS[3], M. P. JADI[2], A. S. NANDY[1];
[1]Dept. of Neurosci., [2]Dept. of Psychiatry, Yale Univ., New Haven, CT; [3]SNL-R, Salk Inst., La Jolla, CA

Abstract: Little is known about the physiological underpinnings that cause correct ('hit') or incorrect ('miss') responses at perceptual threshold. We hypothesized that physiological states in the sensory neocortex help determine whether a trial at threshold will be a hit or a miss. To study threshold behavioral performance, we analyzed cortical layer-specific electrophysiological recordings in visual area V4 collected while monkeys performed a cued attention task that required them to detect an orientation change. Here, we specifically analyze the subset of trials that occurred near perceptual threshold ('target'). We defined perceptual threshold to be the orientation change at which the psychometric function reached 50% accuracy. Our findings suggest that short-term increases in alertness influence threshold performance. We find that hit trials are characterized by a larger pupil diameter and lower microsaccade rate, indicative of increased arousal and greater perceptual stability. We find that target stimuli evoke higher firing rates in V4 neurons in hit trials compared to miss trials, across all cortical layers. Broad spiking neurons (putative pyramidal cells) in the superficial cortical layers exhibit lower variability in hit trials. Hit trials are also marked by a decrease in co-variability among pairs of neurons in the input layer of the cortex. Thus, we find evidence that hit trials are characterized by periods of increased signal to noise ratios in area V4. These results indicate that short term increases in

arousal, perceptual stability, and privileged processing of sensory stimuli contribute to hits near perceptual threshold.

Disclosures: M.P. Morton: None. **S. Denagamage:** None. **J.H. Reynolds:** None. **M.P. Jadi:** None. **A.S. Nandy:** None.

Poster

752. Active Vision and Context Modulation

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 752.03/H37

Topic: D.07. Vision

Title: Dynamic states of population activity in prefrontal cortical networks of freely-moving macaque

Authors: *R. MILTON[1], N. SHAHIDI[2], V. DRAGOI[3];
[1]UTHealth, Houston, TX; [2]Univ. of Texas, Med. Sch. At Houston, Houston, TX; [3]Dept Neurobiol/Anat, Univ. of Texas at Houston Dept. of Neurobio. and Anat., Houston, TX

Abstract: Neural responses in the mammalian cerebral cortex are believed to change dramatically during the course of the day between the 'synchronized' state during sleep and 'desynchronized' state during wakefulness. Although the prevalence of this view seems to suggest that this phenomenon is well established, the previous investigations of the dynamics of cortical population activity at single cell resolution were performed in sensory cortical areas of head-fixed or tethered rodent models. Technical limitations have prevented the analysis of dynamic cortical states beyond sensory areas in larger animals freely moving for several hours. To overcome these limitations, we developed a system integrating wireless transmission of electrical activity, wireless eye-tracking, and real-time video analysis to examine the dynamics of population activity in a high-level, executive area - dorsolateral prefrontal cortex (dlPFC) of unrestrained monkey. This technology allowed us to identify distinct cortical substates during quiet and active wakefulness, and transitions in population activity during drowsiness and rest. We further found that, unexpectedly, putative inhibitory neurons exhibit stronger synchronized fluctuations in population activity than putative excitatory neurons regardless of brain state. Our results show that cortical state in freely moving monkey is controlled by behavioral demands and arousal by asymmetrically modulating the slow response fluctuations of local excitatory and inhibitory cell populations.

Disclosures: R. Milton: None. **N. Shahidi:** None. **V. Dragoi:** None.

Poster

752. Active Vision and Context Modulation

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 752.04/H38

Topic: D.07. Vision

Title: Measuring the effects of locomotion on visual activity in the mouse cortex in the Allen Brain Observatory

Authors: G. K. OCKER[1], D. MILLMAN[2], P. LEDOCHOWITSCH[3], M. D. OLIVER[3], R. ABBASI-ASL[4], M. A. BUICE[1], ***S. E. DE VRIES**[1];
[2]Neural Coding Group, [1]Allen Inst. For Brain Sci., Seattle, WA; [3]Allen Inst. for Brain Sci., Seattle, WA; [4]Allen Inst., Seattle, WA

Abstract: Animal behavior is known to affect neural activity, broadly, as well as evoked sensory responses in the mouse cortex. Here, we use the Allen Brain Observatory to examine the effect of locomotion on the activity and the visually evoked responses of neurons in the mouse visual cortex. This is a systematic survey of physiological activity in the mouse cortex recorded using 2-photon calcium imaging. Neural activity was recorded in cortical neurons of awake mice who were presented a variety of visual stimuli, including gratings, noise, natural scenes, and natural movies. This dataset consists of over 60,000 neurons recorded in over 1300 imaging sessions, surveying 6 cortical areas, 4 cortical layers, and 14 transgenically defined cell types (Cre lines). In these experiments, mice were free to run on a rotating disk and we observe a range of running behavior and find differences across transgenic lines. We measure the correlation of neural activity with running, finding the stronger correlations in inhibitory neurons (VIP and SST) than pyramidal neurons, and also find stronger correlations in V1 than in the higher visual areas. We measure the effect of running on visual responses and find that, consistent with previous literature, neurons (on average) show increased responses, but with diversity in this effect across areas, layers, Cre lines, and visual stimuli. Finally, we use these data to explore how running effects the ability to decode visual stimuli from the population activity and find that, contrary to other reports, running can decrease the ability to decode grating conditions from populations of pyramidal neurons.

Disclosures: G.K. Ocker: None. **S.E. de Vries:** None. **M.A. Buice:** None. **D. Millman:** None. **M.D. Oliver:** None. **P. Ledochowitsch:** None. **R. Abbasi-Asl:** None.

Poster

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Title: The sensory representation of causally controlled objects

Authors: *K. CLANCY[1], T. D. MRSIC-FLOGEL[2];
[1]Sainsbury Wellcome Ctr. for Neural Circuits and Behavior, UCL, London, United Kingdom;
[2]Univ. Col. London, London, United Kingdom

Abstract: Our ability to exert intentional control over external objects is informed by our sensory experience of them, in a continuous dialog between action and sensory feedback. How such control is represented at the sensory level, or its efficacy judged, however, is not understood. In motor learning, the relationship between an action and its outcome can be learned and re-learned throughout adulthood as animals acquire new motor skills. Brain machine interfaces (BMI) are a novel method for investigating how subjects learn such arbitrary action-outcome relationships. Here we devised a brain machine interface (BMI) task that enabled mice to control a visual feedback cursor using neural activity alone. Transgenic mice expressing the calcium activity indicator gCaMP6s in pyramidal cortical cells were trained to control a visual feedback cursor using areal calcium signals. The activity of two small regions, usually over primary or secondary motor cortex, were arbitrarily assigned control of a visual feedback cursor. Fluorescence from these regions was read-out in real time and transmuted into the position of an onscreen cursor. Animals were trained to guide the cursor to a target location to obtain a reward. We found evidence that parietal and higher visual cortices were engaged when expert animals controlled the BMI for reward, but not in naïve mice still learning the task. Single-cell recordings from parietal cortex showed that the same sensory stimuli elicited larger responses when an animal was controlling the cursor than when passively viewing it. This increase was sensitive to cursor trajectory — responses were greater when the cursor was moving towards the target than away from it. Thus, the sensory representation of a causally controlled object is sensitive to the subject's intention, as well as the object's instantaneous trajectory towards or away from its goal. The heightened sensory representation at the target position might serve as a fixed goalpost for

downstream evaluation, given the animal must relearn a changing sensorimotor contingency on the fly, potentially strengthening the signal to adjudicating areas for informing fluent control.

Disclosures: K. Clancy: None. **T.D. Mrsic-Flogel:** None.

Poster

752. Active Vision and Context Modulation

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 752.06/H40

Topic: D.07. Vision

Title: Reading between the lines: The impacts of reading in virtual reality and other mediums on the visual system

Authors: *T. A. DOTY[1], C. Y. DELGADO[3], A. TORRES LOPEZ[1], S. A. LUNDQVIST[2], M. F. AWAD[4], L. E. KNOX[5], L. LOPEZ CANELA[5], S. A. DREW[6];
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Abstract: In recent years, technological advances, including computer screens and tablets, have allowed for more convenient reading. As virtual and augmented reality have become commercially available, new experiences are easier to access while new therapies and training opportunities provide lower traditional occupational risks than their real-world counterparts. However, as technology continues to advance, the need for understanding its health impacts becomes more and more imperative. This experiment aims to understand how the visual system is impacted by reading using different mediums, including virtual reality, augmented reality, computer screens, tablets, and paper. This report will analyze different visual system functions, including vergence facility and accommodative facility, before and after reading for 30 minutes in the previously stated mediums. Participants will also be measured for asthenopia, or visual discomfort, and across mediums. It is hypothesized that virtual reality will elicit the largest negative changes in the visual system as well as the largest increase in visual discomfort symptoms whereas physical paper will elicit the smallest negative changes in both. This study will allow users of such mediums to understand how advances in technology impact their visual system. Preliminary data displays trends of different reading rates where those that read on physical paper read the most pages compared to every other medium. Trends also suggest that those that read in virtual reality have improved accommodation scores compared to all other mediums. Data also suggests that there is an interaction between measure type and if the reader is using virtual reality or not. The data trends to show that those that read in virtual reality also report higher dizziness scores compared to augmented reality. These findings, and others, will be discussed in full.

Disclosures: **T.A. Doty:** None. **C.Y. Delgado:** None. **A. Torres Lopez:** None. **S.A. Lundqvist:** None. **M.F. Awad:** None. **L.E. Knox:** None. **S.A. Drew:** None.

Poster

752. Active Vision and Context Modulation

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Title: Cognitive modulation of interacting corollary discharges in the visual cortex

Authors: M. ABDOLRAHMANI, ***D. R. LYAMZIN**, R. AOKI, A. BENUCCI;
RIKEN Ctr. For Brain Sci., Wako-shi, Japan

Abstract: Perception is an active process involving continuous interactions with the environment. During such interactions neural signals called corollary discharges (CDs) propagate across multiple brain regions informing the animal whether the incoming sensory information originates from animal's own actions or from the environment. Under ethologically natural conditions, such CDs co-occur in close temporal proximity and interact with each other. However, how the interactions between concurrent CDs affect the large-scale network dynamics, and in turn help shape sensory perception is currently unknown. We focused on the effect of saccadic and body-movement CDs on a network of visual cortical areas in adult mice (n=15). CDs alone had large amplitudes, 3-4 times larger than visual responses, and could be dynamically described as standing waves (singular-value decomposition; explained variance 88±3%). They spread broadly, with peak activations in the medial and anterior parts of the dorsal visual stream. Inhibition (I) mirrored the wave-like dynamics of excitation (E), suggesting these networks remained E/I balanced. A generalized linear model (explained variance 36.8±3.6%) showed that CD waves superimposed sub-linearly and asymmetrically: the suppression was 1.5±0.2 times larger if a saccade followed a body movement by 0.59+-0.05 ms than in the reverse order. These rules depended on the animal's cognitive state: when the animal was most engaged in a visual discrimination task (measured using pupil area), cortical states had large variability accompanied by an increase in S/N (max amplitude after the stimulus over pre-stimulus variability, $p = 0.001$) improving the reliability in sensory processing. High-variability states were associated with a smaller non-linearity as well ($p = 0.002$). These results suggest that in high variability states CDs and sensory signals are independently encoded, permitting an

efficient read-out by downstream networks for improved visual perception. In summary, our results highlight a novel cognitive-dependent arithmetic for the interaction of non-visual signals that dominate the activity of occipital cortical networks during goal-oriented behaviors. These findings provide an experimental and theoretical foundation for the study of active visual perception in ethological conditions.

Disclosures: **M. Abdolrahmani:** None. **D.R. Lyamzin:** None. **R. Aoki:** None. **A. Benucci:** None.

Poster

752. Active Vision and Context Modulation

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Program #/Poster #: 752.08/H42

Topic: D.07. Vision

Support: BBSRC: BB/R004765/1
Wellcome Trust: 200501/Z/16/Z

Title: Vision tapers escape behaviours in mice

Authors: ***S. ZUCCA**, T. WHEATCROFT, K. J. JEFFERY, A. B. SALEEM, S. G. SOLOMON;
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Abstract: When encountering a sudden danger, such as a predator, escape can be essential for survival. When a place of refuge is available, prey animals usually escape to the refuge. Locating the refuge is likely to be easier in the presence of visual information. We therefore asked how escape behaviors were influenced by the absence of light. We video-tracked mice (n = 16) exploring an open-field with a refuge on one side, and recorded their responses to a train of ultrasonic up-sweeps that lasted three seconds. We compared responses in two conditions: when the environment was well illuminated or when it was completely dark. Sound stimulation evoked running in both light and dark conditions (light: 75%, 35/47 trials; dark: 69% , 33/48 trials). However, the peak speed of the response was significantly reduced in the dark condition (Light: 51.4 ± 1.6 cm/s [median ± s.e.]; Dark: 40.5 ± 1.8 cm/s, p=0.0003, Kruskal-Wallis test). Moreover, in the illuminated environment, most of the running trajectories (80%) ended with the with the animal escaping to the nest, while this fraction dropped dramatically (33%) in dark. We compared the trajectories of these responses with a straight-line path to the refuge location (i.e. homing vector). To quantify the difference, we calculated the angle between the homing vector and a line joining the start and end of each running response. This angle was significantly larger in the dark condition (Light: 4.1 ± 0.9 deg; Dark: 9.6 ± 5.6 deg, p=0.008, circular Kruskal-Wallis test). Our observations suggest that visual cues improve an animal’s ability to find refuge, and

reduce the time needed to get there. The lack of visual cues might also change animals' escape strategy, where reaching the nest may no longer be the optimal response.

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Poster

752. Active Vision and Context Modulation

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Program #/Poster #: 752.09/H43

Topic: D.07. Vision

Support: NIH P20 GM103650

Title: Dynamic contrast sensitivity during locomotion in humans

Authors: *B. R. SHANKAR, B. J. SZEKELY, P. R. MACNEILAGE;
Psychology, Univ. of Nevada Reno, Reno, NV

Abstract: During locomotion, high-acuity vision is maintained by reflexive head and eye movements that function to stabilize visual targets on the retina. These stabilization behaviors typically succeed in holding retinal slip to velocities less than about 2 deg/s. With retinal slip in this range, dynamic visual acuity is typically reported to be as good as static visual acuity, suggesting visual mechanisms that work to mitigate the consequences of retinal image motion to improve acuity. Here, we investigate these mechanisms further by measuring contrast sensitivity during locomotion and comparing these measures with contrast sensitivity measured while stationary. This work is motivated by recent observations of increased gain of visual responses in mice during locomotion (Mineault et al., 2016). Recent work in humans has also investigated contrast sensitivity during walking and reported little change in sensitivity but increased surround suppression (Benjamin et al., 2018). Building on this work, we developed a paradigm to deliver visual stimuli contingent on head and eye movement during treadmill locomotion. Stimuli were presented on a ProPixx projector and head movement was tracked using Optitrack. We also have the capability to record eye movements using the Eyelink II. On each trial subjects were presented with a Gabor grating on a grey background for 100 ms. The grating was tilted 45 deg in either the clockwise or counter-clockwise direction and subjects reported the orientation. Michelson contrast was manipulated from trial to trial according to a staircase procedure to find the contrast that led to 75% correct performance. We sought to evaluate how contrast sensitivity depends on locomotor phase, so we measured and compared performance during mid-stance and heel strike. We also measured performance during standing. Performance was comparable during all conditions suggesting that contrast sensitivity is similar under static and dynamic conditions,

like visual acuity, and we found no evidence that contrast sensitivity depends on locomotor phase.

Disclosures: B.R. Shankar: None. **B.J. Szekely:** None. **P.R. MacNeilage:** None.

Poster

752. Active Vision and Context Modulation

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Program #/Poster #: 752.10/H44

Topic: D.07. Vision

Support: H.Sanders Chair in visual neuroscience

Title: Sensory substitution and spatial navigation in early and late blind individuals using a new SensoryFusion application installed on a smartphone

Authors: S. PARÉ[1], M. BLEAU[2], I. DJEROUROU[3], C. KNOWLEDGE[4], D. BERNAL[4], M. PISZCZOR[4], R. C. KUPERS[5], *M. PTITO[2];
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Abstract: Blind individuals often report difficulties while navigating in their environment and detecting objects beyond the peri-personal space. Sensory substitution devices are therefore needed to inform them about the environment via other senses like touch and audition. In this study, early blind (EB, n=11), late blind (LB, n=12) and blindfolded-sighted participants (SC, n=20) were tested for their navigation ability in an obstacle course using the Signal Garden Electrolyte Engine platform installed on an ARCore smartphone. The system uses multiple sensors to either detect obstacles at a distance directly in front of the user (**Detection mode**) or to create a 3D map of the environment (**Avoidance mode**) and informs the user with an auditory feedback. The corridor contained 6 identical obstacles randomly placed across trials but always distanced by 3m from each other. Both modes of the SensoryFusion application were tested. For both modes, the task was to cross the corridor as quickly as possible while detecting or avoiding the obstacles. In the **Detection**mode, the participants had todetect obstacles by pointing at them and estimate the distance between them and the object; in the **Avoidance**mode, the participants had to bypass the obstacles without touching them. Our data show that all three groups performed similarly in the**detection**task (72.2%, 78.9% and 82.6%,). EB and SC showed however a significant improvement in the time taken to cross the corridor between the beginning (first trials) and end (last trials) of training (EB: 310s for first trials versus 236s for last trials, p&lt 0.05; SC: 298s for first trials versus 236s for last trials, p &lt 0.05). LB did not significantly

improve their average crossing time (235s for first trials versus 186s for last trials, p= 0.165). In the **avoidance**mode, all groups had similar performances (90.7%, 84% and 86.9%), but LB and EB were significantly faster to cross the corridor than SC (EB&ltSC: p&lt 0.05). Also, error analysis indicated that different strategies were used by blind and blindfolded-sighted individuals. The SensoryFusion application offers a new and accessible way for sensory substitution with the use of smartphones.

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Poster

752. Active Vision and Context Modulation

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 752.11/H45

Topic: D.07. Vision

Support: Wellcome Investigator Award 205093
Wellcome Trust 108726
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Title: Navigational signals along the visual pathway

Authors: *E. M. DIAMANTI, C. REDDY, S. SCHROEDER, K. D. HARRIS, A. B. SALEEM, M. CARANDINI;
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Abstract: The visual system and the navigational system profoundly influence each other. Vision shapes the navigational system's estimates of spatial position, and these estimates in turn influence visual processing. For instance, spatial position powerfully modulates the responses of neurons in primary visual cortex (V1) to otherwise identical visual stimuli (e.g. Saleem et al, 2018). How does this modulation vary along the visual pathway? Is it established earlier than V1, and does it change beyond V1? In addition, does this modulation require that the mouse actively navigates the environment, or is it also present when the mouse is passively viewing the environment's visual scenes?
We recorded activity in V1, six higher visual areas and the thalamic lateral geniculate nucleus (LGN), with 2-photon calcium imaging, while head-fixed mice ran along a virtual corridor with two visually-matching segments. To image cortical activity, we used transgenic mice expressing GCaMP6 in excitatory neurons. To image LGN activity we expressed GCaMP6 in the LGN of wild-type mice and imaged their boutons in layer 4 of area V1. We quantified the degree of

spatial modulation using a spatial modulation index (SMI): a purely visual cell had SMI close to 0 (i.e. it gave similar responses to the visually-matching segments) and a cell that preferentially fired at one position had an SMI close to 1.
Signals related to spatial position were strong both in V1 and in higher visual areas (median SMI between 0.3 and 0.45). In LGN, instead, signals related to spatial position were absent (SMI ~ 0.06). Therefore, responses in LGN were visual, albeit influenced by running speed as shown previously (Erisken et al, 2014).
To investigate the role of active navigation, we compared responses in virtual reality ('VR' mode) to passive presentation of the VR scenes. To determine pure passive viewing periods, we isolated epochs when the mouse was not moving (running speed < 5 cm/s; 'passive' mode). In this mode, in some cortical areas, like areas A and PM, responses were more variable, which suggests that these higher-order areas responded reliably only during active behavior. For the other cortical areas, median SMI in 'passive' mode was significantly reduced, which suggests that spatial modulation markedly decreased. In LGN, instead, there was little room for SMI to decrease relative to 'VR' mode, and indeed the SMI distributions were similar between 'VR' and 'passive' modes.
These results indicate that modulation of visual responses by spatial position is established in cortex. This modulation is present in all visual cortical areas provided that the animal actively navigates the environment.

Disclosures: **E.M. Diamanti:** None. **C. Reddy:** None. **S. Schroeder:** None. **K.D. Harris:** None. **A.B. Saleem:** None. **M. Carandini:** None.

Poster

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Program #/Poster #: 752.12/H46

Topic: D.07. Vision

Support: Tiny Blue Dot Foundation

Title: Cellular imaging of claustrum reveals diverse task-related signals

Authors: *D. R. OLLERENSHAW[1], J. DAVIS[1], E. G. MCBRIDE[1], H. ZENG[2], **S. R. OLSEN**[1], C. KOCH[3];
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Abstract: The claustrum is a subcortical gray matter structure with remarkably extensive connectivity with the neocortex yet its function remains elusive. Based on its widespread anatomical connections and physiological activity, the claustrum has been hypothesized to be involved in various complex phenomena including multimodal integration of stimulus

information into a single conscious percept (binding), amplification of cortical oscillations, salience detection, and allocation of selective attention. To probe the function of the claustrum during behavior, we imaged activity in claustrum cells using a Cre line which expresses preferentially in the claustrum under control of the Gnb4 gene. We have performed single-photon fluorescence imaging of the claustrum using implantable gradient index (GRIN) lenses during passive sensory stimulation, visual task performance (change detection), and during home cage exploration and anesthesia. Claustrum cells are rarely responsive to passive sensory stimulation, but show a diverse range of task-related signals, including both increases and decreases of activity in different sets of cells. The claustrum is virtually silent during isoflurane anesthesia, but shows strong locomotion modulation. Together these results suggest claustrum activity reflects an integration of sensory, motor, and task-related signals.

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Poster

752. Active Vision and Context Modulation

Location: Hall A

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Program #/Poster #: 752.13/I1

Topic: D.07. Vision

Title: Representation of unexpected stimuli across functionally connected cortical columns during visual behavior in mouse

Authors: F. NAJAFI, N. Y. ORLOVA, D. TSYBOULSKI, S. M. SEID, I. KATO, M. GARRETT, P. A. GROBLEWSKI, R. S. LARSEN, D. R. OLLERENSHAW, D. SULLIVAN, W. WAKEMAN, Q. L'HEUREUX, S. R. OLSEN, *J. LECOQ;
Allen Inst. for Brain Sci., Seattle, WA

Abstract: The predictive processing framework for understanding the brain function assumes that the brain contains an internal representation of the world, which is updated by comparing predictions about the external world with the actual sensory inputs. This framework relies on communication across different brain areas in order to generate and update predictions. A major challenge in assessing the predictive processing framework is to simultaneously measure neuronal population activities across multiple cortical areas.
To address this challenge, we have recently developed an advanced two-photon microscope, “multiscope”, that allows us to simultaneously image the activity of neural populations across 8 cortical planes. We leveraged this instrument to measure the activity of 4 cortical layers and 2 cortical areas, while mice were performing a visual change detection task. We used this method, combined with different mouse lines that tagged distinct subclasses of inhibitory and excitatory neurons, to assess how different cell types across two visual areas (V1 and LM) interact and

represent predictions about external stimuli. Our behavioral task involves image change detection: an image is repeatedly flashed, and after a varying number of presentations, it changes to a different image. The animal is trained to detect the change and report it by licking a waterspout. To investigate the neuronal representation of prediction signals, we have omitted the image change in a small subset of trials.
Here, we demonstrate how different cell types (excitatory neurons and inhibitory neurons of VIP and SST subtypes) in all layers of the primary visual cortex as well as a higher order visual area represent prediction signals during visual behavior. Additionally, we have leveraged our simultaneous recordings to study the interactions between cortical columns. Our preliminary findings demonstrate that VIP inhibitory neurons, particularly in superficial cortical layers, signal the violation of prediction significantly more than excitatory or SST cell types. Our correlation analysis of cortical columns reveals how primary and higher order visual areas communicate to represent unexpected sensory perturbations. Altogether, our findings demonstrate the distinct contribution of different cell types across cortical columns in representing predictions about the external world.

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Poster

752. Active Vision and Context Modulation

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Program #/Poster #: 752.14/I2

Topic: D.07. Vision

Support: Allen Institute for Brain Science

Title: Influence of experience and engagement on sensory responses during a visual change detection task

Authors: M. GARRETT, ***R. S. LARSEN**, P. A. GROBLEWSKI, D. R. OLLERENSHAW, A. PIET, N. D. PONVERT, N. H. CAIN, F. NAJAFI, S. NAYLOR, J. LECOQ, S. R. OLSEN; Allen Inst. for Brain Sci., Seattle, WA

Abstract: A fundamental property of the brain is its ability to flexibly process short-term changes in internal state and longer-term changes due to experience and learning. Changes in internal states like engagement, motivation, and arousal modulate sensory perception, potentially sharpening the ability to discriminate between competing options when focused on a goal. To study how neurons dynamically compute information in an experience- and state-dependent

manner, we measured the activity of L2/3 and L5 excitatory cells, and VIP and SST inhibitory neurons in mouse primary visual cortex with 2-photon calcium imaging during goal-directed behavior or during passive viewing. Using a change detection behavioral task in which mice respond when the identity of natural images change, we observed that excitatory neuron responses to image changes were larger during active behavior than passive viewing of the same images. Moreover, the strength of these changes depended on whether the images were novel or familiar. We next compared visual responses to trained, familiar images with responses to novel images that had not previously been associated with reward. While behavioral performance rapidly generalized to new stimuli, the underlying neural representations differed. Responses to highly trained stimuli were more sparse and selective than responses to novel, untrained images. Activity became increasingly sparse with stimulus repetition, suggesting a role for stimulus specific adaptation in facilitating enhanced responses to changes, particularly in excitatory populations. We characterized several response types with different dynamics, including a subset of VIP inhibitory cells exhibiting ramping activity that potentially signaled temporal expectation of a change event. This study forms the foundation for a large-scale dataset, generated on a standardized platform for high-throughput calcium imaging during behavior that will be public data resource for the community (Allen Brain Observatory: http://observatory.brain-map.org/visualcoding/).

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Poster

752. Active Vision and Context Modulation

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 752.15/I3

Topic: H.02. Human Cognition and Behavior

Title: Principles of tactile search over the body

Authors: *E. J. HALFEN, J. F. MAGNOTTI, J. M. YAU;
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Abstract: Although we can experience touch across our entire body, little is known about how multi-site touches are combined over the body and prioritized by spatial attention. To address these questions, we designed a tactile analog of the classic visual search task. On each trial, participants made a present/absent decision about a target stimulus (e.g., 10-Hz vibration) presented on the body (70% target present trials). When present, the target stimulus could occur alone or simultaneously with distractor stimuli (e.g., 30-Hz vibrations) on other body locations. We systematically varied the number and spatial configurations of the distractors (from 1 to 8)

and alternated the target and distractor frequencies (10-Hz or 30-Hz) to test the impact of these factors on tactile search performance. We found that response times were faster on target-present trials (m = 1568 ms) compared to target-absent trials (m = 2309 ms, $p < 0.0001$). Additionally, response times increased with the number of stimulated sites, consistent with a serial search process (mean slope = 136 ms/site). Moreover, search performance differed depending on the target and distractor frequencies implying that tactile search is a feature-dependent behavior. These results reveal a number of ways in which tactile search behavior is analogous to its visual counterpart. We implemented a simple model to explore how tactile search behavior related to the locations of the target and distractor cues. Our modeling results reveal that tactile cues on the hands make relatively greater contributions to search performance - in isolation or through multi-site interactions - as compared to tactile cues experienced on other body sites. Collectively, our findings identify principles of attentional search that are common to visual and somatosensory search, but they also highlight key differences that may be unique to body-based spatial perception.

Disclosures: **E.J. Halfen:** None. **J.F. Magnotti:** None. **J.M. Yau:** None.

Poster

752. Active Vision and Context Modulation

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Program #/Poster #: 752.16/I4

Topic: D.07. Vision

Support: NIH Grant R03HD093995

Title: Limits of visual orientation discrimination in free behaving mice

Authors: *W.-K. YOU[1], S. P. MYSORE[2];
[1]The Johns Hopkins Univ., Baltimore, MD; [2]Psychological and Brain Sci., Johns Hopkins Univ., Baltimore, MD

Abstract: The laboratory mouse is emerging as a powerful model to study the neural circuit basis of visually-guided behavior. Nonetheless, a detailed understanding of the dependence of visual discrimination performance of mice on stimulus parameters is lacking. Here, we explored systematically the stimulus parameter space for visual discrimination in freely behaving mice. Using a touchscreen-based setup, we measured discrimination performance by manipulating the stimulus size, contrast, duration, and delay in the context of a 2AFC, orientation discrimination task. The metrics of performance were accuracy, perceptual discriminability, decision criterion, and reaction time. Our results revealed that the visual capability of mice, which is known to be several-fold poorer than that of primates, has nonetheless been underrated. In general, shrinking the size of the oriented grating stimulus, lowering the stimulus contrast, shortening the stimulus

duration, or adding a delay before stimulus onset all caused deterioration of mice's discrimination performance. However, mice were able to respond to visual stimuli that were smaller, faster, and in general, more demanding than those typically used in literature. In addition, results revealed important insights into the limits of visual discrimination performance in freely behaving mice. Specifically, we were able to quantify the shortest stimulus duration necessary for successful discrimination, the longest effective stimulus duration, and the length of their visual working memory. Our results provide useful information for the design of future visually-guided experiments in mice.

Disclosures: W. You: None. **S.P. Mysore:** None.

Poster

752. Active Vision and Context Modulation

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Program #/Poster #: 752.17/I5

Topic: D.07. Vision

Support: R03HD093995
R34NS111653

Title: R A I L: Rodent automated and integrated learning platform for training freely behaving mice on touchscreen-based visual tasks

Authors: *B. A. D. HOLT, J. GARMON, S. P. MYSORE;
Johns Hopkins Univ., Baltimore, MD

Abstract: We present the Rodent Automated and Integrated Learning (RAIL) visual platform, a custom behavioral training system that flexibly and scalably integrates inexpensive Internet of Things (IoT) hardware with open-source web development software tools for neuroscience applications. By applying readily available components to a neuroscience context, this system makes possible affordable implementation of various rodent behavioral paradigms en masse. As proof of concept, we provide behavioral performance results from five freely moving mice trained simultaneously on a visual task, using the latest version of our touchscreen-based visual training box, thereby demonstrating that RAIL delivers training outcomes equivalent to contemporary commercial systems. Our box redesign is more modular than before and possesses expanded hardware capabilities, such as multiple screen configurations and camera feeds, a rugged chassis, and an external view screen. The RAIL box's added modularity allows researchers to account for individual animal bias, as well as to quickly adjust hardware to support new behavioral paradigms. RAIL has the potential to scale up rodent training many fold without prohibitive financial outlay, thereby accelerating behavioral neuroscience research.

Disclosures: **B.A.D. Holt:** None. **J. Garmon:** None. **S.P. Mysore:** None.

Poster

752. Active Vision and Context Modulation

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Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 752.18/I6

Topic: D.07. Vision

Support: Wellcome Trust
Simons Collaboration on the Global Brain

Title: Citric acid water as an alternative to water scheduling in behaving mice

Authors: V. AGUILLON-RODRIGUEZ[1], *A. E. URAI[1], F. CAZETTES[2], I. C. LARANJEIRA[2], A. M. ZADOR[1], Z. F. MAINEN[2], A. K. CHURCHLAND[1], .. IBL COLLABORATION[3];
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Abstract: Training animals to perform cognitive tasks benefits from a system in which animals obtain their daily water requirements via rewards delivered within the task.This approach represents an effective strategy for achieving stable, accurate behavior (Guo et al. 2014). Water scheduling requires rigorous monitoring of weight and hydration status which can be challenging for some animals. Citric Acid (CA) makes water taste slightly bitter but is harmless to animals. In rats, access to ad libitum CA water allows animals to maintain a healthy weight, with only a subtle impact on willingness to perform behavioral tasks with water rewards (Reinagel, 2018). Here, we extend this approach to mice using a large-scale multi-site collaboration as a test-platform.
We gave mice free access to CA water in their home cage and tracked their weight, health status, water intake and motivation to perform trials for sucrose water rewards. We first observed that free availability of 1% CA water in the home cage caused a rapid, but modest, weight loss in 9 mice (C57/BL6, Lisbon). Body weight stabilized at around 85-90% of baseline levels within a few days and did not further decrease upon switching from 1% to 2% CA water. Intake of ad libitum CA water was around one-third of the intake of regular water. This suggested that mice, like rats, would be motivated to perform trials rewarded with normal water when given ad libitum CA water in their home cage.
To test this, six C57/BL6 mice (CSHL) were trained each weekday, performing a visual decision-making task (Burgess et al. 2017) where correct choices were rewarded with 10% sucrose water (Guo et al. 2014). We used trial counts as a measure of motivation under varying water regimes. As a baseline, when we gave 1mL/day on weekends, trial counts did not change from Friday to Monday. When we gave 2% ad libitum CA water on weekends, trial counts

likewise did not change from Friday to Monday. By contrast, when we provided access to ad libitum 2% CA water throughout the week, trial counts were lower: animals completed only 80% of their baseline trial counts.
Our results suggest that a regimen of 2% CA water on weekends allows animals to maintain their health without diminishing trial counts. While CA water has not been shown to be a viable alternative to water restriction in all cases, we consider it a promising alternative that allows animals more control over their water intake without interference to behavioral performance.

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Poster

752. Active Vision and Context Modulation

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Topic: D.07. Vision

Support: Wellcome Trust 209558
Simons Foundation 543059

Title: The International Brain Laboratory: Standardizing and reproducing a decision making task in mice across laboratories

Authors: *A. PAN-VAZQUEZ[1], G. A. CHAPUIS[2], G. T. MEIJER[3], J.-P. NOEL[4], A. E. URAI[5], V. AGUILLON-RODRIGUEZ[5], D. E. ANGELAKI[4], N. BONACCHI[3], M. CARANDINI[6], F. CAZETTES[3], E. E. E. DEWITT[3], A. K. CHURCHLAND[5], M. FAULKNER[6], T. KAMIGAKI[7], F. HU[7], C. S. KRASNIAK[5], I. C. LARANJEIRA[3], Z. F. MAINEN[3], H. MARTINEZ VERGARA[6], N. J. MISKA[6], J. SANDERS[8], K. Z. SOCHA[6], M. J. WELLS[6], C. J. WILSON[4], O. WINTER[3], I. B. WITTEN[1], L. E. WOOL[6], .. IBL COLLABORATION[6];
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Abstract: The International Brain Laboratory (IBL) is a collaboration of 21 laboratories aiming to understand the neural basis of decision-making. A core goal of IBL is to establish a standardized decision making task in all participating experimental institutions. To support this goal, we implemented a visuo-spatial detection task in which mice report whether a visual stimulus of varying contrast was presented on the left or the right of the screen by moving the stimulus to the center by turning a steering wheel.

We have trained 61 mice in the final standardized implementation of the behavioral task in six institutions (Champalimaud Center for the Unknown, University College London, Cold Spring Harbor, New York University, Princeton and Berkeley). Mice took on average 12.7 ± 6.6 (mean ± s.d.) training days to reach stable psychometric performance as indicated by low bias and lapse rates over multiple days. The training procedure was fully automated to improve reproducibility. When mice showed stable psychometric performance, they transitioned to the final phase of the task in which stimuli were more likely to appear from one of the two sides (80/20 probability, side prior switched in blocks). Mice consistently biased their psychometric function according to the stimulus side prior.
To assess replicability of behavioral results, we trained three classifiers (Random Forest, Naive Bayes and LDA) to decode the laboratory membership of an animal based on behavioral performance and training time parameters. Classifiers were unable to predict in which lab a mouse was trained based on behavioral parameters, arguing there was no significant differences across laboratories.
To further explore which factors may influence animal training and behavior, we scrutinized factors related to environment (e.g., temperature, humidity, light cycle, diet), phenotype (e.g., age, litter, sex, and genetic background) and operation (e.g., trainer, animal-experimenter interaction) factors using metadata shared across IBL laboratories through the Alyx platform (see companion poster). This study provides a deeper understanding of which factors are critical for replicating a behavioral paradigm across institutions. Most importantly, it places the IBL in a position to propose a standardized open-source behavior apparatus and training protocol that can be readily adopted by the neuroscience community.

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Poster

752. Active Vision and Context Modulation

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Program #/Poster #: 752.20/I8

Topic: D.07. Vision

Support: NIH

Title: Signature of exploration in brain state dynamics

Authors: *X. TIAN[1], D. SZCZUPAK[2], A. C. SILVA[3], C. LIU[1];
[1]NINDS/NIH, Bethesda, MD; [2]Natl. Inst. of Hlth., North Bethesda, MD; [3]Dept. of Neurobio., Univ. of Pittsburgh, Pittsburgh, PA

Abstract: In reality, we always meet such a dilemma to choose old things (exploitation) already known or to explore new things. One strategy to solve this exploitation-exploration dilemma is biased toward the new option, as it is more informative than the old. However, we knew little about where and how the brain plans this strategy at a large scale: How many brain areas are involved in the process; which brain regions and networks contribute most; and how functional dynamics changes of these networks are. To investigate this question, we used the common marmoset (Callithrix jacchus) as our experimental subject, which has a small and smooth brain but sharing similar brain architectures as other primates. To avoided confounding effects from any previous behavior training, we screened our marmoset colony and only recruited animals that engaged in the experiment naturally. Then, we performed longitudinal fMRI acquisition to fully track brain states associated with behavioral improvements, in which marmosets learned a novel decision-making task. In the task, we presented a series of movies to marmosets. After a short delay, the marmosets were required to choose between two pictures, one was a screenshot from the previous movie, and the other was a new picture. To avoid the influence of external rewards biasing the animal's internal strategy, we delivered liquid reward randomly regardless of choice made by the animals (50% chance for both choices). We found that the marmosets preferred choosing the novel stimulus rather than the old cue, suggesting a natural strategy of exploration. By analyzing fMRI dynamic functional connectivity, we identified several distinct brain states, one of which has a significant correlation with the exploration behaviors. By comparing this brain state with other states, we revealed that cerebellar-cortical networks contributed most to the distinct patterns of the brain states. Our findings demonstrate that exploration involves brain-wide networks and the dynamics of the cerebellar-cortical networks is an essential feature.

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Poster

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Topic: D.07. Vision

Support: NSF Grant PHY-1532846
Leon Levy Fellowship in Neuroscience

Title: Expectation dependent responses in ventral visual pathway cortical areas

Authors: *T. S. ALTAVINI[1], G. ASTORGA[1], Y. YAN[2], M. CHEN[1], W. LI[2], D. HARARI[3], S. ULLMAN[3], G. N. REEKE[1], C. S. JIANG[1], W. FREIWALD[1], C. D. GILBERT[1];
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Abstract: Neuronal responses to visual stimuli are subject to top-down influences, even in early visual areas. Visual perception emerges from an interaction between bottom-up signals carrying information about stimulus characteristics and top-down signals, derived from experience, that convey expectations and perceptual tasks. To investigate the representation of objects and object components in different areas along the ventral visual pathway and how expectation influences these representations, we trained macaque monkeys on a delayed match-to-sample task. Once the animal learned to respond whether a "cue" image matched a subsequently presented "target" image we presented cropped parts of the target image in order to determine which components of the object were more informative for object recognition. This behavioral paradigm allowed us to study how expectation generated by the cue influences neuronal responses to the target. We performed a series of fMRI experiments to identify areas that were responsive to various object categories, including vegetables, animals, man-made objects and faces, and to our ethologically curated library of informative object components. We then implanted multiple electrode arrays in several of these areas, including V1, V4 and TEO and recorded from single neurons while the animal performed the behavioral task. For cells that responded to selected stimuli within our stimulus set (one sample t-test, $p<0.05$), we found that their stimulus selectivity was influenced by cue induced expectation (two-way ANOVA, $p<0.05$). We found a significant interaction between cue and target in all areas recorded, indicating expectation dependent stimulus selectivity.

Disclosures: T.S. Altavini: None. **G. Astorga:** None. **W. Freiwald:** None. **C.D. Gilbert:** None. **M. Chen:** None. **G.N. Reeke:** None. **Y. Yan:** None. **W. Li:** None. **C.S. Jiang:** None. **S. Ullman:** None. **D. Harari:** None.

Poster

752. Active Vision and Context Modulation

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 752.22/I10

Topic: D.07. Vision

Support: NIH NS U01-107464
Arnold and Mabel Beckman Foundation

Title: Mice preferentially depend on increments in V1 activity to detect changes in visual stimuli

Authors: *J. J. CONE, E. A. PAGE, M. L. BADE, J. H. R. MAUNSELL;
Univ. of Chicago, Chicago, IL

Abstract: Changes in the visual scene evoke diverse responses in the neurons of primary visual cortex (V1). How such changes in neuronal activity are decoded by other brain structures during visually guided behaviors remains poorly understood. Although increments or decrements in neuronal activity both convey information, the emergence of ON and OFF channels in the retina suggests that spike rate decrements might play only a minor role in supporting visual perception. To explore this idea, we used optogenetic stimulation of V1 in trained, behaving mice to determine whether increasing or decreasing population activity impairs or improves perception of visual contrast changes. Mice were trained to do a contrast change detection task while head-fixed. They initiated trials by depressing a lever while viewing a display containing a mid-contrast Gabor (SD: 5-8°). After a random delay (600-3000 ms) the Gabor contrast stepped to a higher or lower level. Mice were rewarded for releasing the lever within a brief response window after step onset. The sign and magnitude of the contrast step was randomly selected, with the step sizes on different trials spanning behavioral detection thresholds. To perturb neuronal activity during behavior, we expressed ChR2 in neurons in the portion of the V1 retinotopic map that included the Gabor representation. ChR2 was expressed in either inhibitory (PV+; n=7 mice) or excitatory neurons (Emx+; n=3 mice), allowing us to moderately decrease (PV+) or increase (Emx+) visually-evoked responses in V1. During experimental sessions, optogenetic stimulation was delivered on a randomly selected fraction of near-threshold contrast changes and we measured the resulting change in behavioral detection. Stimulation of excitatory neurons (Emx+) always facilitated detection of either increments or decrements in contrast. Conversely, activation of PV+ neurons always impaired detection of either contrast change. The effects of optogenetic stimulation on V1 population responses were confirmed with electrophysiology. While changes in visual contrast evoke diverse responses in V1 neurons, our data suggest that the brain preferentially decodes information from neurons whose firing rates increase in response to those changes. Ongoing experiments seek to test more generally if there is an asymmetry in the ability of mice to perceive increments versus decrements in activity using animals trained to respond to ChR2-induced changes in V1 activity in the absence of visual stimuli.

Disclosures: J.J. Cone: None. **E.A. Page:** None. **M.L. Bade:** None. **J.H.R. Maunsell:** None.

Poster

752. Active Vision and Context Modulation

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Program #/Poster #: 752.23/I11

Topic: D.07. Vision

Support: Whitehall Foundation Grant 2015-08-69

Title: Modulation by sounds of visual processing in the primary visual cortex of mice performing an audiovisual discrimination task

Authors: J. P. MCCLURE, Jr., J. CORBO, ***P.-O. POLACK**;
Ctr. for Mol. and Behavioral Neurosci., Rutgers Univ., Newark, NJ

Abstract: Multisensory integration is not restricted to higher-order sensory cortices. Studies in human and rodents have shown that multimodal interactions also occur at the earliest stages of sensory cortical processing. In mice, the presence of sounds improves the representation of the orientation and direction of the visual stimulus by neurons in layer 2/3 of the mouse primary visual cortex (V1). However, sound modulation in the mouse V1 has only been demonstrated in naïve mice passively processing visual and auditory stimuli. Therefore, it remains unclear if the influence of sound on visual processing persists when mice actively process both the visual and auditory stimuli simultaneously. To determine the influence of sound on V1 visual integration during active audiovisual processing, we designed a cross-modal discrimination task for water restricted mice. This task consists in the presentation of one of two pure tones and/or one of two drifting gratings. One stimulus of each modality is a 'Go' signal indicating that a water reward is provided in case of a lick response, while the other stimulus is a 'NoGo' signal generating a timeout in case of licking. Visual and auditory cues are presented either in isolation during unimodal blocks or simultaneously during audiovisual blocks. The analysis of the probability of licking for each unimodal and audiovisual stimulus presentation shows that mice use both visual and auditory cues to determine their behavior. Indeed, mice were significantly more successful at refraining from licking when congruent audiovisual 'NoGo' cues were presented than when each of those cues were presented in isolation. During conflicting audiovisual trials (e.g. NoGo visual cue paired with Go auditory cue or Go visual cue paired with NoGo auditory cue), mice by default licked for water. However, we did not find a difference between the licking probability in response to the unimodal 'Go' trials and audiovisual 'Go' trials likely due to a ceiling effect. We used two-photon calcium imaging to measure the activity of V1 L2/3 neurons while mice were performing the task. At the end of the recording session, we assessed the orientation tuning of the imaged neurons by presenting a series of drifting gratings of 12 evenly spaced orientations. We found that when trained mice performed the task, the activity of V1 neurons tuned to the 'NoGo' visual cue was suppressed during audiovisual blocks. This contrasted with sound modulation measured in naïve mice in which sounds potentiated neurons tuned for the oriented cues. Therefore, our results support the hypothesis that visual processing in V1 is dynamically adapted to the behavioral goal.

Disclosures: J.P. McClure: None. **J. Corbo:** None. **P. Polack:** None.

Poster

752. Active Vision and Context Modulation

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 752.24/I12

Topic: D.07. Vision

Title: Context-switching in a disinhibitory circuit in V1

Authors: *D. VOINA[1], S. RECANATESI[2], B. HU[3], E. T. SHEA-BROWN[2], S. MIHALAS[3]; [1]Applied Mathematics, [2]Univ. of Washington, Seattle, WA; [3]Allen Inst. For Brain Sci., Seattle, WA

Abstract: We investigate minimally complex circuits that perform related but different tasks by using knowledge common to both tasks (transfer learning) and apply them to visual processing of images and visual processing of movies. Experimental evidence suggests that such a circuit exists in the brain's visual area V1, where in addition to excitatory Pyr and inhibitory SST neurons, an additional inhibitory VIP population enables switching between processing of different input types (static and moving). Instead of requiring two circuits to process the two input types, the brain processes scenes using a single circuit, where VIP neurons act as switch units that become activated whenever animals are moving. Could such a flexible circuit operate in both static and moving contexts to perform optimal processing? We use a model for optimal integration of context to predict neuronal connectivities (weights) that achieve optimal processing in the static and moving conditions separately. Instead of using two different sets of weights in two separate circuits, we attempt to find one circuit where VIP neurons interact in a switch-like manner while the Pyr and SST populations remain connected by the weights optimal in the static condition. To find a circuit capable of doing both visual processing tasks, we need to find the VIP contribution during movement that produces the same firing rate statistics as those which would be generated with the set of optimal weights for the movement condition. After finding the VIP contribution by solving a constrained Least Squares problem, we confirm that the network does optimal visual processing of images and, when the VIP are active, of videos. Our network predicts realistic connectivity patterns of Pyr and other neural populations, while also finding the minimal number of VIP neurons that are necessary to achieve an optimal switch circuit. Interestingly, few VIP neurons are required, so that having a low-dimensional switch module added to a circuit could be more favorable than having two separate circuits for the tasks. This provides a concrete example of a model biological circuit - complete with cell type specifications - capable of performing two tasks, further informing the design of bio-inspired multitasking artificial neural networks.

Disclosures: D. Voina: None. **S. Recanatesi:** None. **B. Hu:** None. **E.T. Shea-Brown:** None. **S. Mihalas:** None.

Poster

752. Active Vision and Context Modulation

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 752.25/I13

Topic: D.07. Vision

Title: Neural circuits for visual stimulus competition in zebrafish

Authors: *I. P. LAZARTE, J. SEMMELHACK;
Hong Kong Univ. of Sci. and Technol., Sai Kung, Hong Kong

Abstract: All visual animals must be able to pay attention to important stimuli in a dynamic environment in order to survive. Both a frog hunting flies and a fly escaping a hungry frog need to attend to crucial visual information to perform a specific task. Previous studies in anesthetized owls showed that a midbrain structure, the optic tectum (OT), is important for encoding the location of highest priority stimulus in the visual space through excitatory and inhibitory modulation provided by the isthmic nuclei (NI). However, in that paradigm, a behavioral output was not available to support the behavioral relevance of stimulus competition. The purpose of this study is to elucidate the neural circuitry of visual stimulus competition in a behaving animal using larvae zebrafish, a simple vertebrate model system that heavily relies on vision to hunt prey. Using larval zebrafish, we take advantage of their robust prey capture behavior to establish a paradigm where we tracked their response to competing prey, and formulate an algorithm to tell which stimulus it attended to. Using a head-fixed paradigm with eyes and tail free, we simulate prey by projecting a moving dot on a screen in front of the larva. We first determined the size of an optimal prey that reliably evokes prey capture behavior. Then, we added a competing prey separated in the visual field such that fish selected either right or left side. When the two preys are similar in size, we found around 50% chance of the fish selecting either of the two preys. We found that the chance of choosing the optimal prey depends on the size of competing prey. Larger competing prey increases the chance of choosing optimal prey; indicating a weaker competition. On the other hand, smaller competing prey and closer to the optimal prey size decreases the chance of choosing the optimal prey; indicating a stronger competition. By 2-photon functional imaging, we found the most responsive region in the OT, and confirmed that its calcium activity follows a retinotopic pattern, allowing us to separately monitor the activity on the optimal and competing preys projection sides. Preliminary results show activation of the anterior OT by our prey stimuli, and a decrease in activity with the addition of a competing prey. This could be evidence of the inhibitory response of the midbrain circuitry found in owls. We will confirm this by labelling the GABAergic neurons in the NI, and trace their projections to OT by photoactivatable GFP. We will further provide functional evidence of suppression from NI by observing the NI response during the presence of competing

prey, and the changes in OT response by laser ablation of the NI neurons activated by the competing prey.

Disclosures: I.P. Lazarte: None. **J. Semmelhack:** None.

Poster

752. Active Vision and Context Modulation

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 752.26/I14

Topic: D.07. Vision

Title: Context-dependent neuronal modulation in V1 during selective visual attention

Authors: *D. TRAN[1], M. HAJNAL[2], M. EINSTEIN[1], M. VALLEJO[1], A. FOREMAN[1], B. SEDAGHAT[1], R. GOLI[1], T. SHOOSHANI[1], G. ORBÁN[2], P.-O. POLACK[3], P. GOLSHANI[4]; [1]Neurol., Univ. of California Los Angeles, Los Angeles, CA; [2]MTA Wigner Res. Ctr. for Physics, Budapest, Hungary; [3]Ctr. for Mol. and Behavioral Neurosci., Rutgers Univ. - Newark, Newark, NJ; [4]UCLA Dept. of Neurol., Los Angeles, CA

Abstract: Numerous studies in non-human primates have found that selective visual attention increases the responsiveness of primary visual cortical (V1) neurons. Yet, the precise mechanisms of this attention-related neuronal gain remain unknown. To further dissect these mechanisms, we performed 128-channel extracellular electrophysiological recording throughout V1 in mice performing a cross-modal visual/auditory attention task. During visual attention, water-restricted mice licked for water reward in response to one oriented drifting grating and had to withhold licking when an orthogonal orientation was presented. During this time, they actively ignored auditory stimuli (high or low tone) presented simultaneously with the visual stimuli. During auditory attention, mice were cued to lick in response to one tone and withhold licking to the other tone, while actively ignoring oriented drifting gratings. Visual and auditory attention sessions were presented in random order. Visual cues elicited a larger response from broad spiking (putative excitatory) V1 units in deep cortical layers (layers V and VI) during visual attention trials compared to auditory attention trials. This change in gain was apparent during both Go and No-Go trials but was not observed during fast locomotion. Narrow-spiking (putative inhibitory) units in superficial cortical layers, on the other hand, fired at higher rates during visual stimulation when animals ignored rather than attended to visual cues. Population decoding analysis showed that visual stimuli could be decoded from V1 population firing patterns. Surprisingly, the attentional context (attend visual vs. attend auditory) could also be decoded from the neural activity in V1 even during the inter-trial intervals. These results show that there is robust and opposing attentional modulation of V1 excitatory neuron firing rates mainly in deep layers, and V1 inhibitory neurons mainly in superficial cortical layers. The ensemble neural activity carries rich information about not only the visual stimulus but also the task context. We

are currently optogenetically inhibiting inputs to V1 to determine the mechanisms of this attentional modulation.

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Poster

752. Active Vision and Context Modulation

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Program #/Poster #: 752.27/I15

Topic: H.02. Human Cognition and Behavior

Support: DFG Priority Program SPP 1772, MU 1374-5/2

Title: Investigating response behavior on added semantically specific auditory probe stimuli in motor-cognitive dual tasks

Authors: *J. MUELLER, C. LANGHANNS, H. MUELLER;
Justus-Liebig-University, Giessen, Germany

Abstract: Introduction
Probe-reaction time (PRT) techniques are used to infer the strength of cognitive involvement in a primary task based on reaction time delays in the PRT task (Posner&Boies, 1971). Specific insights into content and temporal dynamics of primary task related processing can be gained by manipulating the temporal locus of the probe (McLeod, 1978; Mattes, 2001). However, manipulating the semantic similarity between tasks and probe stimuli might also affect the processing (Wickens, 2002). Therefore, we use a motor-cognitive dual task (mcDT) in order to understand the dynamic shift of processing resources between the continuous motor task and the cognitive task. In the resulting triple-task, we analyze PRT to auditory probe stimuli at critical moments dependent on their semantic similarity to either the motor, or the cognitive task.
Methods
12 participants conducted a mcDT on three consecutive days. The cognitive task was a visually presented calculation task (subtracting two numbers). The motor task was a force tracking task on a leg press. The auditory probes were two spoken numbers (“4”&“6”, interference with calculation) and pairs of words expected to interfere with either the quantitative (“stronger”&“weaker”) or the spatial (“up”&“down”) aspect of the motor task. Reactions to the probes were given by pinching index finger and thumb. Participants were instructed to perform all tasks as good as possible. RT was recorded from the EMG-signal from M. interosseous dorsalis I.
Results and Discussion

Analyses based on performance differences in PRT (ΔPRT) show a main effect for multi- compared to single-tasking conditions, which is shown in higher RTs for all types of auditory probes during multi-tasking (χ^2=158.87, p<0.01*). Data also support the multiple resource theory (Wickens, 2002) by showing a significant interference of probe stimuli holding numbers with the performance in the calculus task (Z=-1.96, $p_{one\text{-}tailed}$=0.03, d=0.29*). Presented data will further quantify the effect of probe-type and -onset on performance to contribute to neuroscientific attention research.
* statistics based on preliminary data. Full data set will be presented at the conference.
References
Mattes,S.(2001).Reaktionskraft in Sondierreiz-Aufgaben. Experimental Psychology,48(3), p.201-206.
McLeod,P.(1978).Does probe RT measure central processing demand? The Quarterly journal of experimental psychology, 30(1), p.83-89.
Posner,M.I. Boies,S.J.(1971).Components of attention. Psychological Review, 78(5), p.391-408.
Wickens,C.D.(2002).Multiple resources and performance prediction. Theoretical Issues in Ergonomics Science, 3(2), p.159-177.

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Poster

752. Active Vision and Context Modulation

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Topic: D.07. Vision

Support: Whitehall Foundation (2015- 08-69)
Rutgers University- Newark's startup fund

Title: Coincident sound modulates visual processing in V1 and improve the mouse's ability to discriminate orientations

Authors: *J. CORBO, J. MCCLURE, JR, H. KHDOUR, P.-O. POLACK;
Ctr. for Mol. and Behavioral Neurosci., Rutgers Univ. Newark, Newark, NJ

Abstract: To create a coherent perception of its environment, the brain integrates information from multiple sensory modalities. In several species including rodents and humans, visual perception has been found to be modulated by the multisensory context. Previous researches have shown that multimodal integration can occur in the primary sensory cortices, putting into perspective the paradigm of a clear-cut parcellation of early unimodal processing into distinct channels. In V1, the co-presentation of pure tones with oriented drifting gratings were shown to improve the representation of orientation and direction in naïve mice by refining the distribution

of activity in the space of the individual neurons' preferred orientations. However, it is not known if this representational improvement is paired with an improvement of the perception of orientation. Yet, these results suggest that the presence of sound, by sharpening the representation of the orientation and direction of the visual stimuli in V1, could decrease the minimal angular distance that mice can discriminate. To test this hypothesis, we trained mice to discriminate between two gratings orientations in a 'go/no go' task, and gradually reduced the angular distance between the 'go' and 'no go' orientations by making the 'no go' stimulus closer to the 'go', from 45 to 15 degrees. The neural activity was recorded in behaving animals using two-photon calcium imaging in V1 layer 2/3. We find that the co-presentation of pure tones along with the visual stimuli enhances the difference between the neural representations of the visual stimuli and decrease the minimal angular distance between two orientated stimuli that mice can discriminate. This simultaneous sound-induced bias of the representation of orientations in V1 and of the perception of orientation by the mouse supports the emerging theory of V1 as an interface between bottom-up visual input and external or internal top-down influence.

Disclosures: **J. Corbo:** None. **J. McClure:** None. **H. Khdour:** None. **P. Polack:** None.

Poster

753. Visual Cortex: Cell Types, Functional Organization, and Connectivity

Location: Hall A

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Topic: D.07. Vision

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Title: Visualization and mapping of white matter tracts in non-human primate visual system using polarized light imaging

Authors: *H. TAKEMURA[1,2], M. AXER[3], N. PALOMERO-GALLAGHER[3,4,5], D. GRÄßEL[3], M. J. JORGENSEN[6], R. WOODS[7], K. ZILLES[3,5];
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Biosci., Osaka Univ., Suita, Japan; [3]Inst. of Neurosci. and Med. INM-1, Res. Ctr. Jülich, Jülich, Germany; [4]Dept. of Psychiatry, Psychotherapy and Psychosomatics, Med. Fac., RWTH Aachen, Aachen, Germany; [5]JARA - Translational Brain Med., Aachen, Germany; [6]Dept. of Pathology, Section on Comparative Med., Wake Forest Univ. Sch. of Med., Winston-Salem, NC; [7]Ahmanson-Lovelace Brain Mapping Center, David Geffen Sch. of Med., UCLA, Los Angeles, CA

Abstract: Although the primate visual system is one of the most intensively studied systems in neuroscience, there are still controversies regarding the organization of fiber tracts connecting visual areas. Whereas some investigators doubt the existence of the vertical occipital fascicle (VOF) and inferior longitudinal fascicle (ILF), others could demonstrate these fiber tracts using diffusion-weighted magnetic resonance imaging (dMRI)-based tractography (Tusa & Ungerleider, 1985; Catani et al., 2003; Yeatman et al., 2014; Takemura et al., 2017). Also, the distinction between ILF and the sagittal stratum (SS) has been controversially discussed (Schmahmann & Pandya, 2006). The reasons for these confusions are partly found in different methods used (i.e. Klinger's dissection, dMRI, or axonal tracing). While all these methods have own advantages and limitations, the measurement of the anatomical structures of fiber tract itself in the entire hemisphere with ultra-high resolution is essential to resolve existing controversies. Here we analyzed the data collected from fixed but unstained serial microtome sections of two vervet monkey brains (*Chlorocebus aethiops sabaeus*; 2.4 and 1 years old; both male; section thickness, 60 μm) using polarized light imaging (PLI; Axer et al., 2011). This method enables visualization of fiber orientations in each bundle at micrometer resolution (in-plane resolution: 1.3 μm). This resolution enables visualization of how fibers from lateral geniculate nucleus merge to the SS, and also demonstrate the existence of the callosal (tapetum) and association fibers (ILF, VOF, and dorsal occipital bundles) as independent units of white matter architecture in the visual system. VOF occurs between the dorsal and ventral extrastriate areas and has fiber orientations different from that of ILF. We also found that ILF fibers merge with SS at their posterior end, while the ILF is a distinct bundle from SS at inferior temporal gyrus. This organization of SS and ILF explains the historical confusions on distinction between them. The tapetum contains callosal fibers and can clearly be segregated from U-fiber layers of the calcarine sulcus (stratum calcarinum), supporting the idea that the tapetum is a part of callosal fibers from the splenium. In sum, PLI resolves a number of controversies regarding the existence and definition of visual white matter tracts, and provides essential information for integrating findings from axonal tracing and dMRI on primate visual system.

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Poster

753. Visual Cortex: Cell Types, Functional Organization, and Connectivity

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

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Topic: D.07. Vision

Support: Wellcome Trust
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BBSRC

Title: Pattern of feedback connectivity from the frontal eye field of macaque to area lip

Authors: *B. AHMED, M. SMITH, A. J. PARKER, K. KRUG;
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Abstract: Lateral intraparietal (LIP) cortex plays a central role in visuo-motor information processing, saccade-planning and decision-making, and has reciprocal cortico-cortical connections with the Frontal Eye Field (FEF), an area that is involved in planning and execution of eye movements (saccadic, smooth pursuit and vergence). Moreover, there is evidence that FEF neurons display sensitivity to binocular disparity. Here, we report on the distribution of retrogradely labelled cells within primate FEF that project to a single point in area LIP.
In 5 Rhesus macaques (Macacca mulatta), we placed a single injection (~80 nL) of the retrograde tracer Cholera Toxin subunit beta (CTb) into LIP.
Anatomically, LIP can be divided into dorsal (LIPd) and ventral (LIPv) regions based on myelination density. In two macaques, tracer was injected into LIPd, layers 3 to 5; in one macaque at the border of LIPd and LIPv, layers 1 to 3a; and in two others within LIPv. We defined area FEF as the region within the anterior arcuate sulcus, bounded ventrally by the tapering off of layer 4 (Nissl stained sections) and dorsally by a decrease in myelination density (Gallyas stained sections). It's medial and lateral boundaries were based on: Atlas of the Rhesus Monkey Brain (Saleem and Logothetis). In parasagittal sections (1:5 series, 50 um thickness), we marked the position of CTb labelled cell bodies within FEF and surrounding regions using Neurolucida (Microbrightfield Ltd). In general, CTb labelled cells were sparsely distributed throughout the dorso-ventral and medio-lateral extent of FEF, there were regions of higher density which formed one or more clusters. Although labelled cells were located in both supra- and infra-granular layers, there was a preponderance of labelled pyramidal cells within layers 2 and 3.
Attentional cues are known to enhance gamma-band oscillatory coupling between FEF and area V4, a property of FEF supragranular neurons. The large number of labelled supragranular cells suggests a similar linkage between FEF and LIP - a feedback coupling that may enhance a top-down attentional influence on LIP.

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Poster

753. Visual Cortex: Cell Types, Functional Organization, and Connectivity

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 753.03/I19

Topic: D.07. Vision

Support: NIH Grant R01-EY027401
NIH Grant R01-MH111417

Title: Cortical magnification in human V1 and V2 predicts task performance around the visual field

Authors: *N. C. BENSON, M. CARRASCO, J. WINAWER;
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Abstract: Psychophysical performance varies across the visual field. Performance on most tasks drops precipitously with eccentricity. This pattern is reflected in visual cortex: the cortical magnification factor (CMF, cortical area per degree in the visual field) decreases with eccentricity, and population receptive field size (pRF) increases with eccentricity. Performance also varies systematically around the visual field at fixed eccentricity. For contrast sensitivity, acuity, and object recognition, performance is poorer on the upper than lower vertical meridian, and poorer on the vertical than horizontal meridian. These effects are most pronounced near the cardinal meridians [e.g., Carrasco et al 2000; Abrams & Carrasco 2012], rather than being general to hemifields or quarterfields. Silva et al. [2018 DOI:10.1016/j.neuroimage.2017.11.021] reported differences in CMF and pRF size between horizontal and vertical quadrants, and differences in CMF between upper and lower quadrants. Here, using a much larger dataset-181 subjects from the Human Connectome Project 7T Retinotopy Dataset [Benson et al. 2018, DOI:10.1167/18.13.23]-we asked whether there are differences in human V1 and V2 close to the cardinal meridians; horizontal vs. vertical and upper vs. lower vertical meridian. We measured the average width of the cortical representation of the vertical meridian, spanning ±15 degrees of polar angle from the V1/V2 boundary. This measure is robust to small errors in the localization of the V1/V2 border. We also compared pRF size for locations in V1 excluding regions near the vertical meridian to avoid possible blurring between V1 and V2. We found that the width of the upper (ventral) and lower (dorsal) vertical meridians were 5.0 mm and 8.8 mm, respectively, with only small differences in length. As a result, the surface area representing the lower vertical meridian, where performance is relatively good, is ~40% higher than the upper meridian, where performance is poorer. We also found that pRF size was smaller on the horizontal meridian, where performance is best, at all eccentricities than at oblique or vertical meridians. These polar angle patterns parallel the relationship among CMF, pRF size, and performance as a function of

eccentricity. We conclude that the representation of visual space on the surface of V1/V2 reflects task performance around the visual field.

Disclosures: **N.C. Benson:** None. **M. Carrasco:** None. **J. Winawer:** None.

Poster

753. Visual Cortex: Cell Types, Functional Organization, and Connectivity

Location: Hall A

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Program #/Poster #: 753.04/I20

Topic: D.07. Vision

Title: Uncovering network generation rules from large scale connectivity measurements

Authors: H. CHOI, B. H. HU, I. MAGRANS DE ABRIL, ***S. MIHALAS**;
Allen Inst. for Brain Sci., Seattle, WA

Abstract: Neural networks are marked by their complex connectivity at multiple scales, ranging from local cell-to-cell connectivity to large-scale networks of brain regions. Some of the key structural complexities of neural networks include modularity, hierarchical organization, spatial embedding, and sparse long-range connections. While such complexity is believed to underlie the computational flexibility of the brain, the generative principles that drive evolution of intricate connectivity among neuronal populations are not fully known. Here we propose methods to uncover network generative rules based on a single measurement of the state of the network in adulthood. To make this problem tractable, we assume: 1) stationarity of the plasticity rules in the period just before the measurement of the connectome, 2) exclusive dependence of changes in a connection on the activity relation of the nodes connecting it, and 3) dependence of the activity relation on chain graph motifs which begin or end on two nodes. With this set of assumptions, we can describe a family of plasticity rules. We use a Taylor expansion of these rules and search for coefficients of powers of the connection weight matrix and its transpose, to describe the effects of mono-synaptic interactions, di-synaptic interactions, and so on. In other words, these coefficients represent different effects on connection plasticity exerted by both direct and indirect interactions. To search for these coefficients, we implement two methods: a generative method based on generative adversarial networks (GANs) and an inference method based on distributions of connection weight powers. Our GAN method consists of a generator that iterates a fixed number of times over the generative rule defined on learnable parameters, and a discriminator that judges whether a given connectivity matrix is original or generated by the current generative function. On the other hand, our inference method searches for a set of matrix coefficients that minimizes an optimization function derived from Kullback-Leibler divergence between connection strength distributions of the true network and the learned network. To validate the feasibility of the generative rule, we first apply our two methods to artificial datasets generated by known generative rules and initial conditions. Then, we apply our

methods to a data-driven, mesoscopic mouse brain connectome (Knox et al. 2018), to uncover the generative rule for the mammalian cortical structure. We do observe that this method discovers plasticity rules which reproduce well the observed distribution of connection strength and network motifs in the mouse cortex.

Disclosures: H. Choi: None. **B.H. Hu:** None. **I. Magrans de Abril:** None. **S. Mihalas:** None.

Poster

753. Visual Cortex: Cell Types, Functional Organization, and Connectivity

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 753.05/I21

Topic: D.07. Vision

Title: Does the cortex implement dropout?

Authors: *J. SHANG[1,2], B. HU[1], R. IYER[1], S. MIHALAS[1];
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Abstract: Neuronal responses to repeated stimuli are highly variable. This variability has been attributed to state fluctuations (Engel et al., 2016) or intrinsic lognormal distributions (Buzsáki et al., 2014). Several theories propose a role for this variability in neural coding, e.g. sampling-based probabilistic representations (Orbán et al., 2016). Here, we characterize the trial-to-trial variability in large-scale two-photon calcium imaging from the Allen Brain Observatory (de Vries et al., 2018) and electrophysiological recordings using Neuropixel probes across multiple brain areas in response to a wide range of visual stimuli (e.g. drifting gratings, natural images, natural movies), in both passive and active behavioral states, with the goal of linking the observed trial-to-trial variability to cortical computations.
In response to a repeated natural movie stimulus, many neurons show highly variable responses to their preferred movie frame, with response distributions better fit by two-component Gaussian or lognormal distribution compared to one-component Gaussian. We find visual thalamic neurons having a higher fraction fit by a one component gaussian, and small differences across cell types and cortical areas with the highest fraction of one component gaussian in the superficial layers. Additional analyses of two-photon calcium imaging data during a visual change detection task showed similar results. This result cannot be simply explained by correlations with simple behavioral covariates such as the animal's running speed. As an additional control, removing state-dependent fluctuations captured by regressing single neuron responses against the activities of all the other simultaneously recorded neurons and fitting the residuals revealed similar results.
One possible functional interpretation of the observed two-component Gaussian distributions is dropout, a neural network training technique, whereby units are randomly "dropped out", thereby

reducing feature co-adaptation and improving model generalization (Srivastava et al., 2014). We find that units in deep neural networks trained with dropout also show similar two-component Gaussian response distributions. Future work will include other response distribution types and investigate the potential functional role for this variability.

Disclosures: **J. Shang:** None. **B. Hu:** None. **R. Iyer:** None. **S. Mihalas:** None.

Poster

753. Visual Cortex: Cell Types, Functional Organization, and Connectivity

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 753.06/I22

Topic: D.07. Vision

Support: NIH Grant 1U01MH114824-01

Title: Supervised classification of anatomical cell types in mouse visual cortex using arbor density and morphometric feature representations

Authors: *O. GLIKO, C. LEE, R. DALLEY, S. A. SORENSEN, U. SÜMBÜL;
Allen Inst. for Brain Sci., Seattle, WA

Abstract: While the classical approach to anatomical classification of neurons has revealed numerous insights since the time of Cajal, it lacks objective criteria and requires an expert anatomist for identification. On the other hand, unsupervised clustering of anatomical features often conflicts with qualitative insights. Here, we seek to test the objective reproducibility of qualitative definitions of neuronal types. In particular, we propose a new 2d registered arbor density representation of neuroanatomy and compare its performance against morphometric and topological features by training neural network-based supervised classifiers. Our approach is to avoid the calculation of explicit features, and rather treat the arbor trace as an image registered to a common local coordinate axis using the pia/white matter boundaries. We represent apical and basal dendrites of excitatory neurons, and axons and dendrites of inhibitory neurons separately with 2d arrays of size 120x4. While many thousands of traces of neuronal arbors exist, datasets with local anatomical landmarks are much smaller. Therefore, we apply novel data augmentation strategies, including cell type dependent random shift of the arbor density representation in the laminar direction, modulation of the intensity values of the representations, and elastic deformation of the 2d arbor density images. We achieve >80% cross-validated classification accuracy (chance at ~4%) on a dataset with 487 excitatory and inhibitory neurons from mouse visual cortex with 26 expert assigned qualitative types.

Disclosures: **O. Gliko:** None. **C. Lee:** None. **S.A. Sorensen:** None. **U. Sümbül:** None. **R. Dalley:** None.

Poster

753. Visual Cortex: Cell Types, Functional Organization, and Connectivity

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 753.07/I23

Topic: H.02. Human Cognition and Behavior

Support: NRSA to Schintu
NRSA to Freedberg
BCS-1534823 to Shomstein

Title: Inhibitory rTMS over the parietal cortex modulates functional connectivity

Authors: *S. SCHINTU[1,2], C. A. CUNNINGHAM[1], M. V. FREEDBERG[1], S. J. GOTTS[3], S. S. SHOMSTEIN[2], E. M. WASSERMANN[1];
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Abstract: Hemispatial neglect of the right side of space is thought to result from hyper-activation of the left (intact) frontoparietal network, due to its release from inhibition by the right hemisphere. Nominally inhibitory rTMS over the left posterior parietal cortex (PPC) typically improves neglect and normalizes the hyper-active left frontoparietal functional connectivity (FC). Whereas if delivered over the right PPC in healthy participants shifts midline judgment rightward, mimicking neglect behavior, supposedly by changing frontoparietal FC. We investigated whether nominally inhibitory rTMS over the right PPC produces neglect like behavior and changes frontoparietal FC. In counterbalanced order, 17 participants received 40 sec of continuous theta-burst rTMS at 80% of active motor threshold, to the right PPC or vertex (control site) in sessions separated by ≥ 5 days. Before and after rTMS, participants underwent a 10-minute resting state fMRI scan and performed line bisection tasks. The PPC target was area 1 of the intraparietal sulcus (IPS1), where TMS has been shown to affect visuospatial behavior. The dorsal network was defined by intrinsic functional connectivity. As expected, participants exhibited a rightward shift in line bisection judgment after rTMS over the right PPC. However, the direction of FC change in the right hemisphere was highly variable and there was no overall effect of PPC vs. vertex rTMS. A whole brain, seed-based, analysis found an increase in FC between the PPC target and the left superior temporal gyrus (STG), which is a central node for visuotemporal attention. Follow up analysis showed that the left STG increased FC with the right medial frontal gyrus and right precuneus, both nodes of the frontoparietal network. Local inhibition of the right PPC shifts visuospatial behavior to the right through a mechanism that remains ill defined. Here we show that nominally inhibitory rTMS over the right PPC increases FC with STG (critical parts of the visual attention network) in the contralateral hemisphere,

which, in turn, becomes more connected with areas of the right frontoparietal network. These findings show that local inhibition of the right PPC reshapes the attentional network by recruiting regions of the contralateral hemisphere.

Disclosures: S. Schintu: None. **C.A. Cunningham:** None. **M.V. Freedberg:** None. **S.J. Gotts:** None. **S.S. Shomstein:** None. **E.M. Wassermann:** None.

Poster

753. Visual Cortex: Cell Types, Functional Organization, and Connectivity

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 753.08/DP09/I24

ControlExtraData.DynamicPosterDisplay:
Dynamic Poster
Topic: D.07. Vision

Support: Intramural Research Program of the NIH, NINDS

Title: 3d MRI-based marmoset brain atlas version 3: *In vivo* population-based MRI, dti and CT templates, and analysis tools

Authors: *C. LIU[1], C. C.-C. YEN[2], D. SZCZUPAK[3], X. TIAN[1], G. DANIEL[4], A. C. SILVA[5]; [1]NINDS/NIH, Bethesda, MD; [2]NINDS/LFMI/CMS, Natl. Institues of Hlth., Bethesda, MD; [3]Natl. Inst. of Hlth., North Bethesda, MD; [4]NIMH/NIH, Bethesda, MD; [5]Dept. of Neurobio., Univ. of Pittsburgh, Pittsburgh, PA

Abstract: By acquiring super-resolution MRI of ex-vivo brains, we had constructed a full 3D anatomical atlas of the marmoset brain. Version 1 contained the cortical parcellation, and version 2 the white matter pathways. However, these two previous versions were based on only a few brains of male marmosets, which imposes a limitation to their application in neuroimaging studies of large cohorts of animals. To address this problem, we collected in-vivo multi-modal MRI from 27 marmosets of both genders. The new in-vivo MRI dataset includes anatomical T1-weighted, T2-weighted, and multi-shell diffusion MRI, as well as functional resting-state fMRI. From the anatomical MRI, head profiles were created and compared to profiles based on CT images of the same subjects' heads. Analysis of the new MRI- and CT-based dataset revealed significant variations in head and brain shape and size, regional volumes of several brain structures, and brain connectivity, highlighting substantial individual variabilities in the marmoset population. We used the new dataset to create multimodal brain templates and co-registered them into a new and standard population-based template space, which was anatomically labeled using previous versions. We constructed population-based tissue types to facilitate volumetric analyses and built a population-based brain surface to facilitate 3D visualization and surface-based analyses. Combining information obtained from the MRI with

that of the CT dataset allows a more accurate frameless estimation of stereotaxic coordinates of different brain regions, which can be used, for example, for a more precise surgical planning. These templates and associated tools will comprise version 3 of our marmoset brain atlas project, which will significantly aid in a wide range of MRI and connectome studies.

Disclosures: C. Liu: None. **C.C. Yen:** None. **D. Szczupak:** None. **X. Tian:** None. **G. Daniel:** None. **A.C. Silva:** None.

Poster

753. Visual Cortex: Cell Types, Functional Organization, and Connectivity

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 753.09/I25

Topic: D.07. Vision

Support: ARC CIBF Grant CE140100007

Title: Strong correlation between extracellular spike waveform and spatial receptive field type in cat visual cortex

Authors: *S. SUN[1,2], H. MEFFIN[2,1], Y. WONG[3,4], S. L. CLOHERTY[3], A. ALMASI[2], M. YUNZAB[2], Y. JUNG[1,2], M. R. IBBOTSON[2,1];
[1]Optometry and Vision Sci., The Univ. of Melbourne, Parkville, Australia; [2]Natl. Vision Res. Inst., Melbourne, Australia; [3]Physiol., [4]Electrical & Computer Systems Engin., Monash Univ., Clayton, Australia

Abstract: Extracellular spike waveforms from recordings in the visual cortex have been classified into either regular spiking (RS) or fast spiking (FS) units, which are often associated with excitatory and inhibitory neurons, respectively. While both these types of spikes have waveforms with negative first phases, we show that there are also distinct classes with positive first phases, which are not regularly reported. The spatial receptive fields (RFs) of these different spike waveform types were estimated and we found that each spike type had distinctly different RF structures. 837 single units (SUs) in the cat visual cortex were classified into five categories by the shape of their spike waveforms: RS units (52%, 432/837) which are biphasic, have a dominant negative peak, and a slow inclining slope at the end of the waveform; FS units (22%, 185/837) which are biphasic, have a dominant negative peak, and a fast declining slope at the end of the waveform; triphasic spiking units (TS, 9%, 74/837) which have a positive first peak that is >10% of the negative peak, followed by a large negative peak and then a smaller positive peak; compound spiking units (CS, 3%, 27/837) which are also triphasic but with a significantly longer waveform; and positive spiking units (PS, 14%, 118/837) which have a positive peak greater than the negative peak. Of these 837 SUs, 231 had their spatial RFs estimated as the spatial filters in a general non-linear model of response to white-Gaussian noise (WGN) and

classified as either oriented and Gabor-like (orientation bandwidth < 90°) or non-oriented and blob-like (orientation bandwidth > 110°). RS and FS units had mostly oriented RFs (95%, 68/72; 99%, 71/72, respectively), while TS, CS and PS units had mostly non-oriented RFs (56%, 14/25; 75%, 6/8; 78%, 28/36, respectively). These non-oriented RFs are very similar to the centre-surround RFs reported in the lateral geniculate nucleus. We calculated several response properties that are statistically distinguishable between cortical and thalamic neural populations: spike-rate, burstiness, and response latency. On average, PS units had significantly higher spike-rate (t-test, $p < 0.05$), significantly higher proportion of burst spikes ($p < 0.001$), and significantly shorter response latency ($p < 0.05$) to RS and FS units. Thus, our results suggest that PS units, which have mostly non-oriented RFs and thalamic-like response properties, may correspond to recordings from thalamic axons projecting to the visual cortex, while RS and FS units correspond to cortical neurons, which have mostly oriented RFs. This would allow cortically implanted electrodes to record activity from thalamus and cortex simultaneously.

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Poster

753. Visual Cortex: Cell Types, Functional Organization, and Connectivity

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 753.10/I26

Topic: D.07. Vision

Support: NIH Grant 1ROI1EY02231801A1 to KGS
NIH Grant 1RO1EY02391501A1 to KGS
NIH Grant 5T32EY020485 to VSN
NIH Grant F31EY027201 to JG

Title: Apparent cortical thinning in ventral temporal cortex from childhood to adulthood is associated with increased myelination

Authors: *V. S. NATU[1], J. GOMEZ[2], M. BARNETT[3], B. L. JESKA[1], Z. ZHEN[4], E. KIRILINA[5], C. JAEGER[5], S. COX[1], K. S. WEINER[6], N. WEISKOPF[5], K. GRILL-SPECTOR[1]; [1]Stanford Univ., Stanford, CA; [2]Univ. of California Berkeley, Berkeley, CA; [3]Univ. of Pennsylvania, Philadelphia,, PA; [4]Brain and Cognitive Sci. Sch., Beijing Normal Univ., Beijing, China; [5]Max Planck Inst. for Human Cognitive and Brain Sci., Leipzig, Germany; [6]Psychology, Univ. of California, Berkeley, Berkeley, CA

Abstract: Human cortex appears to thin during childhood development. However, the underlying microstructural mechanisms are unknown. Using functional, quantitative, and diffusion magnetic resonance imaging (MRI) in children and adults, we tested three hypotheses

related to cortical thinning in the ventral temporal cortex (VTC) of 26 children (ages 5-12) and 27 adults using independent and complementary measurements of T_1 relaxation time from qMRI and mean diffusivity (MD) from dMRI. ***Pruning hypothesis:*** CT decreases from childhood to adulthood due to tissue reduction. Pruning predicts no changes or increases in T_1 relaxation time and MD across development. ***Growth hypothesis:*** white/gray boundary shifts deeper into cortex due to increased myelination, making the cortex appear whiter in adults. Myelin growth predicts lower T_1 and lower MD in adults than children. ***Cortical morphology:*** A third possibility is that changes in cortical morphology (cortical folding and surface area) during childhood development may result in thinning. Results show that from age 5 to adulthood T_1 and MD decreased in face- and character-selective regions within lateral VTC. These decreases occurred in mid and deep cortex, as well as in the adjacent white matter. T_1 reduction was also observed longitudinally in these brain regions in children. T_1 and MD decreases (i) were consistent with tissue growth and (ii) were correlated with the apparent cortical thinning. Tissue growth is consistent with increased myelination, which we validated using histological analyses in adult post-mortem brain tissue. In contrast, in a place-selective region located in medial VTC, we found no development of T_1 or MD after age 5 even as cortex thinned across development. Here, we found that cortical thickness was correlated with cortical morphology. These findings suggest that lateral VTC likely becomes more myelinated from childhood to adulthood, affecting the contrast of MR images, and in turn, the apparent gray-white boundary. Consequently, our data have broad ramifications for understanding both typical and atypical brain development, as well as for clinical conditions implicating myelin, including dyslexia, autism, and multiple sclerosis.

Disclosures: V.S. Natu: None. **J. Gomez:** None. **M. Barnett:** None. **B.L. Jeska:** None. **Z. Zhen:** None. **E. Kirilina:** None. **C. Jaeger:** None. **S. Cox:** None. **K.S. Weiner:** None. **N. Weiskopf:** None. **K. Grill-Spector:** None.

Poster

753. Visual Cortex: Cell Types, Functional Organization, and Connectivity

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 753.11/I27

Topic: D.07. Vision

Support: Greater Milwaukee Foundation

Title: Evidence of object-based warping in early visual cortex

Authors: G. GURARIY[1], T. J. VICKERY[2], *A. S. GREENBERG[1];
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Abstract: In the visual domain, objects constitute high-level percepts that result from the spatial grouping of low-level sensory information. Interestingly, it has been demonstrated that the visual space within an object appears warped in a systematic manner. Specifically, when two items (i.e., dots) are placed within an object, they are perceived to be further apart relative to equidistant items that are not enclosed within an object. This distortion of space results in a robust visual illusion that has been observed under a variety of parameters and viewing conditions (Vickery & Chun, 2010). However, the neural mechanisms underlying this warping have not yet been explored. Here, we use fMRI to investigate the neural representation of object-based warping in different areas along the visual hierarchy. To measure behavioral effects (outside the scanner), human participants adjusted the perceived distance between two letters so as to perceptually match the distance between two reference letters (appearing either enclosed within an object or not). From this we computed the precise spatial locations at which the letters are perceived as a consequence of the object-based warping. During fMRI, participants performed a discrimination task (among four letters, one located in each screen quadrant) with the following three conditions: (1) all 4 letters were equidistant from one another, (2) two letters in one visual hemifield were enclosed within an object, and (3) two letters in one hemifield appeared without an object at the "warped" distances (from individual participant behavior). Additionally, we ran two separate localizers: (1) a spatial localizer to identify the retinotopic locations of the letters from conditions 1-3, and (2) a meridian localizer to identify early visual areas (V1-V3). The spatial localizer produced (a) two retinotopic ROIs for the letters enclosed by an object (conditions 1 & 2) and (b) two retinotopic regions corresponding to the "warped" spatial positions (condition 3). The mean BOLD response was extracted from each of the four ROIs for all three conditions. With no object present (condition 1), spatially localized ROIs in V1 showed the expected retinotopically-specific activation pattern of equidistant letters. Importantly, however, letters enclosed within an object (condition 2) elicited activity within retinotopic regions corresponding to the "warped" spatial locations (similar to condition 3). We interpret this as evidence of object-based warping in visual cortex, likely caused by feedback from higher level visual areas.

Disclosures: G. Gurariy: None. **T.J. Vickery:** None. **A.S. Greenberg:** None.

Poster

753. Visual Cortex: Cell Types, Functional Organization, and Connectivity

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 753.12/I28

Topic: D.07. Vision

Support: NIH Grant EY021462

Title: Neural straightening of natural image sequences in macaque V1 and V2

Authors: *Y. BAI[1], O. HÉNAFF[2], C. ZIEMBA[1], E. P. SIMONCELLI[3], R. L. T. GORIS[1];
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Abstract: A fundamental goal of sensory processing is predicting future states of the environment. Making visual predictions is challenging: under natural circumstances, visual input (the stream of images on the retina) follows complex temporal trajectories that are difficult to extrapolate. We've hypothesized that the visual system alleviates this problem by transforming its inputs into neural representations that follow "straighter" temporal trajectories (Hénaff et al., 2019), facilitating prediction. Previously, we provided psychophysical (Hénaff et al., 2019) and physiological (Bai & Hénaff et al., SfN 2018) support for this theory. Here, we investigate how temporal straightening emerges from the cascade of transformations performed by the visual system.

If temporal straightening is a fundamental goal of visual processing, we might expect that each stage in the visual hierarchy further straightens its inputs. To test this hypothesis, we compared the straightness of natural videos with the straightness of neural population activity elicited by these videos in the primary and secondary visual cortex (area V1 and V2, respectively). We presented random sequences of static frames taken from 16 short videos and used multi-electrode arrays to record population activity in the visual cortex of awake, fixating macaque monkeys (four V1 populations, ranging in size from 52-87 units; three V2 populations, 84-114 units). We obtained temporal trajectories of population activity by arranging neural responses in the videos' natural order.

We found that neural straightening of natural videos increases along the visual hierarchy. Both in V1 and V2, neural response trajectories were straighter than their pixel-domain inputs. This effect was more prominent in V2 than in V1. To test whether straightening is specific to natural videos, we also presented artificial videos that fade from an initial to a final frame. These movies, which follow straight paths in the pixel-domain, elicited the opposite effect in their neural response trajectories, which were significantly curved. Together, these results suggest that temporal straightening may be an objective that shapes the function of multiple stages of the primate visual system.

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Poster

753. Visual Cortex: Cell Types, Functional Organization, and Connectivity

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 753.13/I29

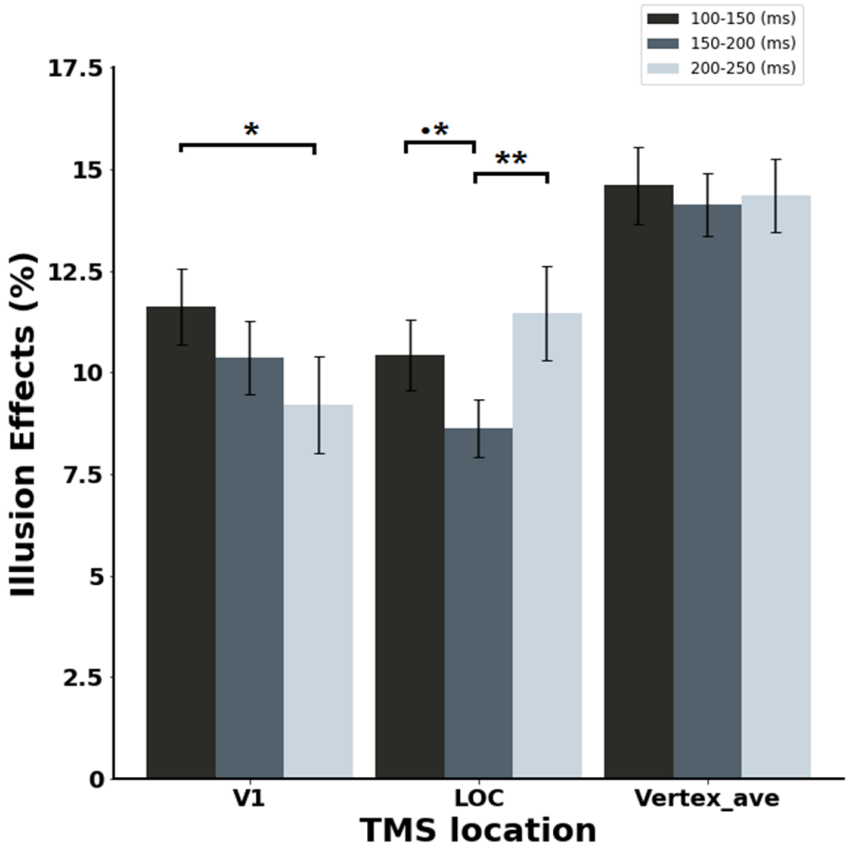
Topic: D.07. Vision

Support: CSC scholoarship
Marga and Walter Boll Foundation

Title: The role of the primary visual cortex and the lateral occipital complex in scaling size information -- A TMS study

Authors: *H. ZENG[1], G. R. FINK[1,2], R. WEIDNER[1];
[1]Res. Ctr. Juelich, Juelich, Germany; [2]Dept. of Neurol., Univ. Hosp. Cologne, Cologne Univ., Cologne, Germany

Abstract: Neural activation in the primary visual cortex (V1) reflects perceived size rather than the retinal size of the stimulus, suggesting that feedback modulations possibly from extrastriate regions alter retinal size information. In particular, lateral occipital complex (LOC) may contribute to such feedback modulation as it is known to be highly involved in object size processing. To test for causal contributions of such feedback modulations from LOC on size representations in V1, we investigated the dynamics of relevant processes using transcranial magnetic stimulation (TMS). Specifically, we briefly disrupted the ongoing activity in V1 and LOC at early (100-150 ms SOA), intermediate (150-200 ms SOA), and late (200-250 ms SOA) time windows while participants performed size judgement tasks in either an illusory or a neutral context. Thus, TMS over V1 and LOC allowed determining whether these two brain regions are relevant for generating phenomenological size impressions. Furthermore, the temporal order of TMS effects allowed inferences on the dynamics of information exchange between the two areas. Notably, if feedback signals from LOC to V1 are crucial for generating altered size representations in V1, then TMS effects over V1 should be observed simultaneously or later than the effects following LOC stimulation.
Data from 20 healthy participants showed that TMS over both V1 and LOC impaired the illusion perception as compared to vertex stimulation. However, the strongest TMS effect of V1 occurred later than those of LOC supporting the view of a functionally relevant feedback modulation from LOC to V1 in scaling size information. The results suggest that perceived size representations are formed after feedback information from higher visual regions has been received. In sum, size perception emerges from the interaction between higher and low-level visual areas and feedback information flow plays an essential role.



Disclosures: **H. Zeng:** None. **G.R. Fink:** None. **R. Weidner:** None.

Poster

753. Visual Cortex: Cell Types, Functional Organization, and Connectivity

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 753.14/I30

Topic: D.07. Vision

Support: NIH EY024662

Title: Neural correlates of target-background orientation similarity masking in primate V1

Authors: *S. C.-Y. CHEN, Y. CHEN, W. S. GEISLER, III, E. SEIDEMANN;
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Abstract: Searching for and identifying targets in the natural environment is a primary function of our visual system. Backgrounds that look similar to the search target are well-known adversaries to visual search. However, there is no common agreement on the neural basis of

target-background similarity masking. Here, we examined how orientation similarity affects behavior sensitivity and neural-detection sensitivity in macaque V1.
Macaque monkeys (n=2) were trained to detect an additive Gabor target (4 cpd, 0.33° FWHM, 1.5-3° eccentricity) on grating backgrounds matched in spatial frequency, but of variable orientation. As the monkeys performed the task, we recorded V1 neural responses using voltage-sensitive-dye (VSD) imaging. As V1 is strongly selective to orientation, we hypothesized that V1 neural activity at the scale of orientation columns would correlate with behavioral detection performance.
As in human subjects, the monkeys' behavioral detection performance was worst when the orientation of the background was aligned to the target. Performance improved as the background rotated towards the orthogonal orientation. When the background was orthogonal to the target and background contrast was low, performance can reached nearly same level as for uniform (blank) background.
We next examined V1 responses at the orientation-columns scale. As expected, in the background-only and target-only trials, the population response peaked in the columns preferring the stimulus orientation. With the target added to the background, the target-evoked response (i.e., target + background response minus background response) displayed complex bi-phasic dynamics. In the first 50 ms, the response was strongest when the target and background orientations were aligned. This paradoxical response is anti-correlated with the behavioral masking effect.
After the first 50 ms, the target-evoked response was strongly suppressed by the aligned background, was less suppressed as the background rotated away, and approached the response level on uniform background when the background was orthogonal. V1 responses during this period are therefore positively correlated with the monkeys' detection performance. In addition, we found that the peak of the target-evoked population response deviated from target orientation, exhibiting a clear repulsion away from the background orientation.
A complete model of how target-background orientation similarity affects behavior may need to include the various components of the V1 neural population dynamics we have observed.

Disclosures: **S.C. Chen:** None. **Y. Chen:** None. **W.S. Geisler:** None. **E. Seidemann:** None.

Poster

753. Visual Cortex: Cell Types, Functional Organization, and Connectivity

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Program #/Poster #: 753.15/I31

Topic: D.07. Vision

Support: National Natural Science Foundation of China(31530029, 31625012, and 31371111)

Title: Mechanisms of motion boundary perception in macaque V2

Authors: *H. MA, P. C. LI, J. M. HU, S. D. ZHU, X. Y. CAI, Q. L. SONG, Y. LI, C. FANG, K. YAN, H. D. LU;
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Abstract: Our visual system can use multiple visual cues to detect the boundary of an object. Among these cues, motion cues are especially useful when luminance and color cues are unreliable (e.g. camouflage). A subset of orientation neurons in the ventral visual pathway have been found (Marcar et al.,2000; Mysore et al.,2006) that are sensitive to motion boundaries (MBs) created by relative motion. However, it is not clear about the neural circuits for such selectivity and whether these MB neurons in deed underlies the behavioral MB detection. To study these questions, we recorded neuronal activity in area V2 of macaque monkeys while they were performing a MB-orientation discrimination task. V2 regions selected for microelectrode array implant included both orientation domains and direction domains that were first identified with intrinsic signal optical imaging. MB stimuli were created by two adjacent patches of random dots in which dots were moving in opposite directions. We found ~30% orientation neurons in V2 exhibited MB-orientation selectivity, and their preferred MB orientations were consistent with their preferences for luminance gratings. When the difficulty of the MB-orientation discrimination task was adjusted by lowering the coherence or brightness of the moving dots, trial-to-trial variability of MB neurons' responses (choice probability, CP) was correlated with the monkeys` behavioral choices. For these MB neurons, their tuning to MB orientation emerged at ~85ms, which was ~50ms later than their visual latency (~35ms). This delay became even longer when the MB was moved away from neurons' RF centers, although their visual latency was not affected. This MB-orientation tuning latency was similar to the surround tuning latency of V2 direction-selective neurons when they responded to motion contrast between their RF center and surround. Pair-wise analysis also showed a general correlation of activity between neuron pairs, including direction-selective neuron and MB neuron pairs. Together, our preliminary results indicate that V2 is an important area for behavioral MB orientation discrimination, and intra-areal circuits in V2 may contribute substantially to this task.

Disclosures: H. Ma: None. **P.C. Li:** None. **J.M. Hu:** None. **S.D. Zhu:** None. **X.Y. Cai:** None. **Q.L. Song:** None. **Y. Li:** None. **C. Fang:** None. **K. Yan:** None. **H.D. Lu:** None.

Poster

754. Visual Cortex: Functional Architecture and Circuits II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 754.01/I32

Topic: D.07. Vision

Support: NIH Grant EY022338

Title: Network analysis of cortical dynamics implicates untuned neurons in visual stimulus coding

Authors: *M. LEVY[1], O. SPORNS[3,4], J. N. MACLEAN[2,1];
[1]Committee on Computat. Neurosci., [2]Neurobio., The Univ. of Chicago, Chicago, IL;
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Abstract: Unbiased and dense sampling of large populations of layer 2/3 pyramidal neurons in mouse primary visual cortex (V1) reveals two functional sub-populations: neurons tuned and untuned to drifting gratings. While tuned neurons have been thoroughly studied, untuned neurons remain poorly understood. Here we construct functional networks (FNs) of up to 350 neurons in V1 (20 datasets), summarizing the partial pairwise correlation structure as a directed and weighted graph, comprised of both tuned (60%) and untuned (40%) neurons. We then employ graph theoretic measures to evaluate the interrelationship between these functional classes of neurons. We find that FNs are stimulus-specific, as graphs of orthogonal directions are highly dissimilar and neighboring directions of drifting gratings are more similar than chance. The dissimilarity between FNs is primarily driven by the functional connectivity between untuned neurons since these connections are consistently different regardless of stimulus similarity. V1 FNs have a rich club topology that spans broad degree distributions and untuned neurons form a rich club of strong edge weights. Untuned neurons tend to be ranked higher than tuned neurons in random walks performed on these networks. Collectively these results suggest that untuned neurons occupy unique topological positions that render them ideal elements to facilitate read out of small differences in grating direction. To assess the potential of untuned neurons for decoding, we establish a two-phase decoding model of V1 and a downstream area, where 12 direction-specific FNs, inferred from data, are instantiated as recurrent neural networks. The spiking output of each model is then used as inputs to a shallow feed-forward neural network trained in a supervised learning manner. We are able to accurately decode the direction of drifting gratings. Permuting connections from either tuned or untuned neurons to the output layer produces a comparable degradation in decoding performance. Taken together, our results demonstrate that untuned neurons are integral to V1 FNs and suggest that tuning properties arise from network interactions involving tuned and untuned neurons in a way that facilitates decodability and separation between similar stimuli downstream.

Disclosures: **M. Levy:** None. **O. Sporns:** None. **J.N. MacLean:** None.

Poster

754. Visual Cortex: Functional Architecture and Circuits II

Location: Hall A

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Program #/Poster #: 754.02/I33

Topic: D.07. Vision

Support: Pritzker Fellowship
NSF GRFP (DGE-1746045)

Title: Functional network topology and computation in mouse visual cortex during stimulus presentation

Authors: *E. DE LAITTRE[1], J. MACLEAN[2];
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Abstract: In the brain, information is computed and transmitted in the activities of networks of interconnected neurons. Analyzing the structure of functional interactions in these networks can provide insight into both processes. Functional networks summarize statistical dependencies in neural dynamics, creating a web of pairwise relationships where nodes correspond to individual neurons and edges correspond to functional (or effective) connections between neurons. Partial information decomposition is a recently developed tool that partitions the information passing from a number of sources (e.g. neurons) to a target (another neuron) into unique, redundant, and synergistic components. In this framework the synergistic component is interpreted as computation. Recent work in organotypic slice cultures has shown that the topological position of a neuron in the functional network relates to the amount of computation it performs (Timme et al., 2016; Faber et al., 2019). Here we explore whether functional networks that summarize *in vivo* cortical activity exhibit this same relationship between functional network topology and computation. Using two-photon calcium imaging, we recorded the activity of large populations of excitatory neurons in layer 2/3 of mouse primary visual cortex while mice viewed drifting gratings. From time series of somatic fluorescence we create functional networks where weighted, directed edges capture the functional relationships between pairs of neurons. At points where two directed edges converge on a single (target) neuron, we use partial information decomposition to quantify the amount of computation performed by the target neuron relative to the input of the two source neurons (i.e. amount of synergistic information present). Collecting data in vivo allows us to also consider how structured input to the circuit (in the form of visual stimulus) influences network topology, computation, and the relationship between the two. To do so we perform these analyses on data from each stimulus condition separately (one of twelve directions of drifting grating) and on data from the presentation of an unstructured visual stimulus (mean luminance matched gray). Partial information decomposition is a promising tool for dissecting functional relationships between multiple dynamic components, such as the activities of neurons in local cortical networks. Identifying components of network topology that support computation has the potential to reveal mechanisms of information processing at the neural circuit level.

Disclosures: E. de Laittre: None. **J. MacLean:** None.

Poster

754. Visual Cortex: Functional Architecture and Circuits II

Location: Hall A

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Program #/Poster #: 754.03/I34

Topic: D.07. Vision

Support: NIH Grant R01EY022338

Title: Prediction of single trial cortical neuronal dynamics through strong positive recurrent interactions

Authors: S. KOTEKAL[1], ***J. N. MACLEAN**[1,2];
[1]Neurobio., The Univ. of Chicago, Chicago, IL; [2]Computat. Neurosci., Univ. of Chicago, Chicago, IL

Abstract: To develop a complete description of sensory encoding, it is necessary to account for trial-to-trial variability in cortical neurons. Using a generalized linear model with terms corresponding to the visual stimulus, mouse running speed, and experimentally measured neuronal correlations, we modeled single trial dynamics of L2/3 murine visual cortical neurons to evaluate the relative importance of each of these factors to neuronal variability. We find single trial predictions improve most when conditioning on the experimentally measured local correlations in comparison to predictions based on the stimulus or running speed. Specifically, accurate predictions are driven by positively co-varying and synchronously active functional groups of neurons. Including functional groups in the model enhances decoding accuracy of sensory information compared to a model that assumes neuronal independence. Functional groups, in encoding and decoding frameworks,provide an operational definition of Hebbian assemblies in which local correlations can largely explain neuronal responses on individual trials.

Disclosures: J.N. MacLean: None. **S. Kotekal:** None.

Poster

754. Visual Cortex: Functional Architecture and Circuits II

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Support: NIH T32 GM007281 (ZAZ)
University of Chicago Naomi Ragins-Goldsmith endowed Fellowship (ZAZ)
NIH R01 EY022338 (JNM)
NIH U19 NS107464 (JHRM)

Title: Divisive normalization in the responses of V1 neurons in alert mice measured using calcium indicators

Authors: *Z. A. ZAYYAD[1,2,3], J. H. R. MAUNSELL[2,3,4,5], J. N. MACLEAN[2,3,4,5];
[1]Med. Scientist Training Program, [2]Dept. of Neurobio., [3]Committee on Computat. Neurosci., [4]Grossman Inst. for Neuroscience, Quantitative Biol. and Human Behavior, [5]These authors contributed equally, Univ. of Chicago, Chicago, IL

Abstract: Divisive normalization is a form of non-linear input summation found in diverse modalities and species. It has been described in systems ranging from the olfactory periphery in fruit flies to higher-order cognitive representations related to attention and decision-making in macaque monkeys. But while divisive normalization is widespread in the brain, the circuit mechanisms that underlie it are not well understood. We imaged hundreds of excitatory L2/3 neurons expressing GCaMP6s under the Thy1 promoter in mouse V1 at ~20-30 Hz in individual animals through a chronically implanted window. During imaging, we presented plaid cross-inhibitory stimuli made of two superimposed orthogonal drifting gratings, each presented at one of five contrasts (for a total of 25 stimuli). We imaged 10 fields of view in five awake, ambulating mice, recording calcium responses from 2949 cells. Of those, 668 preferred one of the orientations in the plaid stimulus. For this subset of neurons, we calculated a divisive normalization index by comparing the response evoked by a plaid stimulus to the sum of the responses to the plaid's component gratings. We observed a range of index values for divisive normalization, with some cells showing robust normalization and others giving responses that were closer to a linear sum of the responses to the individual gratings. The overall distribution was similar to that previously reported in monkey visual cortex. We are currently extending these results with electrophysiological measurements of V1 responses to the same stimuli. Our initial results suggest that the mouse will support combinations of genetic, electrophysiology, imaging, and psychophysics techniques to further elucidate the circuit mechanisms that produce divisive normalization.

Disclosures: Z.A. Zayyad: None. **J.H.R. Maunsell:** None. **J.N. MacLean:** None.

Poster

754. Visual Cortex: Functional Architecture and Circuits II

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Program #/Poster #: 754.05/I36

Topic: D.07. Vision

Support: NIH Grant EY022338

Title: Specific topological features in functional networks contribute to the accuracy of a linear encoding model of single trial neocortical neuronal dynamics

Authors: *C. YU, M. LEVY, J. N. MACLEAN;
Univ. of Chicago, Chicago, IL

Abstract: The activity of neurons in sensory cortices covary on a moment to moment basis. We represent the co-activity of neurons as a directed and weighted functional network, constructed from somatic fluorescence changes from up to 350 neurons in mouse primary visual cortex (V1) in response to 12 directions of drifting gratings. Weights of functional connections, called edges, are assigned using partial pairwise correlation, and the directionality of each edge is assigned according to the lag that produces the maximal correlation, with lag 0 resulting in a reciprocal edge. We find that the resulting functional network is sparse and that reciprocal edges are more frequent than expected by chance, especially amongst the strongest edge weights. Moreover, reciprocal edges lead to enhanced clustering of a higher-order pattern, called motif, in which a neuron acts as a middle-man between two other correlated neurons. We employ functional networks in a simple linear encoding model of a single trial where each neuron's activity is predicted from the activity of its functionally connected counterparts. To determine which specific topological features are crucial for accurately modeling single neuron dynamics, we evaluated the interaction between topology and edge weights by computing the geometric mean of the edge weights in the motifs. We find that middle-man motifs tend to have, on average, large geometric means. In turn, the activity of neurons with high clustering scores of the middle-man motif are more accurately modeled using the activity of their functional neighbors compared to the rest of the population. By treating different directions of drifting gratings as the latent variables in a coupled hidden-markov-model (HMM), we further evaluate the role of reciprocal edges and higher-order motifs in accurate modeling of dynamics. Taken together, our results suggest that functional network topology has highly non-random features and that specific local circuit interactions support stimulus coding.

Disclosures: C. Yu: None. **M. Levy:** None. **J.N. Maclean:** None.

Poster

754. Visual Cortex: Functional Architecture and Circuits II

Location: Hall A

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Topic: D.07. Vision

Support: NIH Ro1NS094184
R01EY022338

Title: Orientation and direction selectivity for neurons in V1 and V2 of the mouse

Authors: *D. RHEE[1], C. MCKINNON[2], J. N. MACLEAN[1], S. SHERMAN[1];
[1]Neurobio., [2]Computat. Neurosci., Univ. of Chicago, Chicago, IL

Abstract: Neurons in visual cortex are known to be highly selective to the orientation and direction of moving stimuli. Orientation and directional tuning have traditionally been assessed using simple geometric stimuli, such as drifting sinusoid gratings. How responses driven by these simplistic stimuli relate to responses to more complex naturalistic scenes is poorly understood. Here, we use 2-photon Ca^{2+} imaging to measure activity of single neurons in response to sinusoidal gratings, visual textures, and natural scenes moving in 12 directions in primary (V1) and secondary (area LM, V2) visual cortex in awake Thy-1 GCaMP6s mice. We then used the vector based approach to establish significant orientation selectivity and direction selectivity [Mazurek M, Kager M, Van Hooser SD (2014) Front Neural Circuits 8:92] to each of these three stimuli within the same neuron in these 2 areas. As expected, neurons in V1 and V2 were highly tuned to both orientation and direction of drifting sinusoidal gratings. Of neurons recorded in V1 >1/3 were tuned for direction and orientation. In contrast, <1/10 were tuned for direction and ~40% for orientation in V2. In comparisons between V1 and V2, grating and movie stimuli elicited different proportions of tuned cells; but texture stimuli elicited roughly equal proportions. Next we examined the differences in the preferred angle of orientation to each stimulus within single neurons. Surprisingly, we found both in V1 and V2 that the difference between preferred orientation for textures versus movies was relatively small, but for gratings versus either textures or movies was much larger. Finally, we examined the strength of tuning of individual neurons (based on normalized vector length) across stimuli and found this to be correlated for all three stimulus types in both V1 and V2. Our primary conclusion is that responses based on gratings serve as a poor predictor of how neurons respond to naturalistic stimuli. Perhaps the use of gratings, where orientation and direction is concatenated, poorly predicts the response to natural stimuli if cells have independent tuning vectors for direction vs orientation.

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Poster

754. Visual Cortex: Functional Architecture and Circuits II

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Program #/Poster #: 754.07/I38

Topic: D.07. Vision

Support: CIHR grant MOP-119498

Title: Laminar functional connectivity in primary visual cortex

Authors: *J. NING[1], G. LI[2], C. BAKER[2];
[1]Dept. of Physiol., [2]Dept. of Ophthalmology, McGill Univ., Montreal, QC, Canada

Abstract: A laminar structure of 6 layers is conserved across different areas of mammalian cerebral cortex. In primary visual cortex, neurons in layer 4 receive direct input from the lateral geniculate nucleus and then project to layers 2, 3 and 5. However the laminar functional connectivity across laminae is not yet well understood. Here, we obtained recordings from linear array multi-electrodes (NeuroNexus, 32 channels, 100 micron spacing), inserted perpendicular to the surface of area 17 of anesthetized, paralyzed adult cats, for broadband recording (OpenEphys) across all 6 cortical layers. Correspondence of recording sites with cortical laminae was first established using current source density analysis (CSD) of low frequency responses to brief flashes of large-field luminance. Neuronal responses to binary sparse noise stimuli were then recorded. Multiunit activity (MUA) was extracted for each channel, as times of level-crossings at 3 SD of the bandpass digitally filtered (300 Hz - 3.0 kHz) signal. Two methods of transforming spike trains into continuous functions were evaluated: conventional binning, and convolution with a Gaussian. We estimated cross-correlations across all pairs of channels with respect to latency, and constructed a 32x32 MUA cross-correlation matrix, in which the diagonal corresponds to a channel paired with itself. The results showed MUA cross-correlation is related to the laminar structure measured by CSD, with greater laminar differentiation from convolution than binning. The pattern of pairwise correlation changes with latency, which provides indications of functional connectivity. Nearby channels usually gave higher cross-correlations than channels far apart, and intralaminar connectivity was dominant at nero-zero latencies. As time lag increases, the main pattern of cross-correlation moved away from the diagonal, suggesting interlaminar connections. In conclusion, MUA cross-correlation can provide a method to characterize vertical functional connectivity in the laminar structure of striate cortex. Interlaminar functional connectivity occurs at significant latencies, which might indicate how information flows between layers.

Disclosures: J. Ning: None. **G. Li:** None. **C. Baker:** None.

Poster

754. Visual Cortex: Functional Architecture and Circuits II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 754.08/I39

Topic: D.07. Vision

Title: Characterization of a mouse V1 model to inputs and perturbations using computational optogenetics

Authors: *B. CAI, Y. N. BILLEH, C. KOCH, A. ARKHIPOV, S. MIHALAS;
Allen Inst. for Brain Sci., Seattle, WA

Abstract: Large scale modeling is a very important tool to begin to tackle the vast complexity of the nervous system. Just in the visual cortex of the mouse we have characterized ~100 transcriptomic (Tasic et al. 2018) and 17 electrophysiological types and 38 morphological types (Gouwens et al 2018). Using this information as well as large collection of literature data, we have constructed a set of large scale models of the mouse primary visual system at multiple levels of resolution.
To investigate underlying characteristics of the V1 cortical area in mice, computational perturbation simulation experiments were conducted on a newly-built V1 column model using a novel point neuron model based on GLIF (Generalized Leaky Integrate-and-Fire) models. Point neuron models have two orders of magnitude speed benefit over biophysically detailed models, which allows us to more rapidly explore the space of inputs. In this study, we focus on the effects of three types of additional inputs on top of the visual inputs have on the simulated activity.
First, computational optogenetic perturbations were performed at the cell type population level to study the functional roles of different cell types in the inter-laminar interactions. Our results are consistent with mechanisms inhibition stabilized networks and inhibitory modulation of L6 on superficial layers (Olsen et al. 2012).
Second, single neuron perturbation simulations were conducted to explore how activity change of one cortical neuron could influence nearby cortical neurons and network activity. The simulation results are consistent with (Chettih & Harvey, 2019).
Finally, to simulate long range inputs we used the characterization of connectivity profiles between different cortical areas (Harris et al. 2018) and the characterization of dendritic profiles of V1 neurons, and we assumed cell-type specific connections being proportional to axo-dendritic overlap ("Peter's Rule"). When simulating additional top-down input we observe a broad increase in activity compared to bottom up input.
The vast array of additional in silico perturbation results from these simulations can establish potential hypothesis of optogenetic perturbative experiments for neuroscience experimentalists to advance our understanding of primary visual cortex.

Disclosures: B. Cai: None. **Y.N. Billeh:** None. **C. Koch:** None. **A. Arkhipov:** None. **S. Mihalas:** None.

Poster

754. Visual Cortex: Functional Architecture and Circuits II

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Program #/Poster #: 754.09/I40

Topic: D.07. Vision

Title: Systematic integration of structural and functional data into a multi-scale model of mouse primary visual cortex

Authors: *Y. N. BILLEH[1], B. CAI[3], S. L. GRATIY[3], K. B. DAI[4], R. IYER[4], R. ABBASI-ASL[3], X. JIA[2], J. H. SIEGLE[3], S. R. OLSEN[4], C. KOCH[3], S. MIHALAS[4], A. ARKHIPOV[4]; [2]Brain Sci., [1]Allen Inst., Seattle, WA; [3]Allen Inst. for Brain Sci., Seattle, WA; [4]Allen Inst. For Brain Sci., Seattle, WA

Abstract: Structural rules underlying functional properties of cortical circuits are poorly understood. To explore these rules systematically, we integrated information from extensive literature curation and large-scale experimental data collection efforts into data-driven, biologically realistic models of the mouse primary visual cortex. The models were constructed at two levels of granularity, using either biophysically-detailed or point-neuron models, and were tested against experimental recordings of neural activity during presentation of visual stimuli to awake mice. We demonstrate how in the process of building these models, specific predictions emerge about structure-function relationships in the cortical circuit. We discuss three such predictions regarding connectivity between excitatory and parvalbumin-negative inhibitory neurons; functional specialization of connections between excitatory neurons; and the impact of the cortical retinotopic map on structure-function relationships.
Our models use the Brain Modeling ToolKit (BMTK, github.com/AllenInstitute/bmtk) to integrate (Gratiy *et al.*, 2018) with NEURON (Hines and Carnevale, 1997) and NEST (Gewaltig and Diesmann, 2007) for parallel simulations. The model architecture and output are saved using the standardized SONATA format (github.com/AllenInstitute/sonata, Dai *et. al*, 2019). The models, code, and all meta-data resources will be publicly available via the Allen Institute Modeling Portal (brain-map.org/explore/models). As a free public resource, these models will be useful to the community for making direct predictions as well as complementing other experimental and modeling endeavors.

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Poster

754. Visual Cortex: Functional Architecture and Circuits II

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Topic: D.07. Vision

Support: NIH Grant EY05253

Title: Direction selectivity is strongly correlated with on/off response balance in primary visual cortex

Authors: *J. JIN[1], S. NAJAFIAN[1], R. MAZADE[1], C. PONS[1], E. KOCH[2], J. ALONSO[1]; [1]SUNY Col. of Optometry, New York, NY; [2]Caltech, Pasadena, CA

Abstract: Neurons in the primary visual cortex respond selectively to the direction of stimulus movement. Based on our previous results (Kremkow et al., 2016), we hypothesized that cortical direction selectivity should be related to the relative strength of ON and OFF cortical responses as is also the case for cortical orientation selectivity. Here, we tested this hypothesis by measuring the ON-OFF response balance and direction selectivity of a large number of cortical multiunit sites recorded with multielectrode arrays in cat visual cortex (n=24,660 recording sites). Because both direction selectivity and ON-OFF response dominance are clustered in cat cortex, a large number of multiunit recordings should allow us to measure any relation between these two stimulus parameters that was unnoticed in the past. The recordings were obtained with multielectrode probes of 16 or 32 recording sites that were linearly arranged (100 microns separation between sites). From all recordings, we selected for the analysis the 24,660 multiunit sites that responded most robustly to moving bars (signal/noise > 4, response per bar sweep > 7 spikes). Cortical multiunit was defined as spiking activity with a voltage larger than 60 microvolts to include only neurons in the immediate neighborhood of the electrode (estimated radius: ≤ 50 microns). We measured the direction selectivity (DS) of each cortical site as DS = (Rp - Rnp) / Rp, where Rp and Rnp are responses to preferred and opposite non-preferred directions (DS equals 1 when the direction selectivity is highest). We measured the dominant contrast polarity (CP) of each cortical site as CP = (ON - OFF) / (ON + OFF), where ON and OFF are the maximum responses to brief light or dark targets presented at the receptive field center of each cortical multiunit site (CP equals 0 when ON and OFF responses are equal in strength and the ON-OFF response balance is highest). Our results revealed a very strong correlation between cortical direction selectivity and ON-OFF response balance that could be accurately fit with a power function ($R = 0.995$, $p = 0.0004$, $CP = -0.2 + 0.2\ DS^{2.4}$). As expected, OFF responses were stronger than ON responses in most cortical sites; however, the OFF cortical dominance decreased with direction selectivity. The average OFF cortical dominance was strongest in cortical sites that were not direction selective (CP = - 0.2 for DS < 0.2) and became weaker as the direction selectivity increased (CP = -0.04 for DS > 0.8). These results demonstrate that, as for cortical orientation selectivity, direction selectivity is strongly related to ON-OFF response balance and increases when ON and OFF responses become similar in strength.

Disclosures: J. Jin: None. **S. Najafian:** None. **E. Koch:** None. **J. Alonso:** None. **R. Mazade:** None. **C. Pons:** None.

Poster

754. Visual Cortex: Functional Architecture and Circuits II

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Topic: D.07. Vision

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NIH Grant EY05253

Title: Receptive field structures in ON and OFF domains of primary visual cortex

Authors: *R. MAZADE, J. JIN, C. PONS, J. ALONSO;
SUNY Col. of Optometry, New York, NY

Abstract: ON and OFF visual pathways signal the presence of light and dark stimuli in visual scenes and segregate in ON and OFF domains within primary visual cortex. We recently demonstrated that ON and OFF responses within a cortical domain have different spatiotemporal preferences: ON responses are strongest when the stimuli are large and slow while OFF responses are strongest when the stimuli are small and brief (Mazade et al., 2019). Here we demonstrate similar spatiotemporal differences between the responses from ON- and OFF-dominated cortical neurons and use these measurements to model their receptive field structures. We measured responses from ON- and OFF-dominated neurons to dark and light stimulus targets presented with different sizes, durations, and under different backgrounds. Cortical receptive fields were classified as ON- or OFF-dominated based on their contrast polarity, which was defined as the ratio (ON - OFF) / (ON + OFF), where ON and OFF are maximum responses to light and dark small brief targets (7 deg / 33 ms). ON- and OFF-dominated neurons showed pronounced differences in their spatiotemporal tuning that resembled the differences between ON and OFF responses from single cortical sites. OFF-dominated neurons responded 36% stronger than ON-dominated neurons when the stimuli were small and fast (e.g. 7 deg / 16 ms target; OFF: 116.8 ± 3.8 vs. ON: 85.7 ± 3.5 spk/s; $p<0.001$, Wilcoxon test). Instead, ON-dominated neurons responded 40% stronger than OFF-dominated neurons when the stimuli were large and slow (e.g. 23 deg / 133 ms target; ON: 75.7 ± 3.3 vs. OFF: 54.1 ± 1.7 spk/s; $p<0.001$, Wilcoxon test). OFF-dominated neurons showed stronger size suppression than ON-dominated neurons (e.g. 133 ms target duration, OFF: 48.1 ± 1.9 vs. ON: 26.3 ± 2.0% suppression, $p<0.001$, Wilcoxon test). However, the size suppression increased with background luminance only in ON-dominated neurons. OFF-dominated neurons also showed strong temporal suppression while ON-dominated neurons showed strong temporal facilitation (e.g. 17 deg target, OFF: 51.7 ± 1.8% suppression vs. ON: -13.9 ± 1.6% facilitation, $p<0.001$, Wilcoxon test). We used these measurements to model the receptive fields of ON- and OFF-dominated neurons with difference-of-Gaussians functions. Our model accurately replicates the experimental measures by assuming that OFF-dominated neurons show stronger spatial and temporal suppression than ON-dominated neurons but background luminance only suppresses ON-dominated neurons. We conclude that ON- and OFF-dominated neurons have different receptive field structures that match the different spatiotemporal properties of light and dark stimuli in visual scenes.

Disclosures: **R. Mazade:** None. **J. Jin:** None. **C. Pons:** None. **J. Alonso:** None.

Poster

754. Visual Cortex: Functional Architecture and Circuits II

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Program #/Poster #: 754.12/I43

Topic: D.07. Vision

Support: EY027361

Title: Diversity of ocular dominance patterns in primary visual cortex originates from variations in local cortical retinotopy

Authors: *S. NAJAFIAN, J. JIN, J.-M. ALONSO;
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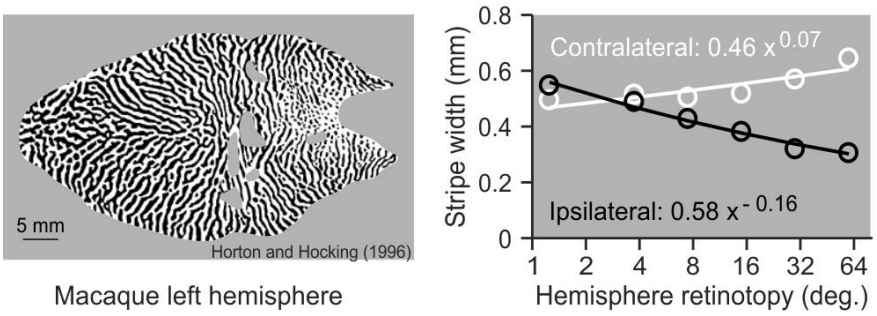
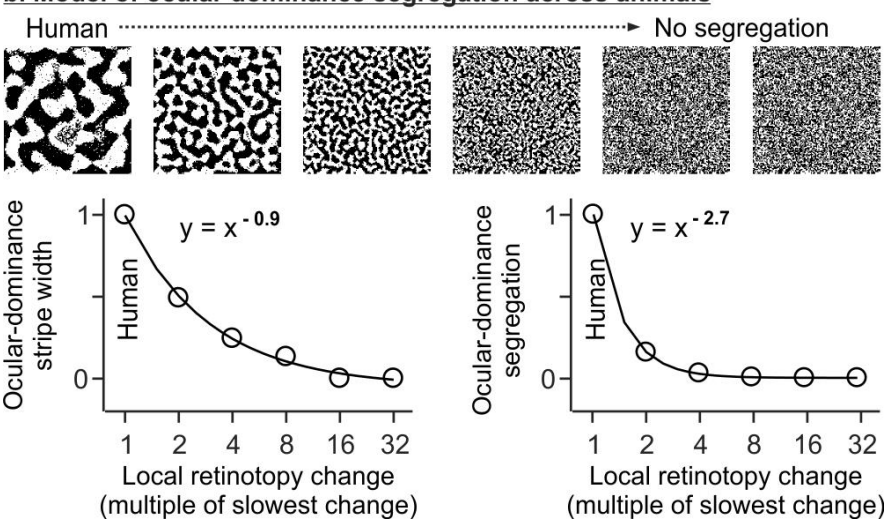
Abstract: The primary visual cortex contains a detailed map of retinal stimulus position (retinotopic map) and eye input (ocular dominance map) that results from the precise arrangement of thalamic afferents during cortical development. For reasons that remain unclear, ocular dominance maps are very diverse across species. They form patterns of highly organized stripes in humans and macaques, disorganized beads in cats and no pattern at all in rodents. Here, we used a new image-processing algorithm to measure published patterns of ocular dominance maps more accurately than in the past. These measurements revealed a tight relation between local patterns of ocular dominance and local changes in cortical retinotopy. This relation could be demonstrated in multiple regions of the primary visual cortex from an individual animal and in different species. For example, the median angle difference between the width axis of an ocular dominance stripe and the axis running along the slowest retinotopy gradient was 28.2 deg. in a human hemisphere, 23.8 deg. in a macaque hemisphere and 26 deg. in a cat hemisphere (26.6 deg. for the 3 hemispheres, n= 63 retinotopic sectors, p=0.02 that the similarity in angles is due to chance, Wilcoxon test). Because the retinotopic gradient increases with visual eccentricity, the relation that we described made us predict that visual eccentricity should be strongly correlated with stripe width, a prediction that we confirmed (e.g. ~10% reduction in ipsilateral-eye stripe width per every log2 degree unit of visual eccentricity, average $R^2 = 0.86$, n=8 hemispheres, example for one hemisphere shown in Figure 1a). Based on these results, we developed a computational model that sorts thalamic afferents by eye input and retinotopy to maximize the binocular retinotopic match at each cortical site. In our model, an increase in the cortical retinotopy gradient makes ocular dominance segregation and stripe width to decrease (Figure 1b). These results strongly suggest that the brain diversity of ocular dominance patterns emerges from variations in local cortical retinotopy.





Disclosures: **S. Najafian:** None. **J. Jin:** None. **J. Alonso:** None.

Poster

754. Visual Cortex: Functional Architecture and Circuits II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 754.13/I44

Topic: D.07. Vision

Support: NIH Grant EY027361

Title: On and off visual pathways in human cortex have different spatial resolution

Authors: ***C. PONS**[1], J. JIN[1], R. MAZADE[1], J. KREMKOW[2], D. R. ARCHER[1], J. ALONSO[1]; [1]SUNY Col. of Optometry, New York, NY; [2]Neurosci. Res. Ctr., Charité-Universitätsmedizin Berlin, Berlin, Germany

Abstract: The visual system encodes light and dark stimuli through ON and OFF pathways that originate in the retina and remain segregated in visual cortex. Recent evidence in cats indicates that ON and OFF cortical pathways differ not only in their responses to light and dark stimuli but also in their stimulus spatiotemporal preferences. The ON pathway shows a preference for large slow stimuli and the OFF pathway for small fast stimuli (Mazade et al., 2019). Here we investigate whether these ON-OFF differences are also present in human cortex. We recorded visual evoked potentials with a customized dry electrode wireless EEG system (Wearable Sensing DSI-7-Flex) that had seven electrodes centered in visual cortex (Oz, O1, O2, POz, PO3, PO4, and Fpz, impedances < 1 MΩ). EEG signals were bandpass filtered between 5 and 100 Hz and response amplitude measured as the difference between maximum and minimum response within 30 to 200 ms. Human observers with normal visual acuity were asked to fixate on a central green dot monocularly (one eye covered with a patch), and refrain from blinking for the 6.6 second stimulus trial (25 to 75 trials). Eye movements were continuously monitored with an EyeLink 1000 Plus and a trial was aborted (and repeated) if the observer blinked or stopped fixating in the middle of the trial. During the fixation time, we presented a sequence of a checkerboard pattern (0.5 seconds) followed by a midgray blank (0.6 seconds), and repeated this sequence six times per trial. We measured OFF responses at the onset of dark-midgray checkerboards and ON responses at the onset of light-midgray checkerboards (VIEWPixx monitor, 120 Hz, luminance for light / dark: 96.48 / 0.46 cd/m^2). We used six different check sizes: 0.22, 0.45, 0.89, 1.78, 3.57 and 7.12 deg. Preliminary results (n=13 observers) revealed stronger responses to dark than light small checks (0.22 deg., 16.95 ± 1.97µV vs. 13.20 ± 1.29µV, p=0.008, Wilcoxon test), confirming the OFF dominance previously demonstrated in human visual cortex (Zemon et al., 1988). However, they also revealed weaker responses to dark than light checks when their size was eight times larger (1.78 deg., 10.58 ± 1.23µV vs. 12.02 ± 1.29µV, p=0.021, Wilcoxon test). Moreover, size suppression was stronger for dark than light checks (50.65 ± 4.51% for darks vs 39.53 ± 6.59% for lights, p=0.03, Wilcoxon test). The check size driving the strongest response also tended to be smaller when it was dark although the difference did not reach significance (0.63 ± 0.25 deg. vs. 1.25 ± 0.55 deg., p=0.12, Wilcoxon test). These preliminary results suggest that ON and OFF cortical pathways have different spatial resolution in humans, as previously demonstrated in carnivores.

Disclosures: C. Pons: None. **J. Jin:** None. **R. Mazade:** None. **J. Kremkow:** None. **D.R. Archer:** None. **J. Alonso:** None.

Poster

754. Visual Cortex: Functional Architecture and Circuits II

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Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 754.14/J1

Topic: D.07. Vision

Support: IARPA contract D16PC00004

Title: Quantitative analysis of somatic and nuclear morphology reflects diverse cortical cell types in mouse visual cortex

Authors: *L. ELABBADY[1], S. SESHAMANI[1], C. SCHNEIDER-MIZELL[1], S. DORKENWALD[2], A. L. BODOR[1], N. L. TURNER[2], T. MACRINA[2], D. J. BUMBARGER[1], J. BUCHANAN[1], M. M. TAKENO[1], R. TORRES[1], G. MAHALINGAM[1], D. KAPNER[1], W. SILVERSMITH[2], E. FROUDARAKIS[3], C. JORDAN[2], N. KEMNITZ[2], K. LEE[2], R. LU[2], W. WONG[2], J. WU[2], J. REIMER[3], A. S. TOLIAS[3], H. SEUNG[2], N. M. DA COSTA[1], R. REID[1], F. C. COLLMAN[1];
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Abstract: In recent years, large scale surveys of the physiological, transcriptomic, and skeletal morphological properties of neurons have expanded our understanding of the diversity of cell types within the mouse visual cortex. Data driven classifications based upon these surveys have in some cases reinforced classical views of neocortical cell types but have also revealed previously unappreciated diversity. However, this same approach has not been applied to the morphological and connectomics-based features that are observable with the ultrastructural resolution of electron microscopy (EM). Here we present the early stages of an EM data-driven approach to distinguish cortical cell types based on synaptic profiles and morphological features of varying cell compartments (e.g. cell body, nucleus, spines etc.). The current data set is comprised of 3D meshes from a densely segmented transmission electron microscopy image volume ($0.56x0.92x0.03mm^3$) taken from mouse primary visual cortex including Layer II/III through Layer VI. From this volume, nuclear, somatic, and synaptic features were collected from over 1300 cells selected across laminar layers. Our analysis presents quantifiable distinctions that reflect changes in laminar depth and broader cell-type differentiation. With a focus on Layer 5 pyramidal cells, nuclear features such as volume, level of invagination and relative orientation allow us to examine the degree to which nuclear morphology can distinguish cell classes such as IT, PT, and NP. While our analysis reveals some clear distinctions, it also presents a vast variability in cell morphology that will require more a comprehensive feature analysis to distinguish.

Disclosures: L. Elabbady: None. **S. Seshamani:** None. **C. Schneider-Mizell:** None. **S. Dorkenwald:** None. **A.L. Bodor:** None. **N.L. Turner:** None. **T. Macrina:** None. **D.J. Bumbarger:** None. **J. Buchanan:** None. **M.M. Takeno:** None. **R. Torres:** None. **G. Mahalingam:** None. **D. Kapner:** None. **W. Silversmith:** None. **E. Froudarakis:** None. **C. Jordan:** None. **N. Kemnitz:** None. **K. Lee:** None. **R. Lu:** None. **W. Wong:** None. **J. Wu:** None. **J. Reimer:** None. **A.S. Tolias:** None. **H. Seung:** None. **N.M. da Costa:** None. **R. Reid:** None. **F.C. Collman:** None.

Poster

754. Visual Cortex: Functional Architecture and Circuits II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 754.15/J2

Topic: D.07. Vision

Support: DoI/IBC D16PC0005
Mathers Foundation

Title: Distinguishing inhibitory axons in an EM volume of mouse V1 L2/3

Authors: *S. DORKENWALD[1], A. L. BODOR[3], N. TURNER[1], C. M. SCHNEIDER-MIZELL[3], T. MACRINA[1], K. LEE[1], J. WU[2], N. KEMNITZ[1], A. A. BLECKERT[3], D. J. BUMBARGER[4], R. LU[1], J. ZUNG[1], D. BUNIATYAN[1], D. IH[1], S. POPOVYCH[1], I. TARTAVULL[1], W. SILVERSMITH[1], W. WONG[1], C. PAPADOPOULOS[5], B. CELII[5], J. BUCHANAN[7], M. M. TAKENO[4], J. REIMER[6], F. C. COLLMAN[8], A. S. TOLIAS[6], R. REID[9], N. M. DA COSTA[3], H. SEUNG[2];
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Abstract: Synaptic inhibition in the cortex is implemented by a group of cell types that shows a wide range of morphologic, physiological, transcriptomic and connectivity properties. They are widely acknowledged to play a crucial role in preventing run-away excitation while implementing sophisticated computations. While the mechanisms of their actions remain unknown they will be greatly dependent of which cells they target and where they target them. In order to quantify the pattern of connectivity of major inhibitory cell types onto their targets we have taken advantage of the fact that different inhibitory cell types target different cellular compartments in different proportions and that the fine morphology of their axons is different. Here we test if when analysed quantitatively, this differential targeting provides a robust bar-code to classify the axons of inhibitory cell types at scale and on densely segmented EM volumes. We analyzed the synaptic innervation patterns and morphology of over 1000 reconstructed inhibitory axonal segments in an EM volume from mouse V1 L2/3. We separated the targeted pyramidal cells into compartments (axon, dendritic shaft, spines) to assess the synaptic innervation patterns. For our morphological analysis, we developed a neural network autoencoder based on PointNet operating on meshes to encode the local morphology of axonal fragments. When comparing innervation patterns with our morphological encoding, we found agreements across these two domains. For instance, we found a putative basket cell type with large and flat boutons targeting only soma and dendrite but never spines whereas other putative

basket cell types distribute their synapses across these compartments. We present our structural analysis of inhibitory axons along with a comparison to described types in the literature.

Disclosures: **S. Dorkenwald:** None. **A.L. Bodor:** None. **N. Turner:** None. **C.M. Schneider-Mizell:** None. **T. Macrina:** None. **K. Lee:** None. **J. Wu:** None. **N. Kemnitz:** None. **A.A. Bleckert:** None. **D.J. Bumbarger:** None. **R. Lu:** None. **J. Zung:** None. **D. Buniatyan:** None. **D. Ih:** None. **S. Popovych:** None. **I. Tartavull:** None. **W. Silversmith:** None. **W. Wong:** None. **C. Papadopoulos:** None. **B. Celii:** None. **J. Reimer:** None. **F.C. Collman:** None. **A.S. Tolias:** None. **R. Reid:** None. **N.M. da Costa:** None. **H. Seung:** None. **J. Buchanan:** None. **M.M. Takeno:** None.

Poster

754. Visual Cortex: Functional Architecture and Circuits II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 754.16/J3

Topic: D.07. Vision

Support: IARPA Contract D16PC00004

Title: A complete map of axo-axonic synapses revealed by a dense segmentation of a volume from layer 2/3 of mouse primary visual cortex

Authors: *C. M. SCHNEIDER-MIZELL[1], A. L. BODOR[1], F. C. COLLMAN[1], S. DORKENWALD[2], N. L. TURNER[2], T. MACRINA[2], D. J. BUMBARGER[1], J. BUCHANAN[1], M. M. TAKENO[1], R. TORRES[1], G. MAHALINGAM[1], D. KAPNER[1], K. LEE[2], N. KEMNITZ[2], J. ZUNG[2], W. SILVERSMITH[2], W. WONG[2], R. LU[2], J. WU[2], D. IH[2], I. TARTAVULL[2], E. FROUDARAKIS[3], S. POPOVYCH[2], D. BUNIATYAN[2], J. REIMER[3], A. S. TOLIAS[3], H. SEUNG[2], R. REID[1], N. M. DA COSTA[1];
[1]Allen Inst. For Brain Sci., Seattle, WA; [2]Princeton Neurosci. Inst., Princeton Univ., Princeton, NJ; [3]Neurosci., Baylor Col. of Med., Houston, TX

Abstract: The structure of inhibition is a key factor shaping the activity of neuronal circuits. Diverse inhibitory cell types can exert their influence in different ways, due not only to characteristic specificity in which cell types they target, but even the precise locations onto which they make synapses. In mammalian cortex, GABAergic chandelier cells (ChC) show particularly exquisite specificity, exclusively targeting the axon initial segment (AIS) of excitatory pyramidal cells (PyC). While ChCs and AIS inhibition have been well-studied at the level of single ChCs or single PyCs, little is known about the structure of connectivity in a larger population context. We sought to address this by reconstructing PyC and ChCs in a 250x150x100 µm serial section electron microscopy volume covering L2/3 of mouse primary visual cortex. Neurons and synapses were computationally segmented and select cells were

manually proofread. We identified 145 PyC AISes fully contained within the volume and found 2091 synapses onto them, of which 1105 were from ChCs. The distribution of net ChC inhibition across PyCs was strikingly broad, ranging from 0-25 synapses (mean: 7.6). Thus in contrast to other forms of perisomatic inhibition, many PyCs escape significant AIS inhibition while other PyCs get many times more than average amounts. We found two correlates of this variability. First, net ChC inhibition positively correlated with the number of perisomatic synapses around the soma. Second, net ChC inhibition varied significantly with depth across L2/3, with upper L2/3 PyCs receiving significantly more ChC synapses than lower ones. Taken together, this suggests that inhibition is coordinated across distinct inhibitory cell types, but that AIS inhibition is distributed heterogeneously across L2/3 in visual cortex. In addition, detailed analysis of morphology found local coordination between distinct ChCs on a given AIS, for example ChC boutons often formed tightly apposed clusters instead of distributing themselves randomly across the AIS surface. This work shows ChCs to be a highly variable component in a coordinated pattern of perisomatic inhibition on PyCs in L2/3.

Disclosures: C.M. Schneider-Mizell: None. **A.L. Bodor:** None. **F.C. Collman:** None. **S. Dorkenwald:** None. **N.L. Turner:** None. **T. Macrina:** None. **D.J. Bumbarger:** None. **J. Buchanan:** None. **M.M. Takeno:** None. **R. Torres:** None. **G. Mahalingam:** None. **D. Kapner:** None. **K. Lee:** None. **N. Kemnitz:** None. **R. Lu:** None. **E. Froudarakis:** None. **S. Popovych:** None. **D. Buniatyan:** None. **J. Reimer:** None. **A.S. Tolias:** None. **H. Seung:** None. **R. Reid:** None. **N.M. da Costa:** None. **W. Silversmith:** None. **J. Wu:** None. **D. Ih:** None. **I. Tartavull:** None. **W. Wong:** None. **J. Zung:** None.

Poster

754. Visual Cortex: Functional Architecture and Circuits II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 754.17/DP08/J4

ControlExtraData.DynamicPosterDisplay:
Dynamic Poster
Topic: D.07. Vision

Support: IARPA D16PC00003
IARPA D16PC00004
IARPA D16PC00005

Title: Functional connectivity of excitatory inputs to excitatory cells in an EM-reconstructed volume of mouse V1

Authors: *.-. NINAI;
Princeton University, Princeton, NJ; Allen Inst. for Brain Science, Seattle, WA; Columbia University, New York, NY; Baylor Col. of Med., Houston, TX

Abstract: Although significant insight can be gleaned from analysis of neural activity or anatomy separately, answering many fundamental mechanistic questions in systems neuroscience requires information about both neural activity and connectivity in the same animal. Enormous strides have been made over the past decade in our ability to record activity from large populations of neurons distributed across multiple regions of the brain, and improvements in EM imaging techniques and the application of modern machine learning methods for segmentation of EM volumes have together enabled accurate reconstruction of increasingly large volumes of neural tissue. Here we describe an analysis of the connectivity of putative excitatory axons in a small volume of mouse primary visual cortex onto functionally-characterized excitatory cells. At Baylor College of Medicine, we recorded visual responses from neurons located in L2/3 of primary visual cortex of a 34 day-old male mouse expressing GCaMP6f in pyramidal cells under control of CamKII-Cre/tTA. The mouse was then shipped to the Allen Institute in Seattle where electron microscopy (EM) was performed on a ~200 x 150 x 100 micron volume, which was subsequently densely reconstructed at Princeton University. The EM data was subsequently used as ground-truth segmentation for a novel method to extract functional data developed at Columbia University. From this data we were able to analyze the projection patterns of tens of thousands of reconstructed axons onto hundreds of functionally-characterized neurons and isolated apical dendrites. Several methodologies have been used to find evidence for “like-to-like” connectivity (increased connectivity for cells with similar tuning preferences) via spine imaging (Iacaruso, et al 2017), combined *in vivo* imaging and *in vitro* multipatching (Ko et al. 2011; Cossell et al. 2015), and combined *in vivo* imaging with EM reconstruction (Bock et al. 2011; Lee et al. 2016). Here, we examine this question in this largest functionally-imaged and densely-reconstructed calcium imaging/EM data set collected to date in order to elucidate the principles of structure/function relationships including shared input and higher-order motifs.
Please see full author list at http://www.ninai.org/sfn2019poster

Disclosures: -. Ninai: None.

Poster

754. Visual Cortex: Functional Architecture and Circuits II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 754.18/J5

Topic: D.07. Vision

Support: IARPA D16PC00003
Deutsche Forschungsgemeinschaft,ZUK 63

Title: Inception in visual cortex: *In vivo-silico* loops reveal most exciting images

Authors: *E. Y. WALKER[1,2], F. H. SINZ[1,3,2,4], E. COBOS[1,2], E. FROUDARAKIS[1,2], P. FAHEY[1,2], T. MUHAMMAD[1,2], A. S. ECKER[6,2,3,5], J. REIMER[1,2], X. S. PITKOW[1,2,7], A. S. TOLIAS[1,2,7];
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Abstract: Finding sensory stimuli that drive neurons optimally is central to understanding information processing in the brain. However, optimizing sensory input is difficult due to the predominantly nonlinear nature of sensory processing and high dimensionality of the input space. Here, we developed *inception* loops, a closed-loop experimental paradigm combining *in vivo* recordings from thousands of neurons with *in silico* nonlinear response modeling. Our end-to-end trained, deep learning-based model predicted thousands of individual neurons' responses to arbitrary, new natural input with high accuracy, and was thus used to synthesize optimal stimuli - Most Exciting Images (MEIs). For mouse V1 these MEIs exhibited complex spatial features that deviated strikingly from the common notion that Gabor-like stimuli are optimal for V1. When presented back to the same neurons *in vivo*, these MEIs drove responses significantly better than control stimuli. Inception loops represent a widely applicable new technique for dissecting the neural mechanisms of sensation.

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Poster

754. Visual Cortex: Functional Architecture and Circuits II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 754.19/J6

Topic: D.07. Vision

Support: D16PC00003

Title: Spatially-variant orientation selectivity in mouse primary visual cortex

Authors: *J. FU[1,3], S. SHEN[4], J. REIMER[2,3], F. H. SINZ[2,3,5,6], X. S. PITKOW[2,3,7], A. S. TOLIAS[2,3,7];
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Tübingen, Tübingen, Germany; [7]Dept. of Electrical and Computer Engin., Rice Univ., Houston, TX

Abstract: A primary role of visual processing is the integration of information over retinotopic space. Visual integration is crucial for visual perception, and it has been studied most extensively in the primary visual cortex (V1). Neurons in V1 respond to stimuli in a confined spatial location, which defines the classical receptive field (CRF), yet visually driven neuronal responses are modulated by stimuli in the surrounding visual space. Characterizing its stimulus selectivity and determine its role in visual processing is a major milestone in understanding the visual system. In the past, researchers have typically assumed spatially uniform selectivity of the surround in V1 and many results have suggested that surround modulation reduces visual responses to repeating spatial patterns. At the same time, many theoretical studies argue that surround modulation reduces redundancy and enhances saliency in visual encoding. However, spatial-uniform tuning of the surround in V1 currently lacks empirical validation, and it is unclear how the theoretical models relate to the observed changes in neuronal responses to the surround. We characterize the spatial profile of one type of selectivity - orientation tuning in mouse V1 and assess changes in orientation coding by building a predictive model based on neuronal responses. We find that in the majority of recorded V1 neurons, orientation tuning changes as a function of stimulus location, violating the assumption that orientation selectivity of a single neuron in V1 is uniform across visual space. Because none of the existing parametric models of visual encoding were able to account for these findings, we trained a more versatile model, a neural network, to predict orientation in the stimuli from populational neuronal responses. Despite the fact that spatial orientation selectivity can vary for single cells, the model still reliably decoded the stimulus orientation. Our finding suggests that while the selectivity of neurons in mouse V1 can be complex, orientation is still robustly encoded in the cortical population response.

Disclosures: **J. Fu:** None. **S. Shen:** None. **J. Reimer:** A. Employment/Salary (full or part-time):; Vathes LLC. **F.H. Sinz:** None. **X.S. Pitkow:** None. **A.S. Tolias:** A. Employment/Salary (full or part-time):; Vathes LLC.

Poster

754. Visual Cortex: Functional Architecture and Circuits II

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Program #/Poster #: 754.20/J7

Topic: D.07. Vision

Support: NIH R01 MH111516
NIH R01 MH112151
NIH R01 NS036715

Title: Calcium-permeable AMPA receptors govern PV interneuron orientation selectivity

Authors: *I. HONG[1,2], J. KIM[3], R. C. JOHNSON[1,2], Z. YANG[4], D. CHEON[3], A. AGARWAL[5], D. E. BERGLES[1], S. P. BROWN[1], R. L. HUGANIR[1,2];
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Abstract: AMPA receptors convey the majority of excitatory synaptic transmission throughout the mammalian cortex. A subset of AMPA receptors that lack the GluA2 subunit display distinct biophysical properties, including calcium permeability. Although these calcium-permeable AMPA receptors (CP-AMPARs) have been shown to trigger non-classical forms of synaptic plasticity, the computational role of these receptors and the wider impact on neuronal activity has not been explored. Here we find that PV and SOM interneurons express low levels of GluA2 protein and mRNA compared to other subunits, and the stoichiometry ratio is conserved from mice to humans, leading to abundant expression of CP-AMPARs. Using *in vivo* two-photon calcium imaging, we observed that replacing CP-AMPARs with calcium-impermeable AMPARs in PV interneurons substantially increased their orientation selectivity. This increase of orientation selectivity was cell-autonomous and could occur well beyond development. Paired patch-clamp recordings indicated that although excitatory-PV neuron connectivity and unitary synaptic strength was not changed, CP-AMPAR replacement led to substantial increases in neuronal excitability. These results demonstrate a novel role of CP-AMPARs in maintaining a low selectivity sensory representation in PV interneurons and suggest a conserved molecular mechanism that distinguishes the synaptic computations of certain inhibitory and excitatory neuron classes.

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Poster

754. Visual Cortex: Functional Architecture and Circuits II

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Program #/Poster #: 754.21/J8

Topic: D.07. Vision

Support: ARC CIBF Grant CE140100007

Title: Orientation maps in the primary visual cortex of an Australian marsupial, the Tammar Wallaby Macropus eugenii

Authors: *Y. JUNG[1,3], M. YUNZAB[3], A. ALMASI[3], S. SUN[1,3], S. CLOHERTY[4], S. BAUQUIER[2], M. RENFREE[2], H. MEFFIN[1,3], M. IBBOTSON[1,3];
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Abstract: Orientation selectivity (OS) is a prominent feature of neurons in the mammalian primary visual cortex, but the spatial organization of these neurons varies across species. In carnivores and primates, orientation-selective neurons are organized into structured orientation columns, which are vertical arrays of neurons with the same orientation preference. These columns are organized into two-dimensional orientation maps in which the different orientations are arranged radially around singular, pinwheel centers. However, rodents and lagomorphs - despite having robust orientation selectivity in individual neurons - do not have orientation columns, but instead the neurons are randomly distributed throughout the cortex, in what is termed a salt-and-pepper organization. We do not know why some mammals have structured pinwheel maps while others have salt-and-pepper maps. We investigated whether the development of orientation maps is influenced by a genetic factor related to phylogeny. The entire mammalian line might have originated with the genetic capacity to develop orientation columns, but perhaps rodents and lagomorphs lost this organization due to a lack of environmental or behavioral drivers. We studied a highly visual marsupial, the Tammar wallaby (*Macropus Eugenii*), which represents a phylogenetically distinct branch of mammals for which the orientation map structure is unknown. If orientation columns are the mammalian norm, we should identify orientation columns in marsupial cortex. We used intrinsic optical imaging and multi-channel electrophysiology methods to examine the functional organization of the wallaby cortex. We found robust OS in a high proportion of cells in the primary visual cortex. Moreover, we found clear orientation columns similar to those found in primates and carnivores but with bias towards vertical and horizontal preferences, suggesting lifestyle-driven variations. The findings suggest that orientation columns are the norm and it might be that the rodents and lagomorphs are unusual in terms of mammalian cortical architecture.

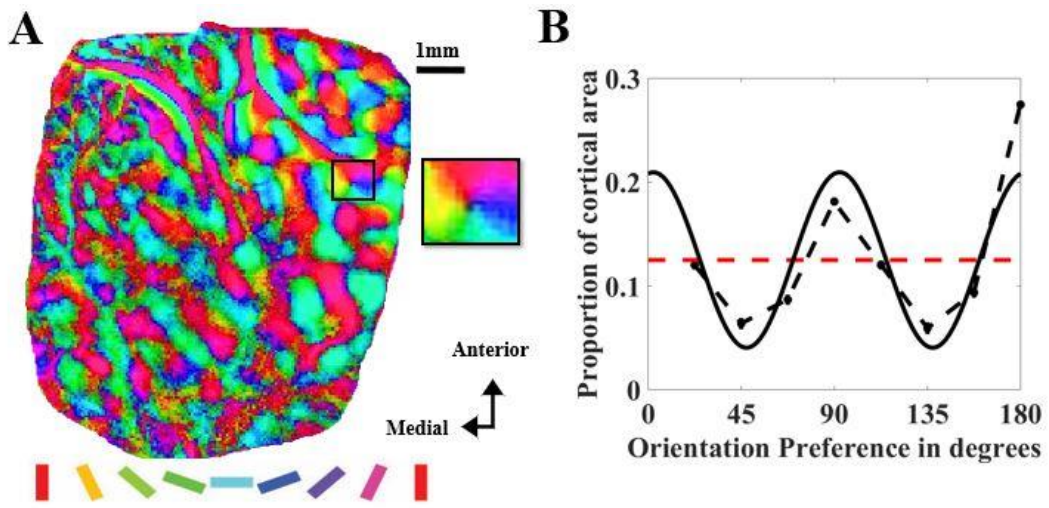

Figure 1. Orientation Preference map. (A) Orientation map showing the orientation preference for every region of the imaged wallaby visual cortex. The angle is color-coded according to the scheme at the bottom of the figure. We zoom in on a pinwheel location. (B) Distribution of orientation preferences. Proportion of cortical area representing different orientations from right eye stimulation (red line ± 1 SEM, thick line: least-squares sine curve fit). The best fitting sine curve with period 90° had peaks at 90° and 180°.

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Poster

755. Visual Systems: Functional Architecture and Circuits

Location: Hall A

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Title: Retinal origin of orientation column, clustered horizontal connections and patterned spontaneous activity in visual cortex

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Abstract: In primary visual cortex (V1) of higher mammals, the orientation preference of neurons develops, organizing in a quasi-periodic pattern across the cortical space known as orientation maps CITATION Bla86 \l 1042 (Blasdel, 1986). In the same developmental period, it was reported that clustered horizontal connections develop to link iso-orientation column (Ruthazer,1996) and patterned spontaneous cortical activity in V1 matches the topology of

orientation map even before eye-opening (Smith, 2018), which suggests that orientation maps, clustered horizontal connections and patterned spontaneous activity might be closely related during their development. Thus, the study suggested that cortical interaction drives patterned spontaneous cortical activity and might form a backbone of clustered horizontal connections and orientation map self-organization, but underlying principle of development and developmental order among these three functional architectures are still unclear. Here, we propose another viewpoint that the inherent pattern of early retinal afferent mosaic instructs simultaneous emergence of clustered horizontal connections and orientation maps, and that patterned spontaneous activity is the result of such functional circuit formation. By assuming that the patterned afferents from retinal ganglion cell (RGC) seeds the layout of orientation map, (Paik and Ringach, 2011), we hypothesized that spatial pattern of retinal mosaic could be projected to cortex by the patterned retinal wave before eye-opening (Kershenstheiner, 2016), and may drive the emergence of orientation-selective horizontal connectivity in the cortex by Hebbian mechanism. Using a computer simulation, our model successfully showed (1) emergence of orientation-selective and horizontally clustered connections and (2) connectivity-driven cortical activity pattern which was refined over time to match the topography of orientation map (Smith, 2018). Our results suggest that early emergence of the functional network in the neocortex may be driven by projected structure and activity of retinal afferents, contrary to the previous notion of self-organization within cortical networks.

Disclosures: **M. Song:** None.

Poster

755. Visual Systems: Functional Architecture and Circuits

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Title: Distinct functional networks of peripheral and central visual representations in primary visual cortex during rest and task

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Abstract: The central and peripheral visual fields, which correspond to the posterior and anterior portions of the primary visual cortex (V1), respectively, are known to play distinct functional roles: The central visual field of V1 is specialized in processing fine-grained visual information whereas the peripheral visual field is involved in monitoring changes in the environment by integrating multisensory information. Although previous work reported distinct patterns of functional connectivity between subregions of V1 and other visual areas, associations of each V1 subregion with functional networks beyond visual areas remain to be known. In the current study, we examine the intrinsic patterns of functional connectivity between subregions of V1 and the whole brain during rest and their modulations during a task. FMRI data during resting state, a visual working memory task, and an auditorily presented language task were obtained from the Human Connectome Project database. Using the connectivity-based parcellation approach, V1 was parcellated into the anterior and posterior portions and the whole brain seed-based connectivity was performed between each subregion of V1 and the rest of the brain. The results showed distinct patterns of functional connectivity between each V1 subregion and auditory, somatosensory, extrastriate visual, and frontoparietal areas, as well as their differential modulation by task. During the resting state, strong functional associations between the anterior V1 and auditory and somatosensory cortex were found. The functional associations of the anterior V1 and other sensory cortices, however, were largely reduced during both tasks whereas the functional connectivity between the anterior V1 and frontoparietal areas increased. On the other hand, the posterior V1 increased its functional connectivity with the extrastriate visual areas when a visual working memory task was performed while the anterior V1 decreased its functional connectivity with other visual areas. Our findings suggest that distinct functional roles of peripheral and central visual field representations in V1 are supported by different functional networks in which each subregion of V1 is embedded: The posterior V1 forms the primary visual network with the extrastriate visual areas supporting the processing of focal visual information whereas the anterior V1 may form long-range functional connections with other sensory cortices for environmental monitoring via multisensory integration during rest but may be reconfigured to participate in the frontoparietal control network when cognitive task demand is high.

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Poster

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Title: Principles of columnar and salt-and-pepper organizations of orientation tuning in visual cortex

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Abstract: In the mammalian visual cortex, spatial organization of orientation tuning in the primary visual cortex (V1) is arranged in different forms across species. For instance, columnar orientation maps are observed in primates while noisy salt-and-pepper organizations are found in rodents. However, it is unknown whether these disparate organizations indeed reflect species-specific developmental mechanisms of cortical circuits in evolution (Kaschube, 2014), or if any biological parameters (such as cortex size) determine it. To address this issue, we first analyzed neural parameter data in eight mammalian species, and found that the retina-to-cortex feedforward sampling ratio is a key factor that predicts the V1 organization of orientation tuning. We show that whether a species would have columnar maps or with salt-and-pepper organization, can be predicted solely by the retinocortical sampling ratio, as estimated from the size of the retina and V1 in each species. In particular, we show that the cortical organization of four species with V1 of similar size (columnar map in ferrets and tree shrews; salt-and-pepper organization in rabbits and gray squirrels) could be readily predicted by the ratio between the sizes of the retina and V1. This was impossible when considering only a single parameter such as V1 size. We confirmed that the sampling ratio between retinal and cortical neurons successfully predicts V1 organization of all eight species examined so far. Interestingly, we found that the results are mathematically consistent with a prediction by the Nyquist theorem in the Paik-Ringach model (Paik, 2011). Our results suggest a simple but fundamental principle of cortical organization: physical constraints in the periphery can initially contribute to the circuit design of the primary sensory cortex.

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Poster

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Title: A multiplicity of connectivity rules in higher-order visual circuits

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Abstract: Vision and visually-guided behaviors in mammals rely on multilateral neuronal pathways linking multiple higher visual areas (HVAs) that process distinct aspects of the visual scene in parallel. Computations and information flows in HVAs and higher-order visual circuits are still poorly understood. Here we developed an *in vivo* approach to map visual pathways anatomically and functionally in the mouse cortex. Combining retrograde and anterograde labeling with widefield, cellular and axonal calcium imaging, we characterized the flow of spatiotemporal information across eight visual cortical areas (V1, LM, AL, RL, AM, A, PM and LI) and a higher-order thalamic nucleus (LP, lateral posterior nucleus). Anatomical circuit tracing revealed HVAs specifically and selectively sample inputs from cortical and thalamic areas. Area AL, for example, receives inputs from a wide extent of cortical areas; PM avoids inputs from most anterior areas; while A selectively receives inputs from anterior areas. Functional cellular imaging revealed HVAs receive and send specific visual signals to distinct areas. For instance, while AL and PM show distinct tuning, they also innervate each other, layer2/3 corticocortical neurons show functional properties different from the general population and biased towards their projection targets. Importantly, the wiring rules are not uniform but strongly depend on source and target areas. For example, while AL sends distinct information to different areas, PM neurons send similar information across areas. Likewise, while AL sends highly specialized information to HVAs, it sends more diverse information to V1 and LM. Finally, projections from LP show the highest level of specificity even exceeding specificity of V1 and LM projections to HVAs. Together, these results provide a blueprint of the functional architecture of mouse higher-order visual circuits and suggest a multiplicity of rules of connectivity across the cortex.

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Poster

755. Visual Systems: Functional Architecture and Circuits

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Title: The distribution of norepinephrine transporter-immunoreactive axons in V1 and V2 of the macaque monkey

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Abstract: Norepinephrine is diffusely released into cortex from fibers originating in the locus coeruleus (LC), which synthesizes norepinephrine via the action of dopamine-beta hydroxylase (DBH). Once in cortex, norepinephrine is free to activate receptors until it is cleared from the extracellular space. Therefore, the presence of DBH and reuptake, via the norepinephrine transporter (NET), together define the extracellular concentration, and the temporal and spatial profile of the incoming noradrenergic signal in any given cortical area. It remains unknown if closely related cortical areas such as primary visual cortex (V1) and secondary visual cortex (V2) differentially use norepinephrine. Furthermore, it is unknown if differences in noradrenergic signaling could help account for differences in response properties between these two areas. Previous studies in primates have shown that V1 receives less dense innervation from the LC than does V2, as assayed by DBH immunoreactivity. None of these prior studies were quantitative and to our knowledge there have been no studies (quantitative or qualitative) of the other factor that defines noradrenergic signaling, the expression of NET. To address the lack of data on NET expression in primate cortex, and to begin building quantitative descriptions and models of cortical neuromodulatory systems, we immuno-labelled NET in tissue sections from 3 adult male rhesus macaques. We stereologically quantified the density of immunoreactive fibers in V1 and V2 and found that the density of NET-positive fibers in V1 is approximately 15% lower than the density in V2. We also dual-labeled sections for NET and DBH. Preliminary examination of these dual-labeled sections indicate that approximately 90% of DBH-positive axons also express NET. Because NET and DBH appear to co-localize on LC axons in both V1 and V2, the relative density of innervation (quantified here) and the laminar distribution of LC fibers emerge as the functionally relevant anatomical features of the noradrenergic system. Interestingly, previous studies have observed differences in the laminar distribution of DBH-positive fibers between primate V1 and V2.

Disclosures: C. Roach: None. **A.A. Disney:** None.

Poster

755. Visual Systems: Functional Architecture and Circuits

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Title: Functional stripes represent juxtaposed maps of central and peripheral space in tree shrew V2

Authors: *M. SEDIGH-SARVESTANI, K.-S. LEE, S. F. LIU, N. C. SHULTZ, R. SATTERFIELD, D. FITZPATRICK;
Max Planck Florida Inst. for Neurosci., Jupiter, FL

Abstract: The tree shrew primary visual cortex (V1) has long served as a model in vision due to its columnar-organized representation of multiple visual properties and resemblance to primate V1. However, the functional organization of the secondary visual cortex (V2) of the tree shrew remains unexplored. Whether tree shrew V2 exhibits an interleaved organization like that found in primate V2 (functional stripes) or a single visuotopic organization as in the mouse extrastriate areas, is unknown. In this study, we used functional imaging, and anatomical tracing, to examine the organization of V2 in the tree shrew.
To study functional responses of neurons in V2, we injected viral vectors expressing the calcium indicator GCaMP in V2, and performed chronic wide-field and two-photon imaging in awake, head-fixed animals viewing visual stimuli. To compare functional organization with anatomical organization, we injected viral tracers in the same or separate animals. Immunohistochemistry was performed on flattened brain sections to ease comparison of functional and anatomical data. Whereas the visuotopic map in tree shrew V1 is smooth and monotonic, the map in V2 is organized into interleaved stripes responsive to either central (-5-10°) or peripheral visual space (10-25°). This organization includes multiple smooth reversals in visuotopy, with continuity in visual space within the same stripe-type. In addition to differences in visuotopy, V2 stripes also differ in other functional properties. Central stripes, and not peripheral stripes, exhibited spatially organized orientation maps and sensitivity to horizontal disparity.
To understand the anatomical source of these functional differences, we studied the pattern of V1 axon projections in V2. As reported previously, single V1 injections produced multiple distinct patches in V2, forming an interleaved pattern of regions receiving inputs from central V1 and regions lacking input from central V1. Notably, the variations in stripe-type and thickness characterized on brain sections matched closely with those characterized via functional imaging. This suggests that the striped pattern in V2 largely stems from precisely organized and inter-leaved inputs from central and peripheral V1. We conclude that tree shrew V2 has a striped functional organization that is similar, although with notable differences in visuotopy, to primate V2.Therefore, the functional stripe organization of V2 is not a unique property of the primate brain and likely has earlier evolutionary origins. Our future studies aim to reveal the advantage of juxtaposed mapping of central and peripheral visual space in the cortex.

Disclosures: M. Sedigh-Sarvestani: None. **K. Lee:** None. **S.F. Liu:** None. **N.C. Shultz:** None. **D. Fitzpatrick:** None. **R. Satterfield:** None.

Poster

755. Visual Systems: Functional Architecture and Circuits

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Topic: D.07. Vision

Support: FRQS Grant 259957

Title: Functional and anatomical alterations in V1 of asymmetric glaucoma patients

Authors: *L. BACHATENE, L. GAGNÉ-BROSSEAU, R. J. BUTLER, S. CÔTÉ, K. WHITTINGSTALL;
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Abstract: Glaucoma alters vision in specific parts of the patient's visual field. Animal studies of glaucoma suggest that its degenerative effects extend from retina to the visual cortex, through trans-synaptic degeneration. However, such a mechanism and its relationship to visual deficits are poorly documented in humans. We sought to investigate the response of the primary visual cortex (V1) to monocular stimulation of either the glaucomatous or fellow eyes in a sample of asymmetric primary open-angle glaucoma (POAG) patients. For this, we used structural and functional magnetic resonance imaging to map the eye-specific retinotopic responses, population receptive field (pRF's) as well as corresponding cortical thickness.
First, we show that V1 responses of each eye were similar across all visual field locations of the stimuli. That is, stimulating within the scotoma (affected regions of the visual field) resulted in less V1 activation in both the glaucomatous and the fellow eyes. In addition, pRF's were similar during the stimulation of either eye.
Second, we found that, cortical areas corresponding to the scotoma (lesion projection zones or LPZ) were thinner than the healthy portions. Therefore, not only were the functional response profiles between both eyes similar, but the structural underpinnings were also identical, suggesting that despite clear differences in conscious vision, cortical alterations are indistinguishable between the diseased and the fellow eye. These findings support the trans-synaptic degeneration described in animal models, and demonstrate that cortical damages may occur while no visual loss is reported by the patient.
A better understanding of the relation between visual field defects and functional and structural changes in the brain may help understanding the neurodegenerative mechanisms of glaucoma and its progression.

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Poster

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Support: National Institute of Mental Health Intramural Research Program

Title: Electrophysiological investigation of posterior curvature-biased patches in monkeys

Authors: *S. R. ROBERT, X. YUE, M. YETTER, A. MESSINGER, L. G. UNGERLEIDER; Lab. of Brain and Cognition, Natl. Inst. of Mental Hlth., Bethesda, MD

Abstract: Curvature is one of many visual features shown to be important for visual processing. For instance, curved features provide sufficient information for categorizing animate vs. inanimate objects without top-down processing in both human (Zachariou et al., 2018) and nonhuman primates (Yue et al., 2018). Results from our fMRI study in rhesus monkeys (Yue et al. 2014) have shed light on some of the neural mechanisms underlying curvature processing. We described a network of visual cortical areas selective for curvature, one of which, the posterior curvature-selective patch (PCP), is located in dorsal V4. The fMRI responses in the PCP correlated significantly with curved Gabor filter values calculated from experimental images. The current study was designed to investigate whether the PCP contains a columnar organization for curvature, similar to the columnar organization for orientation in V1 and that for direction-of-motion in MT. We conducted electrophysiological recordings in awake, behaving macaques (n = 2) as they viewed curved Gabors manipulated along three feature dimensions: degree of curvature, orientation, and size. With electrode penetrations tangential to the surface of PCP, a correlation analysis between penetration distance and curvature revealed a marginally significant trend in one monkey ($p = 0.06$), suggesting that curvature preference increases as distance increases. Further, orientation preference correlated with penetration distance in a positive trend in one monkey and negative trend in the second ($p = 0.07$ and $p = 0.06$, respectively). Together, these data indicate that there may be curvature columns perpendicular to the surface, with orientation of curved surfaces varying across columns in the same layer. Additional data collection, with electrode penetrations both perpendicular and tangential to the surface of PCP, along with further data analysis will provide clearer and more direct evidence for whether columnar structure for the degree of curvature and orientation exists within PCP. The outcome of this study will advance our understanding of how middle-level visual features, such as curvature, are represented within macaque visual cortex.

Disclosures: S.R. Robert: None. **X. Yue:** None. **M. Yetter:** None. **A. Messinger:** None. **L.G. Ungerleider:** None.

Poster

755. Visual Systems: Functional Architecture and Circuits

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Title: The relation between inter-areal functional and structural connectivity is frequency dependent

Authors: *J. VEZOLI[1], M. VINCK[1], A. M. BASTOS[1,2], C. LEWIS[1,3], C. A. BOSMAN[4,5], H. KENNEDY[6], P. FRIES[1,4];
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Abstract: The relationship between on the one hand the strength of rhythmic neuronal synchronization and on the other hand sensory stimulation and cognitive factors is well established. Yet, the relationship between inter-areal synchronization and the strength of anatomical connectivity has remained elusive. In two macaque monkeys, we recorded with 252 channel electrocorticographic grids from the left hemisphere, while animals performed a visual attention task. For 91 pairs of cortical areas, we determined several frequency-resolved metrics of functional connectivity, namely coherence, Granger-causality and power-power correlations. For the same areas, and from an independent cohort of animals, we obtained quantitative measures of anatomical connection strength. Across the 91 area pairs, we directly related functional interactions to the corresponding anatomical connection strengths. First, inter-areal functional connectivity correlates with inter-areal anatomical connection strength. This correlation holds when partialized for distance, either physical distance, distance along the dural surface (relevant for potential volume conduction) or distance through the white matter. The strength of this correlation depends on the frequency and the metric of functional connectivity. Second, gamma band influences are more strongly correlated with the strength of the anatomical projections in the feedforward than the feedback direction; for the alpha-beta band, the opposite relationship holds. We have recently shown that gamma-band influences predominate in feedforward and alpha-beta influences predominate in feedback signaling. Hence, the above described relationship between functional and structural connectivity strength is mediated by frequency-specific directed influences and their corresponding anatomical projections. Finally, we calculated frequency-specific maps of network strength, displaying for each recording site the average strength of the functional connectivity with all other sites. These strength maps reveal distinct topographies: the gamma network dominates early and intermediate visual areas, the beta

network fronto-parietal areas, and the high-beta network pre-motor and motor areas. In summary, we show how stimulus- and task-related changes of inter-areal rhythmic synchronization are constrained by the underlying anatomical backbone in a frequency-specific manner.

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Poster

755. Visual Systems: Functional Architecture and Circuits

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Title: Assemblies of feature representation in a population of early visual neurons in the common marmoset

Authors: *M. M. FABISZAK[1], D. W. WEST[1], D. G. C. HILDEBRAND[1], S. R. SERENE[1], A. C. KOLSTAD[2], Z. WU[2], W. A. FREIWALD[1];
[1]Lab. of Neural Systems, The Rockefeller Univ., New York, NY; [2]Dept. of Cell, Developmental and Regenerative Biol. & Dept. of Neurosci., Icahn Sch. of Med. at Mount Sinai, New York, NY

Abstract: Faces form a unique category of stimuli that bridge visual perception and social cognition. They are processed in dedicated areas of cortex, face patches, which are organized into an interconnected network. While insight into neurons within face patches has been explored through extracellular electrophysiology, the functional architecture of local ensembles of cells has remained elusive. Recently discovered face patches in the lissencephalic common marmoset brain provide the cortical access necessary in order to employ optical techniques to resolve both the functional properties as well as the spatial organization of these neural ensembles. Unique to marmoset face patches, the cortical boundaries of these patches overlap with areas usually attributed to early stage visual processing. In particular, the occipitally located face patch “O” overlaps with V2, an area usually thought to be composed of neurons with tuning properties to low-level visual stimuli such as, but not limited to, orientation and direction. Here, in the anesthetized marmoset, we demonstrate the areal parcelization of function along the dimensions of low-level visual stimuli and high-level visual stimuli including faces, objects, and bodies. The resultant tuning properties are further dissected along stimulus conditions that form an

intersection between high-level and low-level stimuli. Subsequently, we utilize two-photon microscopy to achieve single cell resolution of functional activity of neurons spanning V2 and "O" that are transduced with a viral calcium indicator. Finally, we perform volumetric immunohistochemistry on the entire region of cortex studied in this experiment to both measure the density of different cell types across this span of cortex and co-register the neurons functionally recorded with two-photon microscopy with their histologically identified cell types. Together, the population measurement of intrinsic optical imaging with the histologically identified cell types of single unit recordings of two-photon microscopy provide an unprecedented view into the dynamics underlying the encoding of early stage face perception in the common marmoset.

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Poster

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Title: Neurons exclusively sensitive to texture boundaries in early visual cortex

Authors: Z. LIANG[1,2], *G. LI[3], C. L. BAKER[2];
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Abstract: Natural images from everyday scenes include a complex mixture of boundaries defined by differences of luminance (1st-order) or texture contrast (2nd-order). The majority of neurons found in early visual cortex respond to boundaries defined by luminance differences. However, many of these neurons in cat and macaque also respond to boundaries defined by texture cues (Mareschal & Baker, 1998; Li et al, 2014). Nearly all of the neurons that respond to 2nd-order boundaries, tend to respond more strongly to luminance boundaries. Neurons exclusively responsive to 2nd-order boundaries, which had been suggested by psychophysical and fMRI studies (Smith & Ledgeway, 1997; Nishida et al, 1997; Schofield & Georgeson, 1999; Ashida et al, 2007), have not been previously described in early visual cortex. Here we recorded responses of neurons in area 18 of anesthetized, paralyzed cats to ensembles of abruptly presented, static "flashed" luminance-modulated (LM) and contrast-modulated (CM) stimuli. Data were acquired from 32-channel probes (NeuroNexus, Open-Ephys). Single units were isolated from combined LM and CM datasets, using Kilosort2 and manual refinement with Phy.

Consistent with previous studies, we found neurons responsive only to luminance-defined stimulus attributes such as orientation and spatial frequency, as well as neurons responsive to both luminance- and contrast-defined boundaries. Besides these two common types of neurons, a new group of neurons were identified in our data-sets. These neurons exhibited significant response to contrast-defined boundaries, but produced little or no response to luminance-defined boundaries. Unlike neurons responsive to both luminance- and contrast-defined boundaries, which show clear tuning to carrier spatial frequency and weak tuning to carrier orientation, these neurons were not tuned to carrier properties. These results show that some area 18 neurons' response is specific to 2nd-order stimuli - they were not previously discovered due to methodology limitations. These neurons could serve as "2nd-order decoders" parsing texture contrast boundaries in the early visual system, invariant to the spatial properties of the textures.

Disclosures: Z. Liang: None. **G. Li:** None. **C.L. Baker:** None.

Poster

755. Visual Systems: Functional Architecture and Circuits

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 755.12/J20

Topic: D.07. Vision

Title: Neocortical interneuron subtype dynamics in mouse visual cortex: A potential cortical circuit motif for sensory detection

Authors: *A. I. MORE[1,2], C. A. DEISTER[1,2], A. R. TULETT[1,2], C. I. MOORE[1,2];
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Abstract: Inhibitory interneurons are critical to neocortical computations, and diversity among them is thought to regulate the trial-by trial dynamics that shape perception. Specifically, parvalbumin-positive interneurons (PV) are key components of neocortical circuit motifs. Recent studies in several sensory modalities have tied PV, and their dynamics on single trials, to perceptual success. While PV have often previously been treated as a functionally homogenous populations, recent results from our lab in mouse primary somatosensory cortex (SI) demonstrate distinct dynamics in PV during threshold-level tactile detection. Specifically, two populations of PV exist that show either higher evoked firing rates for hits or for misses. These inhibitory dynamics suggest a specific wiring diagram that, when implemented in a computational model, can explain the rate and correlation dynamics in pyramidal neurons that carry perceptually-relevant signals. Based on additional preliminary evidence from our lab, there are multiple SOM subtypes as well that predict both hits and misses, with a bias toward hit-predictivity. These findings, in combination with our model circuit motif, implicate miss-predictive PV as the regulators of the pyramidal cells that carry the perceptually meaningful signal, and that these cells open a gate for successful sensory perception.

To test whether these distinct functional PV subtypes may be idiosyncratic to vibrissae processing in SI or could be a basic circuit motif for selectively prioritizing information flow through neocortex, we implemented a visual detection task in head-fixed mice during simultaneous two-photon calcium imaging. Under perceptually demanding task conditions, we recorded PV, SOM, and pyramidal cell activity in layers II/III of mouse primary visual cortex during threshold-level contrast detection. We imaged for twenty-five days throughout the acquisition of the task and also during high behavioral performance. The PV-Cre and SOM-Cre driver mouse lines were used to express GCaMP6s to assess basic detection of stimuli with different contrasts and probe PV, SOM, and pyramidal cell function, rate dynamics, and correlation structure (n = 7 mice). Data suggest distinct populations of PV in V1, with PV populations that predict hits and misses during perceptual performance.

Disclosures: **A.I. More:** None. **C.A. Deister:** None. **A.R. Tulett:** None. **C.I. Moore:** None.

Poster

755. Visual Systems: Functional Architecture and Circuits

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 755.13/J21

Topic: D.07. Vision

Title: Augmenting deep neural networks with a recurrent model of grouping and border ownership

Authors: B. HU[1], ***S. KHAN**[2], B. P. TRIPP[2], E. NIEBUR[3];
[1]Allen Inst. For Brain Sci., Seattle, WA; [2]Systems Design Engin., Univ. of Waterloo, Waterloo, ON, Canada; [3]Johns Hopkins Univ., Baltimore, MD

Abstract: Figure-ground segmentation, or the organization of visual input into foreground and background regions, is an important component of scene understanding. Previous experimental work showed that neurons in primate extrastriate cortex can signal figure-ground relationships via differences in firing rates along object contours (border ownership coding). Computational models propose that recurrent interactions between populations of ``border ownership" and ``grouping" neurons, which integrate local feature information from border ownership neurons, provide a perceptual organization of the visual scene and can explain the observed border ownership coding. In these models, the connection weights between populations of neurons were manually specified. In the present work, we allow these connections to be learned in the context of different image segmentation tasks. We developed a convolutional network architecture with putative border ownership cells that were recurrently connected to grouping cells. For the first layer, we used the pretrained kernels from AlexNet, some of which resembled Gabor filters. Each cell in this first layer fed a pair of border ownership cells in the second layer. These pairs of cells were mutually inhibitory. The border ownership cells were also recurrently connected to

grouping cells. The kernels that connected border ownership and grouping cells in each direction were trained via backpropagation, with a regularizer that encouraged ring-shaped kernel structures. We included multiple scales of grouping cells via dilated convolutions.
The network branched out from this early-vision model into two directions, corresponding to outputs for different image segmentation tasks (object contour detection and figure-ground orientation labelling). Ablation experiments with different architectures showed that feedback from grouping cells improved performance by 2-4% on the contour detection task, and 20-27% on the figure-ground orientation task. Our results represent an important step towards incorporating border ownership into deep neural networks that are optimized for different visual tasks, and may provide further insight into its functional role.

Disclosures: **B. Hu:** None. **S. Khan:** None. **B.P. Tripp:** None. **E. Niebur:** None.

Poster

755. Visual Systems: Functional Architecture and Circuits

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 755.14/J22

Topic: D.07. Vision

Support: Whitehall Foundation
University of Texas at Austin
NIH Grant EY028657

Title: Retinotopic dependencies of receptive field properties in mouse V1

Authors: *I. M. NAUHAUS[1,2,3], I. RHIM[1,3];
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Abstract: The mammalian retina distributes its resources across the visual field to more efficiently encode the most relevant statistics at each location of the natural environment. This is especially true in the mouse retina, which exhibits a spatially inhomogeneous distribution of photoreceptors and retinal ganglion cell-type. Retinal inhomogeneity has been linked to rodent behavioral output, yet the recapitulation of these maps at the level of visual cortex has not been thoroughly investigated. With two-photon imaging, we mapped each V1 neuron's retinotopy with a drifting bar stimulus, followed by characterization with a battery of gratings that varied in spatio-temporal frequency and color in cone-ospin (short 'S' & medium 'M') contrast space. First, we are assessing whether retinotopic dependencies of spatial frequency match local distortion in cortical magnification factor, as higher spatial frequencies require greater sampling density to maintain the same coverage. Next, we will show results on color tuning as a function of retinotopy. Color tuning is a particularly attractive avenue to study cortical transformations, as

previous studies in the retina have rigorously modeled S- and M-input to retinal ganglion cells as a function of the dorsoventral axis. We are using these front-end models of the anisotropy to model transformations between the retina and cortex. In addition to chromatically varying gratings, we are using sparse noise in both S- and M-opsin contrast to map the inputs of the cone opsins within each receptive field. We are testing for retinotopic dependence of cone opsin opponency that is predicted by either random or systematic wiring from the retina to V1.

Disclosures: I.M. Nauhaus: None. **I. Rhim:** None.

Poster

755. Visual Systems: Functional Architecture and Circuits

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 755.15/J23

Topic: D.07. Vision

Support: Whitehall Foundation Grant 2018-05-57

Title: Contribution of intracortical inhibition to large-scale functional networks in early visual cortex

Authors: H. N. MULHOLLAND[1], B. HEIN[2], M. KASCHUBE[2], *G. B. SMITH[1];
[1]Neurosci., Univ. of Minnesota, Minneapolis, MN; [2]Frankfurt Inst. For Advanced Studies, Frankfurt Am Main, Germany

Abstract: In the visual cortex of carnivores and primates, large-scale functional networks span millimeters of cortical area. We have previously shown that in the ferret these large-scale networks are evident in the patterns of correlated spontaneous activity well before both eye-opening and the emergence of visually-evoked functional maps. This early correlated spontaneous activity arises from intracortical interactions and is predictive of future visually-evoked responses. Additionally, computational models suggest that propagating activity through purely short-range connections is sufficient to generate long-range correlated networks in the early cortex. These models require the coordinated interaction of intracortical excitation and inhibition, yet previous experiments have only measured the activity of excitatory cells in the early cortex.
Here, we use inhibitory-specific expression of genetically-encoded calcium sensors to monitor the spontaneous activity of inhibitory neurons in the early visual cortex. Inhibitory neurons show highly modular activity patterns, with a spatial scale similar to that observed previously for excitatory cells. Likewise, inhibitory neurons exhibit long-range correlations in their spontaneous activity, demonstrating their participation in millimeter-scale functional networks in the early cortex. Correlated spontaneous activity changed smoothly across cortical locations, punctuated by abrupt shifts in structure, previously termed ‘correlation fractures’, indicating that inhibitory

neurons also show precise fine-scale organization. When inhibitory and excitatory neurons were co-labeled, we found that the patterns of spontaneous activity were highly correlated between nearby excitatory and inhibitory cells, suggesting that inhibitory neurons participate in the same functional networks as excitatory cells. Lastly, we demonstrate that as early as P21 (~10 days before eye-opening), GABAergic signaling has a net inhibitory effect on cortical networks, consistent with our computational models. Taken together, our results show that intracortical inhibition is already highly organized into functional networks in the early visual cortex, and suggest that early inhibitory activity may play a role in shaping mature network organization.

Disclosures: H.N. Mulholland: None. **B. Hein:** None. **M. Kaschube:** None. **G.B. Smith:** None.

Poster

755. Visual Systems: Functional Architecture and Circuits

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 755.16/J24

Topic: D.07. Vision

Support: UM Endownent for the Biosciences

Title: Implementation of human connectome low vision (HCLV) imaging protocol at University of Michigan

Authors: *N. NADVAR[1], J. CHOUPON[2], K. LITINAS[3], Y. SHI[2], L. HERNANDEZ-GARCIA[1,3], J. WEILAND[1];
[1]Biomed. Engin. Department, Univ. of Michigan, Ann Arbor, MI; [2]Lab. of Neural Imaging, Keck Sch. of Medicine, USC Stevens Neuroimaging and Informatics Institute, Univ. of Southern California, Los Angeles, CA; [3]fMRI Laboratory, Univ. of Michigan, Ann Arbor, MI

Abstract: One challenge in merging multicenter neuroimaging data is to derive standardized data features that best signify each center's performance in spite of the inevitable variation in acquisition due to scanners or adopted procedures. In the current work, we aimed to harmonize the acquisition of the magnetic resonance imaging (MRI) data involved in Human Connectome Low Vision (HCLV) project at two imaging centers: University of Southern California (USC) and University of Michigan (UM). To achieve this goal, we executed a case study in which we recruited a traveling subject, a normally-sighted male adult, at both locations. One T1-weighted (T1W) structural and six block-design task functional MRI runs were acquired with identical paradigms at each center. At USC, a 3T Siemens Prisma scanner was used with voxel size 2x2x2 mm (functional) and 0.8x0.8x0.8 mm (structural) and a multiband (MB) factor of 8 for functional runs. At UM, a 3T MR750 GE scanner was used with MB factor of 6, voxel size 2.4x2.4x2.4 mm (functional) and 0.5x0.5x0.8 mm (structural). Preprocessing consisted of

homogeneity, physiological noise, field map, motion and slice-timing corrections as well as smoothing, high-pass filtering, registration to T1 MNI152 template. One T1W and one fMRI run were also obtained from a spherical water-based fBIRN phantom filled with agar gel at each center. In order to quantify the performance of the different scanners, we calculated spatial SNR (Signal-to-Noise-Ratio), spatial CNR (Contrast-to-Noise-Ratio; for gray matter (GM) vs white matter (WM) vs CSF) and temporal SNR. In order to make an equitable assessment between the two centers, same repetition time (TR = 0.8 s) and number of volumes were used for each pair of functional runs; also the spatial and temporal SNR/CNR values were normalized per unit volume to account for differences in voxel sizes at two centers (nSNR/nCNR). Mean spatial nSNR was 42.9/317.1 (human/phantom) at UM and 25.8/54.6 (human/phantom) at USC. Mean spatial nCNR values for GM-WM, GM-CSF, WM-CSF contrasts were respectively 23.6, 15.6 and 39.3 at UM and 9.7, 11.7 and 21.4 at USC. Mean temporal nSNR across voxels of the subject at both locations yielded comparable results (mean of 3.5 vs 3.7 (UM vs USC) across all tasks), whereas this quantity for phantom data was 8.3 vs 16.8 (UM vs USC). Evidently, this study was able to narrow down the potential area of improvement for implementation of the HCLV protocol at UM to improvement in functional acquisitions. Difference in functional acquisition results between the two centers necessitates further investigation and should be accounted for in any combined group analyses of both centers.

Disclosures: **N. Nadvar:** None. **J. Choupon:** None. **K. Litinas:** None. **Y. Shi:** None. **L. Hernandez-Garcia:** None. **J. Weiland:** None.

Poster

755. Visual Systems: Functional Architecture and Circuits

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 755.17/J25

Topic: D.07. Vision

Support: NSF IOS-1455869
NSF GRFP to MMS
UCLA Depression Grand Challenge

Title: Serotonergic neuromodulation in the *Drosophila* visual system

Authors: *M. SAMPSON, K. MYERS GSCHWENG, B. HARDCASTLE, S. BONANNO, M. FRYE, D. KRANTZ;
UCLA, Los Angeles, CA

Abstract: Serotonergic neurons extensively innervate the visual system of the fruit fly *Drosophila melanogaster*, yet the role of serotonin signaling in visual processing is unknown. Identification of individual cells expressing serotonin receptors in visual system circuits will

allow us to determine the contribution of serotonergic modulation to visual processing computations. Five genetically distinct serotonin receptors are expressed throughout the optic lobe and we identified specific neurons and visual processing pathways targeted by serotonin neuromodulation. Single-cell labeling mapped serotonin receptors to specific visual processing neurons: L2, L4, L5, T1, Lawf1, and Lawf2. Lamina monopolar cell 2 (L2) receives direct input from photoreceptors and expresses the serotonin receptor 5-HT2B. Calcium imaging confirmed an increase in baseline calcium in response to bath-applied serotonin in L2 and its electrically coupled partner, L1. L1 and L2 are the first-order neurons in the light-ON and light-OFF pathways, respectively, and both information streams feed into motion detection circuits. L1 neurons do not express serotonin receptors, demonstrating that indirect mechanisms such as gap junctions enable neuromodulators to influence cells in the absence of receptors. We tested whether serotonin modulates visual responses in L2 neurons and found that serotonin increased the magnitude of visually induced calcium transients. This suggests that acute neuromodulation may regulate salience to specific visual stimuli in the light-OFF pathway. To examine long-term effects of serotonergic neuromodulation, we measured transcriptomic changes in L2 neurons following chronic increases in serotonin signaling. Together, these data allow us to compare serotonin modulation over multiple timescales. This work will reveal molecular pathways and transcriptional programs downstream of serotonin signaling cascades that are important for neuromodulation and will contribute to the understanding of how neuromodulatory signaling is integrated into sensory circuits.

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Poster

755. Visual Systems: Functional Architecture and Circuits

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 755.18/J26

Topic: D.07. Vision

Support: NEI Grant EY025858-3

Title: Predicting cortical thickness of primary visual cortex based on curvature and retinotopic eccentricity

Authors: *M. DEFENDERFER, K. M. VISSCHER;
Univ. of Alabama at Birmingham, Birmingham, AL

Abstract: Primary visual cortex (V1) has been one of the most heavily studied areas in the brain due to its role in processing vision, easily defined location at the calcarine sulcus, ease of stimulation, and its well-defined retinotopic organization. High resolution structural analysis of

V1 in humans has been made possible due to advances in MRI and surface reconstruction pipelines such as FreeSurfer (Dale et al., 1999). Measures of cortical thickness and curvature have been used in a variety of contexts, including healthy aging (Salat et al. 2004), cortical plasticity (Burge et al. 2016), and gyrification estimation (Luders et al. 2006). Anecdotal reports suggest that sulci may be associated with decreased cortical thickness compared to gyri, but we are not aware of explicit documentation of that trend. In retinotopic organization, areas of visual cortex associated with central vision (low eccentricity) have been found to have higher cortical thickness than areas associated with peripheral vision (high eccentricity) (Burge et al. 2016). However, to the best of our knowledge, no study has directly examined how eccentricity and curvature jointly predict cortical thickness. Our aim is to determine whether the effects of curvature and eccentricity on cortical thickness are independent and to identify the relationship among the three variables. In order to accomplish this, FreeSurfer outputs from the Human Connectome Project's Young Adult dataset were manually checked to exclude subjects with surface defects resulting in 786 quality subjects. We used a retinotopic atlas (Benson et al., 2018) to assign retinotopic coordinates to each vertex in V1. Curvature and cortical thickness values as defined by FreeSurfer and eccentricity values defined by the atlas were extracted and input to a linear model. Negative curvature values indicate convexity (including gyri) while positive values indicate concavity (including sulci). We found highly significant main effects on cortical thickness showing that thickness decreases with eccentricity ($p < 0.0001$, slope = -0.0025 mm/deg visual angle) and that thickness decreases with more concave curvature ($p < 0.0001$, slope = -.3484 mm/unit curv). We also observed a highly significant interaction of eccentricity and curvature ($p < 0.0001$, slope = 0.0207 mm/(deg*unit curv)). These results show that cortical thickness changes in a predictable manner across the cortical surface. This information is essential to future studies examining individual differences in cortical thickness, for example, determining how cortical thickness may have changed relative to what is expected in individual participants who have visual disorders.

Disclosures: M. Defenderfer: None. **K.M. Visscher:** None.

Poster

755. Visual Systems: Functional Architecture and Circuits

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 755.19/J27

Topic: D.07. Vision

Title: Could a neuroscientist understand a ConvNet?

Authors: *M. D. OLIVER[1], D. MILLMAN[2], S. E. DEVRIES[3], M. A. BUICE[3];
[1]Allen Inst. for Brain Sci., Seattle, WA; [2]Neural Coding Group, [3]Allen Inst. For Brain Sci., Seattle, WA

Abstract: Convolutional neural networks (ConvNets) are inspired by the hierarchical organization of the visual system as described by Hubel and Wiesel. When trained on visual object recognition tasks, ConvNets exhibit internal behavior that appears to resemble processing found in visual cortex. Because the entire architecture of a ConvNet is differentiable, it simple to characterize the artificial neurons within a trained ConvNet in terms of their optimal stimuli. Combined with the fact that the ConvNet provides a complete mechanistic description of unit responses, a trained ConvNet is thus a natural testing ground for the techniques used in visual neuroscience to characterize neurons. In this work we conduct in silico experiments on ConvNets analogous to those performed on animals in many electro physiology and optical-physiology labs. We analyze the responses of several pretrained ConvNets in response to a variety of standard stimuli (i.e. sparse noise, gratings, and natural images) to answer the following questions: Do traditional techniques such as the spike triggered average (STA) and spike triggered covariance (STC) reveal the fundamental tuning properties of the artificial neurons in a ConvNet? How do the features identified by STA and STC relate to the artificial neuron's optimal stimuli? Is spatial frequency tuning as measured with gratings meaningful for higher order artificial neurons? When do these techniques provide useful information and when are they misleading? Can more advanced nonlinear regression techniques provide more accurate characterizations of the selectivity of the artificial neurons? What stimuli work best for characterizing the responses of artificial neurons? How many stimulus-response pairs are necessary for fully characterizing an artificial neuron in the presence of biologically and experimentally realistic levels of noise? In answering these questions, we hope to provide the community with a better understanding of the virtues and drawbacks of current visual neuroscience techniques and provide guidance for effective neural characterization in future electrophysiology and optical-physiology experiments.

Disclosures: **M.D. Oliver:** None. **D. Millman:** None. **S.E. DeVries:** None. **M.A. Buice:** None.

Poster

755. Visual Systems: Functional Architecture and Circuits

Location: Hall A

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Program #/Poster #: 755.20/J28

Topic: D.07. Vision

Support: NIH Grant R01 NS099061
NIH Grant 5T32HD071844-05

Title: Connectivity of the Tool Action Network: Lesion- and connectome-based symptom mapping of limb apraxic deficits after left hemisphere cerebrovascular accident

Authors: *F. GARCEA[1], C. A. GREENE[3], S. T. GRAFTON[4], L. J. BUXBAUM[2];
[1]Moss Rehabil. Res. Inst., Philadelphia, PA; [2]Moss Rehabil. Res. Inst., Elkins Park, PA; [3]UC Santa Barbara, Santa Barbara, CA; [4]Psychological & Brain Sci., UCSB, Santa Barbara, CA

Abstract: Recognizing, imitating, and producing skilled actions requires the integration of diverse computations supported by anatomically remote regions. Understanding how action systems in parietal cortex interface with semantic representations of action in the temporal lobe, and frontal lobe selection mechanisms remains a critical issue to address. Here we present two studies using support vector regression lesion symptom mapping (SVR-LSM) and connectome-based lesion symptom mapping to investigate where lesions perturb long-range connectivity among temporal, frontal, and parietal regions involved in action processing.

In the first study, we used SVR-LSM to investigate where lesion location predicted the severity of limb apraxia, a deficit in skilled action ability following left cerebrovascular accident (LCVA). Sixty-six LCVA participants took part in a battery of neuropsychological tests measuring tool use gesturing, novel gesture imitation, and gesture recognition. Impaired tool use gesturing was associated with lesions to the left inferior parietal lobule (LIPL), superior parietal lobule (LSPL), and left middle (LMFG) and inferior frontal (LIFG) gyri. Impaired novel gesture imitation was associated with lesions to peri-Sylvian regions, including the left superior temporal sulcus, LIPL, and LSPL. Gesture recognition ability was associated with lesions to the LMFG, LIFG, and left posterior middle temporal gyrus (LMTG). Importantly, these data replicate past studies, including findings from our lab.

In the second study, we correlated praxis deficits with the degree of structural connectivity among regions identified with SVR-LSM and remaining cortical and subcortical nodes in left and right hemispheres. Disconnection was estimated by projecting individual lesions into a Human Connectome Project derived structural connectome. The degree of impairment in tool use gesturing was associated with disconnection among right frontal and supramarginal gyri, LIFG, LIPL, LSPL, and LMTG adjacent to the lateral occipital cortex. Impairments in novel gesture imitation were associated with disconnection among left posterior intraparietal sulcus, LSPL, and right premotor and prefrontal cortex. Lastly, error-prone gesture recognition was associated with disconnection among the LMFG, LIFG, a white matter “bottleneck” medial to the insula, and the right MTG and right lateral occipital cortex.

Our findings suggest that praxis function is underpinned by a bilateral network of frontal, temporal, and parietal regions, with dissociable connectivity patterns determined by computations engaged in action recognition, imitation, and production.

Disclosures: F. Garcea: None. **C.A. Greene:** None. **S.T. Grafton:** None. **L.J. Buxbaum:** None.

Poster

755. Visual Systems: Functional Architecture and Circuits

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 755.21/J29

Topic: D.07. Vision

Support: Simons Junior Fellowship
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The Gatsby Charitable Foundation
NVIDIA

Title: Multi-cell-type convolutional recurrent neural network models of visual cortex

Authors: M. SUN[1], J.-A. LI[2], M. DIPOPPA[1], *G. R. YANG[1];
[1]Columbia Univ., New York, NY; [2]Univ. of Sci. & Technol. of China, Hefei, China

Abstract: Deep convolutional neural networks (CNNs) are currently the leading models in explaining neural responses across the visual cortex of mice and monkeys. This success relies presumably on CNN's use of basic biological structural principles, including the hierarchical organization of visual areas. However, further comparisons with biological systems are hindered by CNNs' lack of structural motifs such as segregation of excitatory and inhibitory neurons. Here we ask whether CNNs endowed with multiple cell types and recurrent connections can succeed on the challenging ImageNet object classification task, and whether the network can recapitulate prominent cell-type specific findings regarding neural responses and connectivity from the visual cortex.More than half of the cortical inhibitory neurons express either parvalbumin (PV) or somatostatin (SST). PV and SST neurons are proposed to control the output and input of excitatory neurons, respectively, with local recurrent connections. Incorporating this structural motif, we built CNNs consisting of three model cell types: excitatory, input-controlling PV, and output-controlling SST neurons. Model excitatory neurons form recurrent connections locally and make long-range feedforward connections across areas.The network reached a performance on ImageNet close to that of recently proposed recurrent CNNs without the biological constraints. Experimental findings showed that excitatory and inhibitory neurons in the visual cortex have different response profiles and connectivity patterns. We tested whether these cell-type specific features can naturally emerge in our network through training. Similar to observations from mouse visual cortex, the connections from model inhibitory neurons to excitatory neurons after training were denser than those between excitatory neurons. Furthermore, the model reproduced the observed weaker orientation tuning in inhibitory neurons compared to excitatory neurons. This study demonstrates for the first time that artificial neural networks incorporating key biological constraints can match cell-type specific experimental findings while maintaining the ability to solve challenging tasks.

Disclosures: **M. Sun:** None. **J. Li:** None. **M. Dipoppa:** None. **G.R. Yang:** None.

Poster

755. Visual Systems: Functional Architecture and Circuits

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 755.22/J30

Topic: D.07. Vision

Support: NSERC Discovery Grant 418331

Title: Deep convolutional network model of macaque visual cortex

Authors: *B. P. TRIPP;
Univ. of Waterloo, Waterloo, ON, Canada

Abstract: Computational models can be useful for understanding how neural mechanisms relate to brain function. However, computational models are often capable of only simple behaviour. Deep networks, in contrast, make sophisticated decisions based on naturalistic stimuli, so they may be a good starting point for brain models with more realistic function. I developed a deep-network architecture that closely matches the architecture of primate visual cortex. The model has over 100 layers, corresponding to different cortical layers within 31 different visual areas. Various neuroanatomical properties from the macaque literature were approximated, including data from retrograde tracer studies, estimates of interlaminar connection densities and neuron counts, and receptive field sizes from electrophysiology. Each of these neuroanatomical measures was expressed as a function of convolutional network hyperparameters. An optimization approach was used to find hyperparameters that resulted in realistic neuroanatomical properties. The resulting architecture closely matches the data. Interestingly, the model has qualitatively different connection sparsity than past convolutional networks. Using a standard sparse-connection initialization scheme from the deep-learning literature, part of the ventral stream was trained on the CIFAR-10 dataset. This resulted in performance well below state of the art (79% accuracy on the validation data), suggesting that a somewhat non-standard approach may be needed to initialize and train biologically realistic architectures for high performance. Regardless, the model can process the same stimuli that are shown to humans in visual psychophysics tasks, it can be probed in detail to understand how it makes decisions, and its visual representations can be compared one-to-one with those of corresponding populations in the brain.

Disclosures: **B.P. Tripp:** None.

Poster

755. Visual Systems: Functional Architecture and Circuits

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Program #/Poster #: 755.23/J31

Topic: D.07. Vision

Support: Fondecyt 1170027

Title: Main cell types of the avian pallial visual DVR indeed express a mammalian cortical phenotype

Authors: C. NORAMBUENA, C. GONZALEZ-CABRERA, M. FERNÁNDEZ, G. MARÍN, *J. MPODOZIS;
Univ. de Chile, Santiago, Chile

Abstract: Despite seemingly differences in cytoarchitecture and early gene patterning, avian and mammalian pallial territories exhibit structural similarities that point to the existence of a common anatomical organization shared from early ancestry. The cell-type homology hypothesis, based on similarities in circuitry and neurochemistry, states that layer-specific cortical cell populations have equivalences with specific cell populations forming the nuclear masses of the avian pallial DVR. In the canonical neocortical circuit, layer 4 glutamatergic cells receive thalamic inputs and connect reciprocally, in a columnar fashion, with glutamatergic cells in the upper layers 2 and 3. Similarly, in the avian visual DVR, cells at the nucleus entopallium receive visually driven thalamic afferents and sustain "columnar-like" reciprocal connections with cells in the intermediate nidopallium and ventral mesopallium. Interestingly, layer 4 specific molecular markers such as EAG2 (ether-a-go-go2, a potassium channel gene) and RORβ (RAR-related orphan receptor beta, a transcription factor gene), as well as the vesicular glutamate transporter2 (VGLUT2), are also expressed massively at the entopallium. At present, it is unknown whether the entopallial neurons expressing EAG2, RORβ and VGLUT2 are involved in the columnar projection circuit. In addition, the molecular phenotype of the nidopallial and mesopallial cells involved in the columnar-like circuitry is also unknown. We investigated such issues in chicks (*Gallus gallus*) by combining injections of a fluorescent retrograde neural tracer (CTB-AF555) into the entopallial and nidopallial targets, with fluorescent "*in situ*" hybridization. We found that most "column-forming" entopallial cells were VGLUT2+ and also expressed EAG2 and RORβ. We also found that nidopallial and mesopallial cells involved in the columnar circuitry indeed expressed a glutamatergic phenotype, same as their mammalian hodological equivalents. These results further demonstrate that the avian forebrain contains cell types with connectional and molecular features proper of the cells of the mammalian sensory cortices. In particular, column-forming entopallial cells and cortical layer 4 senso-recipient cells appear to share several unique features, which lend a strong support to the cell-type homology hypothesis.

Disclosures: **C. Norambuena:** None. **C. Gonzalez-Cabrera:** None. **M. Fernández:** None. **G. Marín:** None. **J. Mpodozis:** None.

Poster

756. Decision Making III

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 756.01/J32

Topic: D.07. Vision

Support: Watson School of Biological Sciences
ONR MURI

Title: A two stage Bayesian observer predicts the effects of learning on perceptual decisions

Authors: ***S. PISUPATI**, S. MUSALL, A. E. URAI, A. K. CHURCHLAND;
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Abstract: Perceptual inference and reinforcement learning represent two specializations of Bayesian decision theory, describing optimal strategies in the face of perceptual or value uncertainty respectively (Dayan and Daw '08, Gershman and Daw '12). However, in real-life decisions, subjects may be simultaneously faced with both forms of uncertainty. This occurs, for instance, during early stages of training on perceptual decision-making tasks when subjects are learning stimulus-response-outcome associations from noisy observations. Here we describe a two-stage Bayesian learner that takes both forms of uncertainty into account. First, the observer uses noisy sensory observations on a given trial to update its beliefs about the state of the world. Second, the observer uses outcome observations across trials to update its beliefs about the value of different state-action pairs, taking into account the uncertainty in state estimation. The observer picks actions by sampling from these value beliefs and picking actions that maximize expected value with respect to the sample. This strategy, also known as Thompson sampling, promotes exploratory actions when value uncertainty is high, and automatically becomes more exploiting as this uncertainty decreases with training. The two-stage observer model makes predictions about how psychometric curves should evolve with learning of initial contingencies, reversals and changing priors (for different models of the world and different levels of perceptual and value uncertainty), in particular making strong predictions about changes in performance at the asymptotes of the curve or "lapses". The model also makes predictions about how the effects of sensory or value perturbations should change as animals learn. We compare these predictions to behavior of rats and mice under normal circumstances and following optogenetic perturbations of frontal and parietal cortices.

Disclosures: **S. Pisupati:** None. **S. Musall:** None. **A.E. Urai:** None. **A.K. Churchland:** None.

Poster

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Pew Scholarship in the Biomedical Sciences
McKnight Scholar Award

Title: Distributed neural signatures of evidence integration during prolonged deliberation

Authors: *M. L. WASKOM, L. SIDANI, R. KIANI;
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Abstract: Decisions made under uncertainty can benefit when multiple pieces of relevant information, or evidence, are combined internally through a process of integration. Because evidence must often be accumulated over time, models of evidence integration highlight the close relationship between decision making and memory. Key to the development of such models has been the measurement of neuronal firing rate dynamics during decision formation. In rapid perceptual judgment tasks, ramping neuronal responses reflect a signature of integration, motivating efforts to understand the neural circuit mechanisms that provide a mnemonic basis for decision making. Recently, we reported that humans can produce behavior that approximates normative integration even when they must deliberate over much longer durations than encountered in standard tasks (Waskom & Kiani 2018, Current Biology). This invariance to timescale is inconsistent with the predictions of many existing circuit models, prompting us to seek a broader perspective on the neural substrates of evidence integration. To that end, we have conducted a human fMRI experiment aimed at characterizing the relationship between computational models of prolonged deliberation and measurements of neural activity across the whole brain. On each trial, subjects sequentially viewed 2-5 spatially localized Gabor patches with contrast intensities that had been sampled from one of two overlapping distributions. The subject's task was to make an inference about the generating distribution and, when prompted, signal their choice with an eye movement to one of two targets. The stimuli were briefly presented (200 ms) and separated by long, unpredictable gaps (2-8 s). This temporal control allowed us to model the dynamics of evidence integration at the timescale of the BOLD response. We have characterized these dynamics using intensive sampling of individual subjects (N=3, 240 min of task data per subject) and with respect to functional organization as determined by population receptive field modeling of visually-responsive voxels and resting-state mapping

of association cortex networks. Our results indicate that neural signatures of evidence integration are widespread and diverse, with the amplitude and temporal profile of responses in most visual and association regions exhibiting one of several distinct relationships to components of our evidence integration model. Together, these findings offer new quantitative insights about the interactions between sensory representations, working memory maintenance, and long-term memory storage that confer temporal flexibility on deliberative reasoning processes.

Disclosures: M.L. Waskom: None. **L. Sidani:** None. **R. Kiani:** None.

Poster

756. Decision Making III

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Topic: D.07. Vision

Support: NIH Grant R01EY022930
Simons Collaboration for the Global Brain
McKnight Scholar Award

Title: Continuous decision-making as a lens into neural computation

Authors: *F. BAQAI[1], D. A. RUFF[2], B. D. DOIRON[3], M. R. COHEN[4];
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Abstract: Perceptual decision-making is a multi-faceted process. In natural behavior, decisions are affected by sensory thresholds, global cognitive processes like motivation or concentration, and selective cognitive processes like attention or prior beliefs. In the laboratory, these effects of these processes are typically studied in isolation or, rarely, in pairs. However, interactions between sensory, global, and selective processes might provide important insights into the computations and neural mechanisms underlying decision-making. In order to more sensitively probe these interactions we used a task with a continuous behavioral output in which subjects indicate the perceived direction of motion by looking at a point on a circle (Nichols and Newsome 2002; Cloherty et al 2019). We extended the task to include reaction times, global cognitive processes (by manipulating task difficulty), and selective cognitive processes (by changing the distribution of motion directions presented). Importantly, the changes in task difficulty and motion distributions were unsignaled. This setup allowed us to measure how, for example, concentration affects the ability of rhesus monkeys to notice changes in the distribution of motion directions, or whether there is an interaction between sensory thresholds and overall performance or sensitivity to the distribution of stimuli. To quantify these interactions and make

predictions about behavior and neural responses, we extended a standard accumulation to bound model (Gold and Shadlen 2007) to account for this continuous report by reshaping the bound into a ring. This model gives us interpretable parameters, but is still powerful enough to predict behavior. This model and task combination gives us sensitivity to changes in reaction times and choices associated with cognitive processes. This combination also provides a framework for understanding a subject's strategy, allowing us to investigate implications of the speed-accuracy tradeoff on reward. The model also makes predictions for neuronal mechanisms by determining whether cognitive processes affect the sensory representation (implicating visual cortex) or the starting point or dynamics of the decision (implicating premotor areas). Interactions between sensory and cognitive processes would imply interactions between the areas mediating each process. We will test these predictions in multineuron, multi-area recordings. More generally, combining a task with well-controlled stimuli and a rich behavioral output with a normative model will provide and important framework for designing experiments and interpreting behavioral and neuronal results.

Disclosures: F. Baqai: None. **D.A. Ruff:** None. **B.D. Doiron:** None. **M.R. Cohen:** None.

Poster

756. Decision Making III

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Topic: D.07. Vision

Support: NIH grant R01EY022930
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McKnight Scholar Award

Title: Adapting to an ever-changing world: How the brain makes decisions in the face of evolving behavioral rules

Authors: *C. XUE, L. E. KRAMER, M. R. COHEN;
Dept. of Neurosci. and Ctr. for the Neural Basis of Cognition, Univ. of Pittsburgh, Pittsburgh, PA

Abstract: How do we flexibly adapt to a constantly changing world? While most of our senses are already developed during infancy, it is the capability of learning and updating the behavioral relevance of sensory information that makes animals and humans strong survivors in the wild or within a society. An abundance of psychophysical and electrophysiological studies on behaving animals have revealed how belief about the behavioral relevance of sensory information (often termed attention) modulates perception. On the other hand, it remains an open question how we flexibly change our beliefs based on perceptual evidence and what cognitive and neuronal factors

limit this flexibility.
We recorded simultaneously from groups of neurons in visual cortex (area V1) and parietal cortex (area 7a) while macaque monkeys performed perceptual decision-making tasks with rules evolving over time. The monkeys were required to: 1. discriminate different features of the same visual stimuli depending on the rule, and 2. flexibly update their beliefs about the current task rule (feature to be discriminated) based on what their history of stimuli, behavior, and rewards. Despite the fact that visual perception and task switching are thought to be mediated by different neural mechanisms and brain areas, we that there is a trade-off between the visual discrimination two: whenever the monkey does better at the perceptual task under a certain rule, he becomes less flexible in adapting to a new rule. We built models that predict both the monkey's choice and neuronal activity on a trial by trial basis. Overall, our results imply that there is a cognitive bottleneck that limits the brain's ability to perform well on a task while being flexible to take on other tasks. Models that describe behavior in this task may shed light on the neuronal underpinnings of cognitive flexibility in general.

Disclosures: **C. Xue:** None. **L.E. Kramer:** None. **M.R. Cohen:** None.

Poster

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Topic: D.07. Vision

Support: NIH Grant R01EY022930
Simons Collaboration for the Global Brain
McKnight Scholar Award

Title: A multi-population, multi-task framework yields new insights about decision-making mechanisms

Authors: C. XUE[1], **L. E. KRAMER**[2], *M. R. COHEN[2];
[1]Ctr. for the Neural Basis of Cognition, Pittsburgh, PA; [2]Dept. of Neurosci. and Ctr. for the Neural Basis of Cognition, Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Perceptual decision-making, which is perhaps the premiere system for studying the relationship between neurons and behavior, has been dominated by two largely non-overlapping approaches. One approach aims to correlate the activity of sensory neurons with choices, typically in two-alternative forced-discrimination tasks. The other approach compares different task conditions to measure how cognitive processes like attention affect sensory responses. Some important conclusions from the two lines of work seem contradictory. Specifically, the former approach suggests that decision or feature attention mechanisms provide feedback to sensory

neurons, increasing correlated response variability (decision-feedback modulation) between choice-predicting neurons. However, the latter approach shows that attention decreases correlations among sensory-informative neurons in the same brain area but increases correlations between areas (attentional modulation).
We addressed this inconsistency by combining approaches. We recorded from areas V1 and V4 while the monkey performed two tasks: discriminating a subtly-changed location or spatial frequency of a Gabor patch. The monkey indicated the direction of perceived change by choosing the same left / right saccade targets in both tasks. This paradigm allows us to dissociate the two modulations by comparing noise-correlations based on the neurons' association with decisions or their feature preferences. Our analyses of noise correlations revealed both weak signatures of decision-feedback (increased correlation between neurons associated with the same choice) and strong signatures of attention-like selective modulation (lower noise correlations between sensory-informative neurons within areas and higher correlations between neurons in different areas). Future population measures of the animals' decision and task selection state on individual trials will further reveal how the two modulations work together to produce the cognitive flexibility that allows task-dependent mapping from vision to action.

Disclosures: C. Xue: None. **L.E. Kramer:** None. **M.R. Cohen:** None.

Poster

756. Decision Making III

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Title: Using interactions between pharmaceutical stimulants and selective attention to test hypotheses about neuronal population activity in areas V4 and 7A

Authors: *A. M. NI, B. S. BOWES, D. A. RUFF, M. R. COHEN;
Dept. of Neurosci., Univ. of Pittsburgh, Pittsburgh, PA

Abstract: We recently showed that cognitive processes like learning and attention, which improve performance on visually guided tasks, reduce shared trial-to-trial response variability (termed noise correlations or spike count correlations) between pairs of visual neurons, and that

there is a strong, quantitative relationship between performance and shared variability. This leads to the hypothesis that performance improves exactly when noise correlations change. A strong test of this hypothesis lies in the performance changes associated with artificial manipulations like the systemic administration of pharmaceutical stimulants. We investigated the effects of the most frequently used stimulant in the world, caffeine, and the most commonly prescribed pharmaceutical drugs used to treat Attention Deficit Hyperactivity Disorder (ADHD), methylphenidate and amphetamine, on the performance of rhesus monkeys performing a visual change detection task with an attention component. We found that even though these drugs are administered systemically, they have highly focused effects on performance, improving change detection at the attended but not the unattended locations. This result contrasts with naturally occurring global processes like the changes in arousal or motivation induced by a large unexpected reward, which did not interact with the selective effects of attention. Our behavioral results lead to specific, testable hypotheses about the neuronal population mechanisms underlying the effects of these drugs. For example, if the drugs selectively affect behavioral performance at attended versus unattended spatial locations, they should also differentially affect the shared variability of the neuronal populations with receptive fields that overlap the attended locations versus those with receptive fields that overlap the unattended locations. We are testing these hypotheses by recording the activity of neuronal populations in visual area V4 and simultaneously in area 7A, an area that may be related to the possible reward and decision-making effects of these stimulants. These results should shed new light on our understanding of the neuronal mechanisms that underlie selective processes such as attention and how such mechanisms are affected by both natural global cognitive processes and commonly used stimulants.

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Poster

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Support: NIH grant R01EY022930
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Title: Simultaneous population recordings from both superior colliculi do not support a limited resource theory of attention

Authors: *D. A. RUFF, M. R. COHEN;
Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Visual spatial attention has long been known to lead to faster and more accurate perceptual performance. Given these improvements, it is reasonable to wonder why subjects do not attend to everything all of the time. A leading hypothesis suggests that attention is a limited resource and that subjects can only focus their 'spotlight' of attention on a subset of possible locations because of those limits. Support for this hypothesis has been found using both behavioral and neurophysiological approaches. However, in a situation when stimuli are in opposite visual fields, we have previously found that the neuronal signatures of attention in each hemisphere of visual cortex are independent (Cohen and Maunsell, 2010). This result suggests that the resource bottleneck does not reside in the visual system, but it remains possible that the resource bottleneck is in the motor system. For example, the fact animals cannot simultaneously move their eyes to multiple locations might impose a limit on subjects' abilities to plan responses to multiple stimuli.

We tested this hypothesis by measuring the trial-to-trial fluctuations in attention to each hemifield that are reflected in the responses of populations of pre-oculomotor neurons. While monkeys performed a difficult visual task that required them to shift attention between hemifields, we recorded simultaneously from populations of neurons in both hemispheres of the superior colliculus (SC), which is involved in the planning and execution of eye movements. We used the responses of the simultaneously recorded neurons in each hemisphere to estimate the amount of attention allocated to the contralateral hemifield during each stimulus presentation (Cohen and Maunsell, 2010). The limited resource hypothesis predicts that attention to the two hemifields will be anti-correlated on a trial-to-trial basis. However, despite the fact that our neuronal estimates of attention robustly predicted behavioral performance, we found no relationship between the trial-to-trial estimates of attention based on SC neurons in the two hemispheres. This lack of correlation was in contrast to the large positive correlation that we observed between populations of simultaneously recorded neurons in visual cortex (the middle temporal area, or MT) and the SC in the same hemisphere, which shows that these methods can consistently detect fluctuations in attention that are consistent between areas. Our results suggest that the limited resource hypothesis cannot explain attention to opposite hemifields.

Disclosures: D.A. Ruff: None. **M.R. Cohen:** None.

Poster

756. Decision Making III

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Topic: D.07. Vision

Support: NIH R01EY019041
NINDS U19NS107609

Title: Dissociating cognitive and sensory representations in posterior parietal cortex

Authors: *B. PEYSAKHOVICH, O. ZHU, G. IBOS, W. J. JOHNSTON, D. FREEDMAN; Univ. of Chicago, Chicago, IL

Abstract: Primates and other animals are remarkably skilled at visual categorization. Through experience, we can learn to treat visually dissimilar objects (e.g., a conifer and maple tree) as belonging to the same category (trees) and visually similar objects (e.g., a leafy oak tree and a stalk of broccoli) as belonging to different categories (tree and vegetable). In this study, we investigated how neurons in primate lateral intraparietal area (LIP) represent categories consisting of stimuli that differ in their sensory features. Previous studies have shown that LIP neurons encode category membership of motion stimuli. In these studies, monkeys were trained to group 360° of motion directions into categories based on a single arbitrary boundary. However, in this task, there is a strong correlation between category membership and motion direction: neighboring motion directions are more likely to belong to the same category than distant motion directions. In order to disambiguate cognitive (category) and sensory (motion direction) signals in LIP, we trained one monkey to perform a delayed match-to-category task in which he had to group twelve motion stimuli into two categories based on two orthogonal boundaries, such that motion directions that are 180° apart belong to the same category. Motion directions were separated into quadrants with 3 directions per quadrant, such that stimuli within one quadrant were 22.5° apart and near-boundary directions were 22.5° away from the boundary. We recorded from area LIP using single-channel electrodes (n = 8 sessions) and 16-channel Plexon V-probes (n = 41 sessions) while the monkey performed this categorization task. The monkey's accuracy was >80% for all conditions on included sessions. Preliminary analyses indicate that LIP neurons preferentially respond to all motion directions within one category, even when those motion directions are in opposite quadrants. These findings indicate that, through training, posterior parietal cortical circuits can reorganize to accommodate representations of categories that consist of visually dissimilar stimuli. Next, we will record in middle superior temporal area (MST) to better understand the transformation from sensory to categorical representations along the dorsal visual processing stream.

Disclosures: B. Peysakhovich: None. **O. Zhu:** None. **G. Ibos:** None. **W.J. Johnston:** None. **D. Freedman:** None.

Poster

756. Decision Making III

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Title: Lateral prefrontal cortex (LPFC) is a likely contributor to task-related activity in area MT during the memory for motion task

Authors: *M. ISLAM[1], S. ZHU[1], K. WIMMER[2], T. PASTERNAK[1];
[1]Dept of Neurosci., Univ. of Rochester, Rochester, NY; [2]Campus de Bellaterra, Edifici C, Ctr. de Recerca Matemàtica, 08193 Bellaterra (Barcelona), Spain

Abstract: There is strong evidence that the circuitry sub-serving memory-guided comparisons of visual motion involves two reciprocally interconnected regions, the lateral prefrontal cortex (LPFC) and the motion processing area MT (e.g. Zaksas and Pasternak, 2006; Lui and Pasternak, 2011; Hussar and Pasternak, 2012). Specifically, when monkeys compare directions of two stimuli, S1 and S2, separated by a memory delay, both areas carry behaviorally relevant signals suggestive of active interactions between the two areas throughout the task. Thus, in response to motion in S1 and S2, LPFC neurons show direction selective (DS) activity, reminiscent of signals recorded in MT during the same task. During the memory delay, many neurons in the LPFC and to a lesser extent in MT, carry transient signals reflecting remembered direction in S1. In both areas, the activity during the delay increases in apparent anticipation of the comparison S2. During S2, neurons in both areas carry memory-related comparison effects (CE) reflecting remembered direction of S1, with some neurons showing stronger responses on trials when the preceding S1 moved in a different direction and some neurons showing stronger responses on trials when S1 direction was the same. In the LPFC, the majority of these signals weaken dramatically when the animals are rewarded without having to report their decision at the end of the trial (passive fixation task)(Hussar and Pasternak, 2009; 2012). To examine the top-down influences provided by the LPFC, we recorded from area MT during the passive fixation task, when many of the task-relevant signals in the LPFC, including DS, anticipatory and stimulus-selective delay activity and CE, are nearly absent. We found a significant reduction in the anticipatory delay activity, accompanied by increased trial-to-trial variability during the delay. On the other hand, in contrast to the near absence of the CE in the LPFC during the passive fixation, these effects appear to be preserved in MT, suggesting limited contribution of the LPFC to these signals. Similarly, responses to motion were equally DS during the active and passive tasks, suggesting that the influence of DS activity in the LPFC on processing of visual motion in MT is limited. These results show that during the motion comparison task, LPFC is a likely source of anticipatory delay activity in MT and contributes to the control of trial-to-trial variability of this activity. The preservation of CE in MT during the passive fixation task despite its absence in the LPFC, suggests either that these signals do not depend on the LPFC and are generated locally and/or rely on the influences contributed by other brain regions.

Disclosures: **M. Islam:** None. **S. Zhu:** None. **K. Wimmer:** None. **T. Pasternak:** None.

Poster

756. Decision Making III

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Topic: D.07. Vision

Support: Chicago Fellowship

Title: Learning dependency of motion direction tuning in the lateral intraparietal area during a categorization task

Authors: *K. W. LATIMER, D. J. FREEDMAN;
Neurobio., Univ. of Chicago, Chicago, IL

Abstract: Spiking responses in the lateral intraparietal (LIP) area in macaque cortex correlate with animals' perceptual and categorical visually-based decisions. Previous work has examined visual motion category encoding in LIP during a delayed match-to-category (DMC) task, as well as motion encoding during a similar motion direction discrimination task, the delayed match-to-sample (DMS) task. Here we examined LIP activity in monkeys at multiple stages of training on DMS and DMC tasks, and examined how neuronal responses during the DMC task varied according to the monkeys' prior training history. Specifically we examined neural activity during the DMC task in two groups of monkeys with different training histories. One group had been trained extensively on the DMS task (which required fine direction discrimination and comparison of motion directions) prior to learning the DMC task (Sarma et al., 2016). The second group had not been trained previously on the DMS task prior to the DMC task (Swaminathan & Freedman, 2012). Our analysis reveals that LIP neurons show motion direction tuning after both training conditions using a generalized linear model framework. Moreover, model-based dimensionality reduction reveals a distinct difference in motion direction tuning the DMS-trained monkeys: direction tuning in the DMC-only monkeys showed stronger transient tuning than the DMS-trained monkey. Training history can therefore impact the neural integration and representation of task-relevant sensory signals in LIP.

Disclosures: K.W. Latimer: None. **D.J. Freedman:** None.

Poster

756. Decision Making III

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Topic: D.07. Vision

Support: MSC AMD-708146-6

Title: Comparative decision-making in posterior parietal cortex: Proof of concept

Authors: H. LADRET[1,2,3], ***G. IBOS**[2,3];
[1]Visual Neurosci. Lab., Montreal, QC, Canada; [2]Inst. de Neurosci. de la Timone, CNRS, Marseille, France; [3]Aix-Marseille Univ., Marseille, France

Abstract: Deciding whether what we are looking at matches what we are looking for is a complicated task which requires to compare sensory and cognitive information. Recent publications (Ibos & Freedman, 2017; Freedman & Ibos 2018) proposed that neurons from lateral intraparietal area (LIP) are involved in such comparative process. These studies proposed that LIP neurons integrate bottom-up sensory signals and compare them to information related to the stimulus kept in working memory (presumably reflecting the integration of top-down signals originating in the prefrontal cortex). LIP neurons sequentially process and multiplex the information used by non-human primates performing a delay match to sample task: (i) selectivity to the identity of the stimulus kept in working memory; (ii) selectivity to the identity of the test stimuli; (iii) selectivity to the match/non-match status of the stimuli. This sequential processing suggests that LIP plays a specific role in the comparison of different sources of information. However, we still lack a computational framework which would validate LIP's putative role in such comparative decision-making. Here we present, as proof of concept, a spiking neural network (SNN) based on LIP neuronal activity during a delayed conjunction matching task (Ibos & Freedman, 2017). We demonstrate LIP's matching discrimination capacity based on the integration of both sensory and cognitive information. Specifically, we test that non-uniform distributions of synaptic weights and delays inside given groups of excitatory and inhibitory neurons create a spectrum of selectivity to the identity and the match status of the stimuli. We show that neurons from this SNN multiplex bottom-up sensory and top-down cognitive information as well as robustly encode the match status of the stimuli, reproducing previously presented experimental results.
This study demonstrates that biologically plausible organization could mimic LIP neuronal activity and confirms LIP's putative role in comparative decision-making. This model is encouraging further investigation, in order to test LIP's interaction with visual and prefrontal cortical areas in different behavioral framework.

Disclosures: H. Ladret: None. **G. Ibos:** None.

Poster

756. Decision Making III

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Title: Two tradeoffs between local accuracy and catastrophic errors in a solution to the representation assignment problem

Authors: *W. J. JOHNSTON, D. J. FREEDMAN;
Dept. of Neurobio., Univ. of Chicago, Chicago, IL

Abstract: The brain has multiple distinct representations of the external world. In part, these distinct representations arise from different sensory modalities, like vision and touch, but they also arise within sensory modalities in cortex, in which different subsets of brain regions are thought to represent different features of the world (e.g., visual form and motion). Thus, information about a single set of stimuli is spread across many distinct sets of representations in different brain regions -- yet all of this information may potentially be relevant to behavior. In this work, we demonstrate a mechanism by which the brain can integrate information from these distinct representations. In particular, given a set of stimuli represented in two distinct brain regions, giving rise to two distinct sets of representations, we show how the brain can reliably discover the correct assignment between the two sets of representations. Importantly, an incorrect assignment (i.e., an assignment error) results in the representation of a non-existent stimulus, constructed from mismatched features across brain regions.
Here, we analyze a particular solution to this assignment problem: the representation of some of the same stimulus features in both brain regions. Using a statistical model, we derive the assignment error rate in terms of the number of stimuli, the number of overlapping features, and the distortion (i.e., the variance of an optimal estimator) of each of the features within each region. Using rate-distortion theory, we derive the amount of information in bits that an optimal system would need to implement this solution to the assignment problem, including an additional dependence on the total number of stimulus features and their distortion. Thus, we can fix the total amount of information used by the system and describe how changing the number of overlapping stimulus features, the relative distortion of those overlapping features across the two brain regions, and the number of stimuli affects both the assignment error rate and the achievable feature distortion. In this analysis, we demonstrate two tradeoffs: (1) increasing the number of overlapping features decreases the assignment error rate by almost an order of magnitude but

increases feature distortion by half an order of magnitude; (2) increasing the asymmetry of feature distortion across the two regions increases the assignment error rate as well as markedly slows its decay with additional bits but decreases overall feature distortion and speeds its decay. Finally, we explore how the brain may navigate this tradeoff within and across different sensory systems and link these theoretical results to experimental data.

Disclosures: W.J. Johnston: None. **D.J. Freedman:** None.

Poster

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Title: Common rules guide memory-guided comparisons of motion directions and locations in the lateral prefrontal cortex (LPFC)

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Abstract: We previously showed that neurons in the lateral prefrontal cortex (LPFC) carry mnemonic signals for visual motion direction and speed during a working memory task (Hussar & Pasternak, 2012; 2013). During this task, monkeys compared the directions or speeds of two motion stimuli, S1 and S2, separated by a brief memory delay. We found that many LPFC neurons showed stimulus selective activity in response to S1 and S2 and transient signals during the memory delay. During the comparison S2, some LPFC neurons fired more vigorously when its direction/speed matches that of the earlier S1, while other neurons showed stronger responses when its direction/speed differed from that of S1. We asked whether these memory-related signals, termed “comparison effects”, are specific to the type of information being compared (i.e., visual motion), or are domain independent indicators of comparisons *per se* by recording from the same neurons during two matched tasks involving comparisons of either directions or locations of the same motion stimuli. We found that during S1 and S2, neurons were selective for motion direction during direction comparisons and for location during location comparisons. Delay activity showed similar transient signals reflecting remembered stimulus appropriate to the task. The comparison signals during S2 were also analogous for the two tasks, with some

neurons responding more to S2 when it matched the preceding S1, and some neurons responding more when the S1 was different. Importantly, often the same neurons showed comparison signals of the same sign for stimulus location and direction. These results reveal strong parallels between the way LPFC neurons represent motion and location information during memory-guided comparison tasks, suggesting a common, or analogous neural substrate for representing sensory information in LPFC during such tasks. They also demonstrate that prefrontal neurons flexibly alter their tuning properties to meet task demands.

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Poster

757. Decision Making IV

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Title: Cortical computations underlying categorization task switching

Authors: *K. MOHAN, O. ZHU, S. SWAMINATHAN, D. FREEDMAN;
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Abstract: Primates exhibit exceptional flexibility in their behavior. Indeed, we can flexibly adapt to changes in task context with the same stimuli eliciting dramatically different behavioral responses. Yet, it remains unclear how neural circuits mediate such flexible behavior. To understand flexible decisions, we trained monkeys to alternate between motion categorization tasks in which they categorized the same random-dot motion stimulus in two different task contexts. The tasks differed both in the effector used for reporting the decision (eye vs. hand movement) and in the sequence of task events on which decisions were based. In the first task (one-interval categorization (OIC)), a single sample stimulus was presented and the monkeys rapidly reported its category membership by making a saccade to either a red or a green target to indicate “category 1” or “category 2” respectively. In the second task (delayed match-to-category task (DMC)), a sample stimulus was followed by a test stimulus after a 1 second delay and the monkeys reported whether the sample and test stimuli belonged to the same category by releasing a manual lever to indicate “category match”. While the monkeys performed the two tasks in alternating blocks of trials, we recorded neural responses from 102 neurons in the lateral intraparietal cortex. Single neuron responses were heterogeneous, non-linear and exhibited mixed tuning and dynamics for task-relevant variables - motion direction, category, and choice.

However, the neuronal population showed remarkably similar category selectivity in both tasks, despite differences in task demands like short-term memory and match/non-match judgments (accuracy of a linear category decoder: 85% OIC, 95% OIC with chance at 50%). By contrast, other task-relevant variables such as motion direction and choice varied between the two tasks. First, we found higher within-category direction information in the OIC, but not the DMC task (accuracy of a linear direction decoder: 74% OIC, 65% DMC with chance at 20%), suggesting that task demands differentially modulate neuronal responses. Second, we found that choice information was encoded independently in both tasks, thus revealing a transformation in information formats as "shared" category signals are routed to "distinct" action circuits. Our findings demonstrate that parietal neural circuits mediate flexible task-switching by differentially formatting relevant information in a task-dependent manner.

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Poster

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Support: Marie Skłodowska-Curie Grant 795846
Wellcome Trust Grant 106101
Wellcome Trust Grant 205093

Title: Sensory evidence and expected reward are integrated beyond primary visual cortex

Authors: *L. E. WOOL, A. LAK, C. REDDY, K. D. HARRIS, M. CARANDINI;
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Abstract: Choosing between alternatives requires integrating available sensory evidence with expected reward. This integration may be performed throughout sensory processing or occur at later stages. Given that primary visual cortex (V1) carries signals related to reward outcome (Shuler & Bear, 2006), we asked if it might combine visual evidence with information about expected reward value.
We used two-photon microscopy to measure neuronal activity while mice performed a visual decision-making task (Burgess et al., 2017). We used transgenic mice that expressed GCaMP6s in cortical excitatory neurons. When mice correctly detected the location of a grating in the left or right visual hemifield, they were given a water reward. The reward amount for correct-left and correct-right choices was unequal and changed over blocks of trials (Lak et al., 2018).
Changes in expected reward profoundly affected the animals' choices. Psychometric curves shifted between blocks, favoring choices promising larger rewards. This shift affected choices on

low-contrast trials (12%) and catch trials (0% contrast) more than on high-contrast (50%) trials. Therefore, behavior was informed by a combination of strength of sensory evidence and size of expected reward.
Changes in expected reward, however, had no significant effect on activity in V1. We measured V1 responses during the task, computed contrast-response functions at stimulus onset, and compared these between blocks. There was no difference between contrast-response functions between blocks. Some neurons also responded around the time of action, but these responses were again unchanged between blocks.
We are currently investigating whether expected reward has a neural correlate elsewhere in dorsal cortex. We are imaging neurons in secondary motor cortex (M2). Preliminary results suggest that some M2 neurons carry information about the upcoming reward during the response epoch, showing enhanced responses at the time of action during blocks with larger rewards.
We conclude that the integration of visual evidence and expected reward occurs only after primary visual cortex. This integration might occur when signals reach frontal cortex, where expected reward may modulate the activity of neurons that fire around the time of the action.

Disclosures: L.E. Wool: None. **A. Lak:** None. **C. Reddy:** None. **K.D. Harris:** None. **M. Carandini:** None.

Poster

757. Decision Making IV

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Topic: D.07. Vision

Support: National Alliance for Research on Schizophrenia and Depression Young Investigator Award
Whitehall Foundation Grant

Title: Context determines the timescale of evidence evaluation for decision-making

Authors: R. HARUN, E. JUN, H. PARK, P. GANUPURU, A. B. GOLDRING, *T. D. HANKS;
Univ. of California-Davis, Davis, CA

Abstract: Decisions are based upon evidence and context, but how does context alter the timescale of evidence evaluation? To investigate this question, we examined how subjects utilized evidence in an auditory change detection task. 11 human subjects listened to streams of stochastic auditory clicks and were trained to respond when there was an increase in the generative click rate within a specified response window. Subjects performed this task in two contexts governed by the response window duration, a long response window (LRW:1000ms) or

a short response window (SRW: 500ms). To optimize performance, subjects had to adapt their timescale of evidence evaluation by evaluating evidence over a longer period when they had longer to respond and vice versa. We found that subjects adapted their timescale of evidence evaluation to match the task demands through *three* different analyses. 1) Reaction times were longer in the LRW compared to the SRW context, suggesting that subjects evaluated longer periods of evidence to form their responses in the LRW context. We next assessed the timescale of evidence utilization by examining the mean click rates that preceded false alarm (FA) responses. FAs were trials in which there were no changes in the generative click rate, but on average, FAs followed a period of increased click rates because subjects generally responded to local increases in the click rate that were present in the stochastic stimuli. 2) On average, longer periods of increased click rates preceded FA responses in the LRW compared to the SRW context (893 ± 7 ms vs 592 ± 4 ms, respectively), suggesting that longer periods of evidence were utilized in the LRW context. Lastly, we constructed a quantitative model to account for behavior in this task. We determined the model parameters that maximized the likelihood of observing the experimental trial outcomes (i.e. Hits, Misses, and FAs) given the auditory stimuli on each trial. 3) Behavior was best explained by a wider temporal evidence filter in the LRW compared to the SRW context, indicating that evidence had a longer influence on decisions in the LRW context. Our findings show that subjects contextually adapt their timescale of evidence evaluation to optimized decision-making behavior.

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Poster

757. Decision Making IV

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Topic: D.07. Vision

Support: Kavli Inst. Brain and Mind IRB2013-007

Title: Differences between rat and human decision making confirmed and attributed to different forms of behavioral variability

Authors: C. A. SHEVINSKY, Q. N. NGUYEN, ***P. REINAGEL**;
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Abstract: In perceptual decision-making tasks, the unmodified drift diffusion model predicts that accuracy should be independent of a trial's reaction time. Humans and monkeys are widely reported to violate this prediction - their accuracy declines with reaction time. We have reported that rats also violate the prediction, but in the opposite direction- their accuracy improves with

reaction time (1,2). Here we replicate this result for N=18 rats in the random dot motion discrimination task. We also tested N=60 human subjects in the identical task and confirm that accuracy falls with reaction time, ruling out task differences as the cause of the discrepancy. Although we limit analysis to data that are apparently stationary, we argue that either the human or rat finding could be an artifact of undetectable and unavoidable non-stationarities on short timescales. To address this we introduce a new temporally-local analysis, which confirmed our findings in both humans and rats, and showed that the magnitude of the effect increases with stimulus strength in both species.
The behavioral data were fit with a hierarchical drift diffusion model (HDDM) (3) using free parameters for threshold (A), drift rate (V), non-decision-time (T), starting point variability (SZ), drift rate variability (SV), and non-decision-time variability (ST). Species-level hierarchical priors and individual parameters were fit simultaneously. Comparison of the species-level priors revealed that humans had higher drift rate variability SV than rats. Rats had lower threshold A, higher starting point variability SZ, longer and more variable non-decision time (T, ST). Together these differences account for the species-specific dependence of accuracy on reaction time, without postulating a decaying decision bound. Allowing the model parameters to depend on response side improved the model fit for each species, even after accounting for the increase in parameters (DIC). Allowing further dependence of parameters on the response and reward outcome of the previous trial improved the mode fit further. We conclude that much of the 'variability' is reducible to systematic and predictable effects of behavioral context. Such effects are equally prevalent, but differently manifested, in the two species. Perceptual decision making of rats and humans can thus be understood as fundamentally similar computations, with quantitative differences in exactly how behavioral context influences choice.
1. Reinagel (2013) Front. Neural Circuits 7:200. 2. Reinagel (2013) PLoS-ONE 8(6):e68505. 3. Wiecki, Sofer & Frank (2013) Neuroinform. 7:14.

Disclosures: **C.A. Shevinsky:** None. **Q.N. Nguyen:** None. **P. Reinagel:** None.

Poster

757. Decision Making IV

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Topic: D.07. Vision

Support: Wellcome Trust 106101 (AL)
Wellcome Trust 205093 (MC and KDH)

Title: Distinct roles for dopaminergic projections to dorsal and ventral striatum in sensory decisions

Authors: M. M. MOSS[1,2], K. D. HARRIS[1], M. CARANDINI[1], **A. LAK**[1,2];
[1]Univ. Col. London, London, United Kingdom; [2]Univ. of Oxford, Oxford, United Kingdom

Abstract: Dopaminergic (DA) projections to striatum have specialized roles in reward processing and movement regulation, depending on their anatomical targets within the striatum (Parker et al., 2016; Howe and Dombeck, 2016). However, the roles of striatal DA projections in sensory decision making are unknown.
We trained mice in a visual detection task in which the reward for correct choices to the left and right was unequal and switched across blocks of trials (Lak et al., 2018). Mice exhibited steep psychometric curves with negligible lapse rates, and shifted their psychometric curves between blocks to favor the side paired with larger reward.
To measure the activity of striatal DA projections during the task, we expressed GCaMP6 in midbrain dopamine neurons of DATCre mice, and implanted optic fibers above dorsal or ventral striatum.
DA projections to the ventral striatum encoded reward prediction error (RPE). Their activity in this task was similar to that of DA cell bodies in the ventral tegmental area (Lak et al., 2018). They were active at both stimulus onset and trial outcome. Their activity reflected sensory evidence and reward size, and differed between error and correct trials as predicted by RPEs of a reinforcement learning model that integrates sensory evidence and reward value (Lak et al., 2018).
In contrast, DA projections to the dorsal striatum encoded sensory information independent of choice accuracy and reward value. These projections responded at the stimulus onset, during which animals were instructed not to move, and also during choice execution. Their activity at the stimulus time reflected the strength of visual signals in a highly lateralized manner, appearing only in response to contralateral stimuli. This activity did not reflect the size of the upcoming reward, and was indistinguishable between correct and error trials. Their activity at the time of choice execution was also lateralized, appearing only during contralateral choices.
These findings indicate that the roles of DA projections during sensory decisions depend on their targets in striatum. The results suggest a novel role for DA projections to the dorsal striatum in encoding sensory information, independent of choice accuracy and expected reward size.

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Poster

757. Decision Making IV

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Program #/Poster #: 757.06/K4

Topic: D.07. Vision

Support: NIH EY103692

Title: Superior colliculus inactivation impairs perceptual decision-making in monkeys

Authors: *E. JUN[1], A. BAUTISTA[1], T. TAK[1], A. FABRO[1], N. WEBSTER[1], E. ALVAREZ[2], M. A. BASSO[1];
[1]Dept. of Psychiatry and Biobehavioral Sci. and Neurobio., Univ. of California Los Angeles, Los Angeles, CA; [2]UCLA, Los Angeles, CA

Abstract: Recent work in rodent posterior parietal cortex and reversible inactivation experiments in monkey area LIP calls into question the causal role of area LIP in perceptual decision-making. Therefore, we tested the hypothesis that the monkey superior colliculus (SC), another sensorimotor area involved in perceptual decision-making and attention, plays a causal role in perceptual decision-making. Two trained male rhesus monkeys performed a two alternative choice task in which they reported whether they perceived leftward or rightward orientation in a dynamic Glass pattern stimulus. We parameterized the difficulty of the decision by varying the coherence of the Glass pattern stimulus among 0, 3, 5, 10, 17, 24, 36, 50%. Monkeys reported their choices by making a saccade to a location corresponding to the orientation; to the right for rightward orientation and to the left for leftward orientation. We plotted psychometric functions and fitted the choice performance data with logistic functions to extract the choice bias and slope parameters. Monkeys also performed a simple saccade task in which a red and white target appeared in the same positions as those of the choice targets in the Glass pattern decision task. Monkeys made saccades to the white target and we measured the proportion of saccades made to the left and right hemifields. Using a custom-designed injectrode system, we infused muscimol (1μl, 0.5μg/μl at a rate of 0.1μl/min) into the intermediate layers of the SC at sites where we recorded delay-period and saccade-related neuronal activity. Results from five injections in two monkeys show that muscimol into the SC results in changes to monkeys' decisions. After muscimol, monkeys consistently showed a choice bias away from the target in the affected field and predominantly for lower coherence stimuli. Control injection of the vehicle saline did not change choice bias. Importantly, the distribution of left and right saccades in the simple saccade task did not change after muscimol injection, ruling out an interpretation based on purely a motor bias. Our results support the hypothesis that the SC of monkeys plays a causal role in perceptual decision-making independently of its role in saccade generation.

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Poster

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Title: Distinct representations of decision variable and task difficulty in the monkey lateral intraparietal cortex

Authors: *G. OKAZAWA, R. KIANI;
New York Univ., New York, NY

Abstract: The neural population of the monkey lateral intraparietal (LIP) cortex represents the formation of perceptual decisions communicated with saccadic eye movements. For example, in the direction discrimination task with random dots, the average PSTHs of LIP neural population ramp up at a rate proportional to the motion strength supporting a saccade toward the neurons' response field (Shadlen & Newsome 2001). These classic experimental results have motivated models in which neurons integrate sensory evidence into a decision variable (DV). In these models, the DV magnitude dictates the choice and confidence associated with the choice.
Here we show that LIP population responses also reflect stimulus difficulty distinct from DV in two perceptual tasks: direction discrimination with random dots (Shadlen & Newsome 2001) and a novel face categorization task (Okazawa et al 2018). We varied stimulus difficulty by changing motion coherence in the direction discrimination task and the distance of facial features to prototypes in the face categorization task. In both tasks, the LIP population simultaneously represented both the stimulus difficulty and the DV; population responses at each moment fell along a convex curve in the state space, where the location on the curve corresponded to the DV and depth from the base of the curve represented stimulus difficulty. The curves expanded over time, creating a 3D manifold that reflected the variety of neural trajectories in the state space during decision formation.
This simultaneous representation of the DV and stimulus difficulty suggests the possibility for choice-independent encoding of confidence, as opposed to a choice-dependent representation based on the DV (Kiani & Shadlen 2009; Beck et al 2008). However, by analyzing neural data while monkeys performed a post-decision wagering task to report their confidence, we show that the monkeys' confidence judgment did not correlate with fluctuation of population neural responses along the stimulus difficulty axis. We therefore suggest that the choice-independent representation of stimulus difficulty is most likely an implementational feature of the computations performed for integration of sensory evidence, but it is not read out by downstream areas for confidence reports or utilization of confidence for guiding behavior.
[1] Shadlen MN, Newsome WT (2001) J Neurophysiol 86:1916-36 [2] Okazawa G, Sha L, Purcell BA, Kiani R (2018) Nat Comm 28:3479 [3] Kiani R, Shadlen MN (2009) Science 324:759-64 [4] Beck et al. (2008) Neuron 60:1142-52

Disclosures: G. Okazawa: None. **R. Kiani:** None.

Poster

757. Decision Making IV

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Topic: D.07. Vision

Title: The neural dynamics of deliberation and commitment during dynamic decision making in humans: A MEG study

Authors: *T. THIERY, P. RAINVILLE, P. E. CISEK, K. JERBI;
Univ. of Montreal, Montreal, QC, Canada

Abstract: Imagine you are driving to a new destination, deciding on the best route. As you drive, your decision is informed by road signs, advice from your passengers, your GPS, etc. Crucially, as you approach a potential turn, you are urged to make your decision even if you are not yet fully confident. In ecological settings, the available information for making a choice can change without warning, and the urgency to choose one way or another is among many factors influencing the decision process. Recently, neurophysiological studies in monkeys performing perceptual decision-making tasks, combined with computational models, have paved the way for theories about how the brain makes decisions in a constantly changing environment. However, the underlying mechanisms and whole-brain dynamics involved in processing sensory information and making a variety of trade-offs between the speed of a decision and its accuracy in humans are still poorly understood. Here, we recorded whole-brain rhythmic synchronization using magnetoencephalography in human participants (n=30) performing the “tokens task”, in which they must guess which of two targets receives the majority of tokens jumping from the center every 200ms, reporting their decision with a right or left button press. We show that while participants are deliberating about their choice, source-reconstructed local field potentials in the beta band [15-30 Hz]) build up in an evidence-related manner in sensorimotor regions, reflecting the competition between response options biased by sensory information provided by the tokens. In the same regions, theta oscillations ([4-8 Hz])] are involved in executing motor commands after participants have committed to a choice. Finally, we found increased high gamma oscillations ([60-90 Hz]) in the insula after participants made an error. This may indicate that high-frequency field potentials play a crucial role in our ability to evaluate choices by monitoring errors. Taken together, these results are congruent with previous studies looking at specific brain regions in monkeys, but they provide a more complete picture of how decisions evolve across a distributed network.

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Poster

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Wellcome Investigator Award: 205093
Wellcome Trust 102264
ERC 694401
Gatsby Foundation

Title: The role of frontal cortex in multisensory decision-making

Authors: *P. COEN, M. J. WELLS, S. KACKAR, P. ZATKA-HAAS, M. CARANDINI, K. D. HARRIS;
Univ. Col. London, London, United Kingdom

Abstract: Several recent studies have shown that the mouse frontal cortex plays a key role in transforming sensory stimuli into appropriate motor actions during decision-making tasks. However, real-world decisions are invariably multisensory. Does frontal cortex combine information across sensory modalities when required for decision making, or does it represent separate modalities independently?
We trained head-fixed mice to perform an audiovisual spatial task where animals turn a steering wheel to indicate whether a stimulus appeared on the left or right. The stimuli can be auditory, visual, or a combination of the two, presented in coherent or conflicting locations. In one set of experiments, we optogenetically inactivated different spots across dorsal cortex on individual trials while mice performed this task. In a second set of experiments, we are currently inserting Neuropixels probes in frontal cortex while mice performed the task.
We found that auditory and visual primary sensory cortices were both required for the processing of modality-specific sensory information, and that the effect of inactivation in these regions was highly lateralized. The effects of inactivation on secondary motor cortex (M2) were also robust, but they were independent of modality. Inactivation of M2 in either hemisphere, irrespective of stimulus location, increased mouse reaction time, supporting a cooperative model of multimodal decision-making in M2.
To determine whether individual neurons in frontal cortex carry separate or merged representations of the two modalities, we are currently recording neural activity in M2 with Neuropixels probes. In initial experiments, we have observed neurons exhibiting a variety of response patterns: some neurons respond to both modalities, while others are selective for only one modality.

Overall, our results suggest a key role for secondary motor cortex in the processing of audiovisual information for multisensory decisions.

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Poster

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MarieCurie 656528

Title: Cortical states during sensory decision making

Authors: *E. A. K. JACOBS[1], N. A. STEINMETZ[4], A. J. PETERS[2], M. CARANDINI[3], K. D. HARRIS[2];
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Abstract: Cortical desynchronization is associated with improved performance in sensory detection tasks. A current view holds this improvement occurs because desynchronization enhances cortical sensory coding. We tested this hypothesis in mice, by asking whether cortical desynchronization is specific to the cortical areas of the sensory stimuli being processed, and whether it leads to increased selection of correct stimuli in multiple-alternative choice tasks. We monitored cortical activity using widefield imaging of genetically encoded calcium indicators, while mice performed variations of a visual alternative choice task (Burgess et al. 2017), as well as auditory and audio-visual alternative choice tasks. We quantified movement by monitoring the motion of the steering wheel the animals were using during the task to make choices, and acquired simultaneous pupil measurements to assess overall arousal level. We validated that synchronized and desynchronized states could be detected in widefield data by comparing it to simultaneously-recorded electrophysiology.
In a 3-alternative task (where subjects had the option to choose left, right, or nogo), cortical desynchronization was associated with increased probability of making an action (choosing left

or right), but was uncorrelated with accuracy: the probability that animals would select the correct vs. incorrect side was independent of desynchronization. Action probability was more strongly correlated with desynchronization of somatomotor cortex than of visual or auditory cortex, in both visual and auditory versions of the task. The correlation of desynchronization with action probability could not be fully explained by a measure of arousal as inferred from pupil size.
We conclude that, at least in this task, cortical state relates more to behavioral engagement than to sensory accuracy, and that this state is global rather than localized to cortical regions where the stimuli are processed.

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Poster

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Title: Different influences of explicit and implicit Bayesian priors on perceptual decision-making

Authors: V. THAKUR[1], J. DITTERICH[3], M. A. BASSO[2], ***B. J. KNOWLTON**[1];
[1]Psychology, [2]Psychiatry and Biobehavioral Sci. and Neurobio., UCLA, Los Angeles, CA; [3]Ctr. for Neurosci. & Dept. of Neurobiology, Physiol. & Behavior, Univ. of California, Davis, CA

Abstract: Previous experience can lead to biases in decision-making. We assessed whether Bayesian priors could be learned implicitly in a perceptual decision making task and attempted to characterize differences in the implementation of biases between subjects who were aware of the priors and those who remained unaware using the Drift Diffusion Model (DDM) of decision-making. Participants observed a dynamic Glass pattern (Glass, 1969) and had to determine the orientation direction of the stimulus. The difficulty of the decision was varied across trials by varying stimulus coherence. The stimuli appeared in two different colors (red or green) and we varied the priors in two experimental conditions across groups of participants. In the first experiment (75-25), Glass patterns of one color were presented with a direction prior of 75% left, 25% right, and Glass patterns of the other color had the opposite direction prior (25% left, 75% right). In the second experiment, Glass patterns of one color were presented with a direction prior of 75% left, 50% right, and Glass patterns of the other color had equal priors (50% left,

50% right). In both experiments, one group of participants was told about the priors (the Explicit group) and another group was not (Implicit group). At the end of the session, participants were asked if they thought the colors were equally distributed in both directions and, if not, which direction was dominant for each color. Based on their responses, participants in the Implicit groups were excluded if they reported that they became aware that the different colors were associated with different priors. For each experiment there were 20-25 participants in each condition and they completed 1200 trials. In both experiments, both Explicit and Implicit subjects were able to incorporate the stimulus-specific priors into their decisions according to their psychometric functions, but Explicit subjects did to a larger extent. Using the DDM, we observed that in both experiments, drift rate was different for each color in both Explicit and Implicit groups. This effect was stronger in the Explicit groups than in the Implicit groups. Participants in the Explicit groups also showed changes in the starting point of evidence accumulation, while this effect on start point was much less pronounced in the Implicit groups. These results suggest that implicit learning of Bayesian priors in perceptual decision-making is supported by changes in drift rate in the direction of the more frequent orientation. Awareness of the priors increases these changes in drift rate but also leads to changes in start point consistent with the priors.

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Poster

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Title: Representation of an evolving decision spanning eye movements in area LIP

Authors: ***N. SO**[1], M. N. SHADLEN[2];
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Abstract: Many decisions are based on evidence gathered before and after unrelated activities. Hence, the decision process may need to pause, store the accumulated evidence and resume acquisition of new evidence later. Intervening actions may affect the context or reference frame in which evidence is acquired, necessitating invariance with respect to such action-induced changes. It is not known how the representation of an incipient decision is maintained across intervening actions. To address this, we recorded from a population of neurons in the lateral intraparietal area (LIP) that are known to represent neural computations over flexible timescales

but in a fixed oculocentric frame of reference. Two monkeys reported the direction of motion in a dynamic random dot display comprising two 80 ms pulses (D1 and D2) separated by ~2s, during which the monkey made intervening eye movements (IEMs). In the *main version* of the task, a set of IEMs ultimately brought the monkey's gaze back to the initial fixation point (FP), such that the eye-centered positions of the choice targets remained the same during the two decision epochs. In the *allocentric variant*, the IEM brought the monkey's gaze to a new FP, such that the eye-centered positions of the choice targets differed during the two decision epochs. In both variants of the task, monkeys made their choices based on both D1 and D2 pulses. During the initial decision, neurons with response fields (RFs) aligned to one of the choice targets (N1 neurons) responded in a graded manner to D1 despite the fact that the choice target was never the object of the next eye movement. During the IEM, these N1 neurons lost their decision-related information, but other neurons represented the information as the choice target entered their RFs (N2 neurons). When the monkey returned its gaze to the initial FP, the N1 neurons recovered their initial decision information and then updated this activity with new evidence from D2. In contrast, when D2 was presented at the new FP (allocentric variant), the N2 neurons responded to D2 by updating their newly acquired representation of D1. These results suggest that LIP neurons, as a population, can represent the evolving decision across IEMs in a way that achieves invariance to gaze, despite individual neural RFs defined in an oculocentric frame of reference. We also present evidence from mulitneuron recordings that the mechanism involves passing information between subpopulations, like N1 and N2, within LIP. The finding extends neural mechanisms thought to support the stability of space across eye movements to the generalization of a decision in which evidence accumulation is tied to specific action plans.

Disclosures: **N. So:** None. **M.N. Shadlen:** None.

Poster

757. Decision Making IV

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 757.13/K11

Topic: D.07. Vision

Support: NIH R01EY019041

Title: Posterior parietal cortex plays a causal role in perceptual and categorical decisions

Authors: *Y. ZHOU[1], D. J. FREEDMAN[2];
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Abstract: Decision making requires evaluating incoming sensory stimuli in order to select task-appropriate motor responses. The primate posterior parietal cortex (PPC) is well suited to

mediate decision making because of its anatomical position at a midpoint in the sensorimotor cortical hierarchy. Indeed, neurophysiological recordings have demonstrated a correlation between PPC activity and monkeys' decisions during visually-based discrimination and categorization tasks, with much of this work focusing on the lateral intraparietal (LIP) area of PPC. Yet, PPC's causal role in visual decisions has been debated, with recent work showing that PPC inactivation had no discernable impact on task performance during a widely studied visual motion discrimination task. However, that study focused on PPC's contribution to motor aspects of decisions (deciding where to move), but not sensory aspects (deciding what you are looking at). Thus, we tested whether LIP plays a causal role in visual decisions, and directly compared its role in sensory evaluation and motor planning functions, by reversibly inactivating LIP during visual discrimination and categorical decision tasks. Here we show that LIP inactivation affected both sensory and motor aspects of behavior, but preferentially impaired decisions when visual stimuli, rather than motor response targets, were in the inactivated visual field (IVF). To further test LIP's role in sensory evaluation during perceptual decisions, we recorded neuronal activity in the same LIP regions targeted for inactivation. We recorded from 194 LIP neurons in the same two monkeys used in the inactivation experiment, during the performance of the motion direction discrimination task. In these experiments, motion stimuli were shown at multiple levels of coherence and were always placed within LIP neurons' receptive fields. This revealed neuronal activity that was highly correlated with monkeys' trial-by-trial decisions about the stimuli shown within neurons' RFs, including for stimuli with zero motion coherence. Taken together, this work demonstrates that the primate PPC plays a significant role in mediating visual decisions, with a preferential role in sensory evaluation compared to motor planning during visual perceptual and categorical decision-making tasks.

Disclosures: Y. Zhou: None. **D.J. Freedman:** None.

Poster

758. Oral Motor Behavior and Speech

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 758.01/K12

Topic: E.04. Voluntary Movements

Title: Neural processing of somatosensory feedback and pre-motor planning in children with childhood apraxia of speech

Authors: *A. ENGELHART[1], A. MCILRAITH[2], J. IUZZINI-SEIGEL[3], J. R. GREEN[4], T. P. HOGAN[4], T. M. CENTANNI[1];
[1]Psychology, Texas Christian Univ., Fort Worth, TX; [2]Univ. of Houston, Houston, TX; [3]Marquette Univ., Milwaukee, WI; [4]MGH Inst. of Hlth. Professions, Boston, MA

Abstract: Childhood apraxia of speech (CAS) is a neurological pediatric speech disorder characterized by poor planning of speech sound sequences in the absence of neuromuscular deficits. Children with CAS evidence a constellation of symptoms including, but not limited to, inconsistent speech sound production, vowel errors, difficulty with coarticulatory transitions, and prosodic disturbances; in addition, poor response to intervention is common and many will participate in speech treatment throughout childhood and into adolescence. The underlying neural mechanisms of CAS are still largely unknown, which leads to inconsistencies in both diagnosis and response to intervention. According to the Directions Into Velocities of Articulators model (DIVA) of speech motor acquisition, two main deficits may be present in CAS. One of these is a weakness in feedforward control, hereafter referred to as motor planning. Under this hypothesis, neural encoding of somatosensory information is intact but the pre-motor planning area for speech (Broca's area) fails to develop an accurate motor sequence for the intended utterance. The other is an overreliance on afferent feedback mechanisms including auditory or somatosensory. The latter system processes somatosensory information regarding the articulators (e.g. the lips, cheeks, and tongue), which is needed to properly plan and produce speech as well as evaluate the accuracy of the executed movement. In the current study, children with or without CAS and typically developing adults were assessed and then completed two tasks while magnetoencephalography (MEG) recordings were acquired. These tasks were designed to evaluate the neural markers of CAS and determine whether deficits in somatosensory processing and pre-motor planning exist in isolation or in tandem. The first task aimed to evaluate somatosensory feedforward processes by lightly stimulating participants at two articulator locations: the lip and the tongue, while MEG data were acquired. The second task aimed to evaluate the motor planning deficit. Participants completed a non-word repetition task to allow for imaging of the pre-motor planning process in Broca's area. We evaluated neural activation in two regions of interest: primary somatosensory and Broca's area. We present our findings in the context of these two deficits and evaluate whether these deficits occur in tandem or separately. Implications for diagnosis and treatment will also be discussed.

Disclosures: **A. Engelhart:** None. **A. Mcilraith:** None. **J. Iuzzini-Seigel:** None. **J.R. Green:** None. **T.P. Hogan:** None. **T.M. Centanni:** None.

Poster

758. Oral Motor Behavior and Speech

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 758.02/K13

Topic: E.04. Voluntary Movements

Support: NIH Grant DC017091

Title: Previous exposure to sensory feedback noise causes a decrease in online compensation for sensory perturbations

Authors: *B. PARRELL, C. NIZIOLEK;
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Abstract: In motor control, sensory afferent information is combined with forward model predictions into a single estimate of the current state of the motor plant, which is then used by the controller to generate motor commands. The integration of sensory and predictive signals is typically understood as a (quasi-)Bayesian process, where the weight assigned to each signal is proportional to its reliability. Consistent with this, previous work has shown that increased noise (decreased reliability) in the visual signal leads to a decrease in the use of visual feedback for hand position estimation. However, how long-term exposure to unreliable feedback affects the sensory integration process remains unclear. Here, we leverage the unique characteristics of the speech motor control system to test the hypothesis that persistent exposure to unpredictable noise in sensory feedback changes the relative weighting of sensory and predictive signals. In speech, online compensation for sensory perturbations is typically incomplete (10-25%); this partial response allows us to test for potential increases, as well as decreases, in the reliance on sensory afferent information during motor performance. In a within-subjects experiment, we first manipulated the reliability of the auditory feedback received during speaking, then assessed the compensatory response to large auditory perturbations. In two separate sessions, participants first produced a baseline block of under one of two conditions: 1) a veridical baseline in which speech feedback was unperturbed, or 2) a noisy baseline in which small alterations to auditory feedback of vowel formant frequencies were drawn from a normal distribution with a standard deviation of 15 mels. In each session, this baseline block was followed by a test block where vowel feedback was shifted by +/- 125 mels on a random third of trials. We test two competing hypotheses. H1: If the feedback mismatch during the noisy baseline block is attributed to inaccuracies in forward model prediction, reliance on sensory feedback should increase, leading to a larger compensatory response to test-block feedback perturbations in the noisy compared to the veridical session. H2: If the mismatch is attributed to errors in the sensory system, reliance on sensory feedback should decrease, leading to a smaller compensatory response in the noisy session. Results show that participants produce smaller responses to auditory perturbations during the test block in the noisy session compared to the veridical session. This suggests that exposure to random sensory prediction errors causes a downweighting of sensory feedback and increased reliance on forward predictions.

Disclosures: **B. Parrell:** None. **C. Niziolek:** None.

Poster

758. Oral Motor Behavior and Speech

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 758.03/K14

Topic: E.04. Voluntary Movements

Title: Naturalness of transformed auditory feedback sounds changes the patterns of compensatory articulatory responses and self-agency ratings in speech production

Authors: *Y. UEZU, S. HIROYA, T. MOCHIDA;
NTT Communication Sci. Labs., Kanagawa, Japan

Abstract: Speech conveys linguistic information and speaker's individuality somewhat irrespective of the naturalness of sounds. On the other hand, from the viewpoint of speech motor control, the sound quality of auditory feedback might affect the speaker's own articulatory movement due to sensorimotor error correction mechanisms. To investigate whether the naturalness of feedback speech sound contributes to articulatory motor control, we have performed formant transformed auditory feedback (TAF) experiments where a low-pass filter (LPF) controlled high-frequency component of feedback speech sound. Results have shown that the lower the LPF's cutoff frequency (Fc), the larger the compensatory response error, indicating that stable articulatory control requires speech information in high-frequency component. However, few studies have been conducted on the relationship between articulatory motor control and sound naturalness by adding noise to feedback sound. In this study, formant TAF experiments were performed where the naturalness of feedback speech sound was controlled by LPF, and adding high-pass or broadband noises. Self-agency ratings for feedback speech sound were also conducted during TAF experiments. Native Japanese speakers were participated in the experiments. They were instructed to repeat 100 Japanese syllable /he/. Formant frequencies of speech sound are gradually shifted and the maximum (F1, F2) perturbations were (+150, - 300) Hz. They were also asked to answer, "Do you feel like you're speaking to the feedback sound?" in 5-Likert scale for every 5 utterances. The condition of the Fc was 3, 4 and 8 kHz. We had three noise conditions: no noise, high-pass and broadband noises. In the high-pass noise condition, speech-shape noise over Fc was added to the LPF speech of Fc. In the broadband noise condition, pink noise under Fc and speech-shape noise over Fc were added to the LPF speech. Results showed that the compensatory response of F2 under high-pass noise condition at Fc = 4 kHz was equal to that for no noise condition at Fc = 8 kHz, indicating that high-pass noise may recover the naturalness of feedback speech sound. Compensatory responses of F2 under the noise conditions were larger than those of no noise condition at Fc = 3 and 4 kHz. However, self-agency ratings increased for broadband noise but decreased for high-pass noise compared to no noise. This means that a relationship between compensatory responses and self-agency ratings cannot be explained by a simple mechanism. Therefore, we speculate that articulatory motor

control strategy may change depending on characteristics of naturalness of feedback speech sound.

Disclosures: **Y. Uezu:** None. **S. Hiroya:** None. **T. Mochida:** None.

Poster

758. Oral Motor Behavior and Speech

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Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 758.04/K15

Topic: E.04. Voluntary Movements

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DSF Charitable Foundation Grant 132RA03 (CMC)

Title: Differences between the cortical substrate for vocalization and grasping in the marmoset

Authors: *C. M. CERKEVICH[1,2], J.-A. RATHELOT[4], P. L. STRICK[1,2,3];
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Abstract: Marmosets exhibit a high degree of vocal communication and remarkable capacity for precise control over their vocalizations. We have undertaken a series of studies to explore the neural substrate that supports these unique abilities. To gain further insights into this issue, we compared the distribution of output neurons in the cerebral cortex that are concerned with the control of a laryngeal muscle to that of output neurons involved in the control of a hand muscle. In several marmosets, we injected rabies virus, a retrograde trans-synaptic tracer, into the right extensor digitorum communis (EDC) of the hand (n = 2) or the right cricothyroid (CT) muscle of the larynx (n = 2). We set the survival time to label the output neurons in layer V of the cerebral cortex with disynaptic inputs to motoneurons of the injected muscle.
Our results indicate that the primary motor cortex (M1) is the main origin (96%) of the layer V neurons with disynaptic input to EDC motoneurons. Much less substantial outputs originate from two premotor areas on the medial wall of the hemisphere: the supplementary motor area (SMA: 3%), and the ventral cingulate motor area (CMAv: 1%). Overall, the ratio of M1 to premotor output for descending control of a hand muscle in the marmoset is 24:1.
In contrast, M1 is the origin of less than one third (32%) of the layer V neurons with disynaptic input to CT motoneurons. Smaller, but substantial outputs also originate from four premotor areas: the SMA (20%), the CMAv (19%), the rostral cingulate motor area (CMAr: 19%), all on the medial wall of the hemisphere, as well as the ventral area 6 (6V: 19%) on the lateral surface.

Overall, the ratio of M1 to premotor output for descending control of a laryngeal muscle in the marmoset is ~0.47:1.
These results suggest that the marmoset's exquisite control of vocalization is accompanied by a major expansion of descending outputs from premotor areas in the frontal lobe. Thus, the enhanced control of vocalization may depend on parallel pathways from multiple cortical motor areas to brainstem vocal control centers. The increase in output from two premotor areas in particular, the SMA and 6V, may be especially critical to marmoset vocal abilities (Cerkevich & Strick, 2018).
Cerkevich CM, Strick PL. Cortical Adaptations to Enable Enhanced Vocalization. Program No. 588.21. 2018 Neuroscience Meeting Planner. San Diego, CA: Society for Neuroscience, 2018. Online.

Disclosures: C.M. Cerkevich: None. **J. Rathelot:** None. **P.L. Strick:** None.

Poster

758. Oral Motor Behavior and Speech

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 758.05/K16

Topic: E.04. Voluntary Movements

Support: NSERC-Canada

Title: Ultrasound visual feedback of the tongue influences speech adaptation to a palatal perturbation

Authors: G. BARBIER[1], M. BAL[1], R. MERZOUKI[1], S. BAUM[2], ***D. SHILLER**[1];
[1]Univ. de Montréal, Montreal, QC, Canada; [2]McGill Univ., Montreal, QC, Canada

Abstract: Clinical studies have suggested that ultrasound feedback of the tongue during speech — providing real-time visualization of the tongue surface in the mid-sagittal or coronal plane — may be beneficial in the treatment of speech errors. Visual feedback of intra-oral movement is not a typical condition of speech production, however, and it remains unclear how it might interact with existing mechanisms of speech motor learning and control. In the present study, we experimentally altered the vocal tract of healthy adult talkers using a palatal prosthesis to perturb the production of the alveolar fricative "s". This physical manipulation was combined with the controlled application of ultrasound visual feedback during a 20-minute practice phase with the prosthesis in place. Acoustic changes in speech output related to the perturbation and subsequent adaptation were examined in three separate groups of talkers (n=15): two receiving visual ultrasound feedback of the tongue during speech practice (in either the mid-sagittal or coronal plane), and a control group receiving no visual feedback. The availability of visual feedback of the tongue, as well as the axis of feedback, was found to influence the pattern of compensation to

the palatal perturbation as well as the learning after-effect. The results indicate that talkers will readily integrate real-time visual feedback of the tongue into the sensorimotor processes driving speech adaptation, with the nature of that feedback (e.g., the visualized axis of tongue movement) further playing a role.

Disclosures: D. Shiller: None. **G. Barbier:** None. **M. Bal:** None. **R. Merzouki:** None. **S. Baum:** None.

Poster

758. Oral Motor Behavior and Speech

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 758.06/K17

Topic: E.04. Voluntary Movements

Title: Local cooling reveals brain stem pattern generator mechanisms for vocalizations

Authors: *K. HARTMANN, M. BRECHT;
Humboldt University/ BCCN Berlin, Berlin, Germany

Abstract: Vocalizations in mammals require precise timing and control over a multitude of muscles. While there is agreement that the vocal pattern generator (VPG) is situated in the brain stem, the exact identity of these circuits and their functionality are debated. Specifically, three alternatives have been suggested to form the VPG based on [i] electrophysiological evidence the reticular formation (RF), right above the superior olivary complex (Hage and Jürgens 2006), [ii] anatomical and lesion studies in the nucleus retroambiguus (NRA) (Holstege 1989), or [iii] a delocalized VPG that involves the reticular formation, the NRA and other circuits in between these two nuclei (Hage 2009). Here we evaluate these alternatives in rats. To this end we applied microstimulation in the periaqueductal gray of anesthetized rats, and induced natural calls. To perform a functional mapping of brain stem circuits, we adopted the local cooling strategy of Long and Fee (2008), which has revealed much about the functionality of bird song circuits. Specifically, we used localized cooling by placing a gold pin, attached to a peltier-element along with multiple thermistors, on the exposed brainstem. Both local temperature measurements and moving of the cooling probe suggested a specificity of cooling effects in the sub-millimeter range. We made six observations: [1] Call production was strongly affected and often totally aborted by cooling an anterior position above the RF. [2] Call production was strongly affected and often totally aborted by cooling a posterior position above the NRA. [3] Call production was only weakly affected by cooling intermediate positions between the RF and the NRA. [4] In a fraction of cases, cooling the position anterior to the RF resulted in a selective loss of high-frequency call components ($\geq$ 40 kHz). [5] In a fraction of cases, cooling the posterior position above the NRA resulted in a selective loss of low-frequency call components ($\leq$ 40 kHz). [6] Cooling often led to abbreviated calls and almost never led to a consistent call prolongation. We

conclude the rat VPG likely consists of both the RF and the NRA without a major contribution of circuits in between these structures. Finally, the cooling induced call abbreviation and the absence of call prolongation suggest that these nuclei do not control call production in a clock-like fashion as the bird HVC does, but that they act more like steam engines for call production.

Disclosures: K. Hartmann: None. **M. Brecht:** None.

Poster

758. Oral Motor Behavior and Speech

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 758.07/K18

Topic: E.04. Voluntary Movements

Support: R01NS100440
R01DC013979
R01DC017696

Title: Cortical dynamics of the speech motor control network in the non-fluent variant of primary progressive aphasia

Authors: *H. KOTHARE, K. RANASINGHE, L. B. HINKLEY, D. MIZUIRI, M. LAURICELLA, S. HONMA, V. BORGHESANI, C. L. DALE, W. SHWE, A. WELCH, Z. MILLER, M. GORNO-TEMPINI, J. F. HOUDE, S. S. NAGARAJAN;
Univ. of California, San Francisco, San Francisco, CA

Abstract: Primary Progressive Aphasia (PPA) is a clinical syndrome in which patients progressively lose speech and language abilities. The nonfluent variant of PPA (nfvPPA) is characterised by impaired motor speech and agrammatism. These speech and language deficits are often associated with left fronto-insular-striatal atrophy in nfvPPA patients. Functional magnetic resonance imaging as well as diffusion tensor imaging studies further suggest impaired connectivity of neural circuitry involved in speech motor control. However, none of these studies provide sufficient temporal resolution to document the dynamics of the recruitment of the speech motor control network during vocal production.
In this study, we employed magnetoencephalographic (MEG) imaging to investigate sensorimotor integration during an altered auditory feedback paradigm in 18 nfvPPA patients and 17 healthy controls. Participants were prompted to phonate the vowel /ɑ/ for ~2.4s. Unbeknownst to them, following a randomly jittered delay of 200 to 500 ms after voice onset, the pitch of their feedback was shifted either up or down by 100 cents (1/12th of an octave) for a period of 400ms. Vocal pitch responses were examined as the participants responded to this pitch perturbation. Task-induced neural oscillations relative to a pre-perturbation baseline were examined in the theta-alpha (4-13 Hz) and the beta bands (13-30 Hz) associated with attention

and sensorimotor integration respectively. Nonparametric statistical tests were performed to look at neural activity differences in patients compared to healthy controls with cluster-threshold corrections for multiple comparisons.
Behaviourally, nfvPPA patients showed a smaller compensation response to pitch perturbation than controls. Baseline pre-perturbation pitch variability did not differ significantly between the two groups, indicating that reduced vocal compensation cannot simply be attributed to insufficient vocal control range in patients. Patients also exhibited reduced task-induced theta-alpha neural activity in the right superior temporal gyrus, right superior temporal sulcus, right middle temporal gyrus and the right temporoparietal junction. Patients also showed increased task-induced beta-band activity in the left dorsal sensorimotor cortex, left premotor cortex and the left supplementary motor area.
Collectively, these results suggest significant impairments in processing of auditory feedback during vocal production in nfvPPA patients.

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Poster

758. Oral Motor Behavior and Speech

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 758.08/K19

Topic: E.04. Voluntary Movements

Support: R01 DC014519

Title: Intent matters - Laryngeal mechanosensory evidence of efference copy with voice and intent to voice

Authors: T. FRODEL[1], H. SAKE[1], S. ZORN[1], S. WILSON[1], M. SMARZINSKI[1], S. A. PALM[1], ***M. J. HAMMER**[2];
[2]Airway Sensory Physiol. Lab., [1]Univ. of Wisconsin-Whitewater, Whitewater, WI

Abstract: Laryngeal mechanoreceptors provide perceptual and proprioceptive afference for a variety of essential human functions including airway protection, breathing, deglutition, speech, and voice. It is interesting that mechanosensory information that yields a defensive airway response when a healthy individual breathes may go largely unnoticed when the individual voices. Modulation of laryngeal mechanosensory detection may be critical to maintain an uninterrupted speech/voice pattern in the presence of potentially distracting self-generated sensory input. However, it remains unknown whether the intent to voice itself may result in

sensory modulation, even in the absence of actual phonation. We used an endoscopic technique to measure laryngeal mechanosensory detection thresholds in healthy participants during tidal breathing, during a voice task, and during an interrupted voice task. We found that mechanosensory detection thresholds were similarly elevated for all participants during the voice and interrupted voice task. However, we found that during the voice tasks women maintained more sensitivity (smaller increases in detection thresholds) than men. Based on our recent findings, we would suggest: (a) Efference copy and laryngeal mechanosensory modulation are important for healthy speech/voice sensorimotor control. (b) Motor intent itself may result in laryngeal mechanosensory modulation. (c) Voice-related laryngeal mechanosensory modulation appears to be a sex-dependent phenomenon. (d) Mechanosensory modulation, motor intent, and efference copy each have important implications for clinical manifestations of speech/voice disorders such as Parkinson's disease and Spasmodic Dysphonia.

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Poster

758. Oral Motor Behavior and Speech

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 758.09/K20

Topic: E.04. Voluntary Movements

Support: NIH R01 DC014519

Title: Auditory-vocal control systems are affected by predictive processing within extended time ranges

Authors: *O. KORZYUKOV[1], T. FRODEL[2], Y. LEE[3], A. BRONDER[3], M. WAGNER[4], V. GUMENYUK[2], C. R. LARSON[3], M. J. HAMMER[2];
[1]Univ. of Wisconsin - Whitewater, Whitewater, WI; [2]Univ. of Wisconsin-Whitewater, Whitewater, WI; [3]Northwestern Univ., Evanston, IL; [4]Compumedics, Hamburg, Germany

Abstract: The human brain generates implicit expectation about the future, representing one of the fundamental principles of neural computations for driving neural/cognitive processes and behavior. Aberrent neuronal mechanisms of predictive processing are linked to brain pathology. Although the auditory-motor control system relies on neural processes that predict the sensory consequences of self-generated actions within milliseconds, our previous study shows that this system can be involved in predictive processing in a time range of seconds. Theoretical frameworks suggest that prediction error minimization is one of the fundamental principles of brain organization. We tested this hypothesizes with Event Related Potentials (ERP) for auditory-motor control system in the time range of seconds. The non-parametric permutation test

of differences in ERP scalp topography identified 2 sequential stages of predictive processing associated with (i) prediction error monitoring of incoming sensory information for detection of potential prediction errors, and (ii) evaluation of error monitoring output in order to optimize top-down predictions until prediction error is minimized. Our results suggest that reflexive brain mechanisms that control accuracy of vocalizations can be affected by inputs from brain levels associated with predictive coding in more extended time scales. Results provide empirical support that temporal hierarchy is recapitulated in the macroscopic organization of the cortex. The brain models slower environmental changes providing a context for more rapid reflexive corrections.

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Poster

758. Oral Motor Behavior and Speech

Location: Hall A

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Program #/Poster #: 758.10/K21

Topic: E.04. Voluntary Movements

Support: NIH R01 DC017444
NIH R01 DC014510

Title: Speech auditory-motor adaptation is driven by implicit learning

Authors: K. S. KIM[1], ***L. MAX**[2];
[1]Univ. of Washington, Seattle, WA; [2]Univ. Washington, Seattle, WA

Abstract: Recent work on sensorimotor learning has dissociated explicit and implicit contributions. The explicit component involves intentional strategy use and is driven by target error. The implicit component involves the updating of an internal forward model without awareness of the learner and is driven by sensory prediction error. In studies of reaching in a perturbed visual environment, it has been possible to estimate the explicit contribution by asking subjects to report intended aiming direction before each trial. The strength of the implicit contribution can then be estimated by subtracting this explicit aiming direction from the actual movement direction.
Sensorimotor adaptation also occurs in speech production (e.g., with shifts of vowel-specific resonance frequencies in the auditory feedback). For speech, however, it is not clear how to dissociate the contributions of explicit and implicit learning components, or even to determine if there indeed are contributions from both components: naïve subjects have no explicit knowledge of the mapping between speech articulator positions and resonance frequencies in the auditory feedback, and efforts to ask subjects about intended auditory “aiming” have been unsuccessful.

Approaches such as constraining planning duration or examining interference from a second task could be considered, but would negatively impact speech execution or leave open alternative interpretations. We report an initial attempt at determining the existence of an explicit component in speech auditory-motor learning while also examining changes in auditory targets. Typical adults and adults who stutter (a population with limited adaptation) produced words in baseline, perturbation, and post-perturbation phases. The perturbation consisted of shifting the first resonance frequency of the produced words "bed" and "pet" such they perceptually moved toward "bad" and "pat." After each trial, subjects used a scale on a touch-screen monitor to indicate how much they had intentionally changed their speech. Every 10 trials, they used a similar scale to listen to unaltered and altered versions of their own production of the target word and to select the best match for what the word "should sound like" (estimating the current target). Stuttering adults showed substantially less learning than nonstuttering adults. Neither group showed a systematic target shift in parallel with learning. With very few individual exceptions, neither group reported any intentional (explicit) adjustments in their speech. Speech auditory-motor adaptation may be an entirely implicit learning process, but improved experimental paradigms should be explored.

Disclosures: L. Max: None. **K.S. Kim:** None.

Poster

758. Oral Motor Behavior and Speech

Location: Hall A

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Program #/Poster #: 758.11/K22

Topic: I.06. Computation/ Modeling/ and Simulation

Support: NSF EPSCoR Award #1632738

Title: Simultaneous decoding of attentional and reward modulations in human EEG

Authors: *M. RAKHSHAN[1], M. MAECHLER[1], T. LYTCHENKO[2], N. HELLER[1], A. SOLTANI[1], G. CAPLOVITZ[2];
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Abstract: Reward expectation can modulate different aspects of behavior and cognitive processes including the deployment of attention. In addition, it has been proposed that the subjective sense of certainty (confidence) is influenced by what is attended and can modify how reward feedback is incorporated. However, it is currently unclear how expected reward and attention interact to determine confidence. To study this interaction, we developed a novel detection paradigm with two RSVP streams while simultaneously recording EEG signals. Human subjects (N=20) were instructed to covertly attend to one of the two streams and respond once they detected a target stimulus (if present) in the attended stream. Target in the unattended

stream required no response. Importantly, each trial was associated with different amounts of reward expected upon a correct response. In addition, the subjects also had to report their confidence in their choice on each trial before receiving reward feedback. Analyses of choice and reaction time data revealed significant effects of expected reward on reaction time such that subjects were faster with larger expected reward. In addition, reaction time was shorter and accuracy was higher on trials in which the confidence was higher. At the neural level, we used a combination of frequency-tagging, MVPA and independent component analyses to identify neural correlates of the location of covert attention and the fate of the target in the attended and unattended streams. In addition, we examined how these neural correlates were modulated by expected rewards, and level of confidence. Together, these findings indicate the feasibility of our approach in decoding reward and attentional signals in EEG data and exploring how their interaction determines confidence.

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Poster

758. Oral Motor Behavior and Speech

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 758.12/K23

Topic: E.04. Voluntary Movements

Support: Leon Levy Neuroscience Fellowship

Title: Distinct auditory neural populations track vocalization feedback delays

Authors: *M. OZKER SERTEL[1], Z. HUANG[1], Q. ZHU[1], B. MAHMOOD[1], D. MAKSUMOV[1], W. DOYLE[2], O. DEVINSKY[1], A. FLINKER[1];
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Abstract: Neural responses in the auditory cortex are suppressed during self-generated vocal sounds. This auditory suppression mechanism has been hypothesized to facilitate the detection of vocalization errors. Nevertheless, while such a link has been demonstrated in the primate vocalization literature, it remains unclear in humans. To test this hypothesis, we conducted an auditory repetition task and a delayed auditory feedback task with neurosurgical human subjects using electrocorticography (ECoG) recordings. Neural responses in the high-gamma broadband frequencies (70-150 Hz) were used as the primary measure of neural activity. In the auditory repetition task, subjects listened to a word and repeated it afterwards. In line with previous findings, auditory responses were suppressed during speaking compared to listening, but to a different extent in different electrodes. In the altered feedback task, subjects read aloud visually presented words, while their voice was recorded by a microphone and played back to them

through earphones in real time with 0, 50, 100 or 200 millisecond delays. Behaviorally, articulation duration increased with increasing amount of delays. Recordings from auditory cortex exhibited different types of responses to delayed feedback. Some electrodes showed a response profile sensitive to articulation duration, exhibiting longer response durations for increasing delays. While other electrodes showed sensitivity to the amount of feedback perturbation, exhibiting larger response amplitudes for increasing delays. Moreover, the degree to which electrodes were sensitive to feedback delays was significantly correlated with the amount of suppression in each electrode. These results suggest that distinct neural populations of the auditory cortex are sensitive to articulation duration and alterations in the auditory feedback during speech production and these responses are linked to vocalization-induced suppression in the auditory cortex. These findings constitute one of the first reports from neural recordings in humans, providing direct evidence that auditory suppression is linked to a mechanism for vocalization error detection.

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Poster

758. Oral Motor Behavior and Speech

Location: Hall A

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Program #/Poster #: 758.13/K24

Topic: E.04. Voluntary Movements

Support: NIH R00DC014520
NIH 5T32DC005359-13

Title: Sensitivity to natural and altered auditory feedback in L1 and L2

Authors: ***S. BAKST**, C. A. NIZIOLEK;
Communication Sci. and Disorders, Univ. of Wisconsin–Madison, Madison, WI

Abstract: We listen to ourselves while talking, comparing our acoustic output to an internal auditory representation of how our speech should sound. Because these representations of speech targets may be less robust in a second language (L2), self-monitoring may be less successful, resulting in less native-like speech. Here, we investigate language learners' responses to both natural variability in their own speech as well as experimentally-induced errors in order to measure speakers' sensitivity to internally- and externally-generated errors.
In the first study, participants who had studied French in adulthood were recorded producing monosyllabic words in L1 (English) and L2 (French) during a magnetoencephalography (MEG) scan. The vowels tested were English {i, ɛ, æ} ("Eve", "eff", "add") and French {i, ɛ, œ} ("Yves", "hais", "oeuf"). We investigated functional differences while speaking and listening to

acoustically-matched productions played over headphones in L1 and L2. Neuroimaging studies have previously shown that the auditory cortical response to hearing one's own speech during L1 production is suppressed in comparison with silent listening to those same productions (Houde et al. 2002; Niziolek et al. 2013). MEG data show left auditory cortical suppression in both L1 and L2, providing evidence for similar predictive success in both languages.
Furthermore, this suppression has been correlated with a behavioral response in L1, where speakers steer deviant productions towards their auditory targets while speaking (Niziolek et al. 2013). This corrective behavior is evident in the magnitude and direction of vowel formant trajectories throughout an utterance. In the first study, speakers showed such corrective behavior while speaking L1, but in L2, utterances were both more acoustically variable and showed less self-correction. In L1, acoustic variability is positively correlated with self-correction, but the increased acoustic variability in L2 vowels did not trigger commensurate self-correction, indicating a weakened ability to self-correct in L2. In a second study, speakers produced English and French monosyllables under conditions of altered auditory feedback. On one-third of trials, the vowel formants of produced words were shifted up or down, creating the perception of an error. We will compare correction of internally- and externally-generated error to understand speakers' sensitivity to auditory feedback in native and learned languages.

Disclosures: S. Bakst: None. **C.A. Niziolek:** None.

Poster

758. Oral Motor Behavior and Speech

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 758.14/K25

Topic: E.04. Voluntary Movements

Support: NIH DC005808

Title: Characterization of movements evoked from electrical stimulation of motor cortex in awake marmoset

Authors: *S. C. STERRETT, L. ZHAO, X. WANG;
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Abstract: Understanding the neurobiology of vocal control in non-human primates is important as an evolutionary and physiological basis of understanding human speech control. The common marmoset (Callithrix jacchus) exhibits highly active and diverse vocal behavior in captivity, which makes it an interesting model of study in this area. Anatomic evidence in marmoset suggests that motor cortical areas in the frontal lobe could modulate vocal articulators and possibly aspects of vocal production. Recent neural recording studies have showed that neural activities in motor, premotor, and prefrontal cortical regions of marmoset are associated with

certain aspects of vocal production. It remains an open question how these cortical regions are functionally related to particular aspects of vocal production. Previous studies in marmoset have shown that facial muscle twitches can be evoked by intracortical microstimulation from various regions in cortex in an anesthetized preparation. Additionally, studies using long-train stimulation in non-human primates have shown evoked complex motor movements. In the present study, we used intracortical microstimulation to map simple and complex movements in an awake marmoset preparation. We showed that simple movements of vocal articulators, including the jaw and tongue, can be evoked by short train electrical stimulation. Additionally, we showed that complex orofacial movements can be evoked by long-train stimulation. Finally, we investigated modifications of vocal output by electrical stimulation of motor and premotor cortical regions while a marmoset engaged in natural vocal behaviors.

Disclosures: S.C. Sterrett: None. **L. Zhao:** None. **X. Wang:** None.

Poster

759. Motor Impairment and Recovery

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 759.01/K26

Topic: E.04. Voluntary Movements

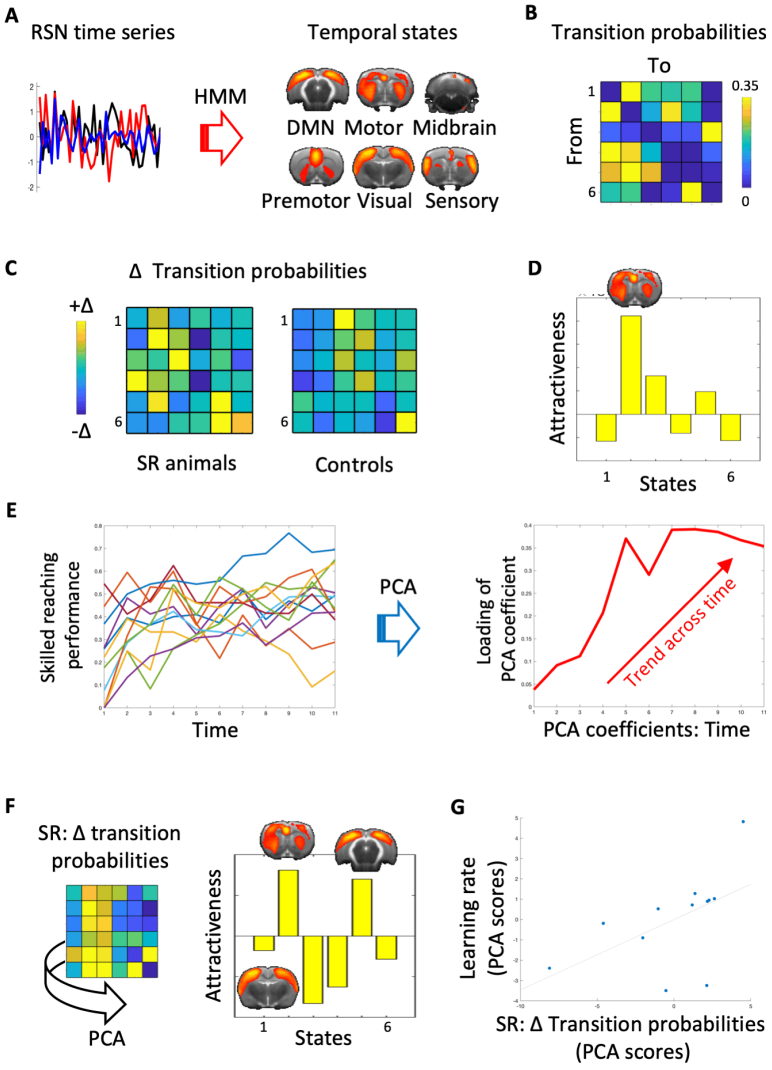
Support: HMR00670
WT090955AIA
WT110027

Title: Learning a novel motor skill reshapes the temporal organisation of activity in the rat brain

Authors: *P. SALVAN, A. LAZARI, C. SAMPAIO BAPTISTA, H. JOHANSEN-BERG; WIN, FMRIB, Univ. of Oxford, Oxford, United Kingdom

Abstract: Motor skill learning results in synaptogenesis and long-term potentiation in the rat motor cortex. Such functional and structural plasticity at the synapse might be expected to alter the temporal organisation of brain activity at larger spatial scales but this has not yet been tested. Here we used longitudinal resting-state fMRI to compare rats who underwent skill reaching (SR) training with (active and passive) controls and asked whether longitudinal changes in time-varying brain activity 1) could discriminate SR animals from controls; and 2) could predict SR learning rates. We studied time-varying patterns of BOLD fluctuations in whole-brain resting state networks (RSNs) through hidden Markov models, describing RSNs' time-series as a sequence of transient, repeating states of activity (Fig A); and describing RSNs' temporal organisation as the state-to-state transition probabilities (TPs) (Fig B). Based on longitudinal changes in brain states' TPs (Fig C), we found that a classifier was able to reliably and significantly discriminate SR animals from controls (median over 10 separate runs: accuracy =

71%; p-value = 0.0470). SR animals compared to controls exhibited greater *attractiveness* for the motor state: brain activity transitioned more frequently towards rather than away from the motor network (Fig D). Crucially, a classifier based on changes in functional connectivity was not able to significantly discriminate between SR animals and controls (p-value = 0.2920). In SR animals we then studied SR performance over time and extracted individual learning rates (Fig E). We then tested whether changes in brain states' TPs (Fig F) were related to motor learning performance. We found that increased attractiveness for the motor states was significantly correlated with individual learning rates (Spearman's rho = 0.69; p-value = 0.01) (Fig 1.G). Together, these results show that the temporal organisation of brain activity changes during motor learning in rats, and that it does so in a behaviour-relevant manner.



Disclosures: **P. Salvan:** None. **A. Lazari:** None. **C. Sampaio Baptista:** None. **H. Johansen-Berg:** None.

Poster

759. Motor Impairment and Recovery

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 759.02/K27

Topic: E.04. Voluntary Movements

Support: EU Grant Luminous

Title: NMDA receptor-mediated motor cortex plasticity after 20 Hz transcranial alternating current stimulation

Authors: *M. A. NITSCHE[1], A. SALEHINEJAD[2], M.-F. KUO[2], D. SCHUTTER[3], M. WISCHNEWSKI[3];
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Abstract: Background: Transcranial alternating current stimulation (tACS) has been shown to modulate neural oscillations and excitability levels in the primary motor cortex (M1). These effects can last for more than an hour and an involvement of N-methyl-D-aspartate receptor (NMDAR) mediated synaptic plasticity has been suggested. However, to date the cortical mechanisms underlying tACS after-effects have not been explored. Methods: 11 participants completed the study and were included in all analyses (mean age ±standard deviation, 23.1 ±3.4; 9 Female). We applied 20 Hz beta tACS to M1 for 20 min with an intensity of 2 mA peak to peak while participants received either the NMDAR antagonist dextromethorphan (150 mg) or a placebo. The effects of the intervention on cortical beta oscillations were explored via EEG, and on motor cortical excitability alterations via transcranial magnetic stimulation single pulse-elicited motor evoked potential amplitudes. Results: When a placebo medication was administered, beta tACS was found to increase cortical excitability and beta oscillations for at least 60 minutes, whereas when dextromethorphan was administered, these effects were completely abolished. Conclusions: These results provide the first direct evidence that tACS can induce NMDAR-mediated plasticity in the motor cortex, which contributes to our understanding of tACS-induced influences on human motor cortex physiology.

Disclosures: **M.A. Nitsche:** F. Consulting Fees (e.g., advisory boards); cientific Advisory Board Neuroelectrics. **A. Salehinejad:** None. **M. Kuo:** None. **D. Schutter:** None. **M. Wischnewski:** None.

Poster

759. Motor Impairment and Recovery

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 759.03/K28

Topic: E.04. Voluntary Movements

Title: Effects of electrode orientation on the impact of transcranial direct current stimulation on motor cortex excitability

Authors: *M.-F. KUO[1], A. FOERSTER[1], F. YAVARI[1], L. FARNAD[1], A. JAMIL[1], W. PAULUS[2], M. A. NITSCHE[1,3];
[1]Leibniz Res. Ctr. for Working Envrn. and Human Factors, Dortmund, Germany; [2]Georg-August-University Göttingen, Göttingen, Germany; [3]Neurol., Univ. Med. Hosp. Bergmannsheil, Bochum, Germany

Abstract: Background: For effects of transcranial direct current stimulation (tDCS), electrical field distribution and coverage of the target areas play a decisive role. **Methods:** We explored the effect of different angle-orientations of tDCS electrodes applied over the upper limb motor cortex (M1) on motor cortex excitability in healthy volunteers. Sixteen individuals received 1 mA anodal or cathodal tDCS through 35cm² electrodes over M1 for 15 minutes. Transcranial magnetic stimulation was used to examine tDCS-generated cortical excitability effects. The M1 electrode-orientation was following the right-left longitudinal plane, or positioned with 45° deviation from the midsagittal plane. Coverage of underlying brain and electrical field orientation were also investigated. **Results:** Cortical excitability modulation was observed only when the electrode was aligned with 45° angle, which covered a larger area of the motor cortex. **Conclusion:** an electrode angle-orientation of 45° induces superior neuroplastic effects of M1 due to a better alignment with the motor cortex.

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Poster

759. Motor Impairment and Recovery

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Topic: E.04. Voluntary Movements

Support: Wellcome Trust Grant 092995/Z/10/Z
International Spinal Research Trust Grant NRB118

Title: Long-term changes in the neural coding of primate finger movements induced by paired nerve stimulation

Authors: *M. GERMANN, B. HABEKOST, S. N. BAKER;
Inst. of Neurosci., Newcastle Univ., Newcastle upon Tyne, United Kingdom

Abstract: Non-invasive methods relying on stimulating pairs of afferent nerves have been shown to induce plastic changes in the sensorimotor cortex. Associative (AS) and non-associative (NAS) peripheral nerve stimulation might be of therapeutic use for the treatment of a number of neurological conditions associated with a dysfunction of afferent processing leading to maladaptive cortical and sub-cortical plasticity including stroke, spinal cord injury, neuropathic pain, and dystonias. Despite promising results and applications in human subjects using these methods, little is understood about the underlying basis for the observed changes. This study aimed to investigate the underlying cortical mechanisms induced by AS and NAS nerve stimulation. To this end, two female macaque monkeys were trained to execute selective finger movements with the thumb and index finger. The task performance was compared before and after one hour of paired AS and NAS median and ulnar nerve stimulation. Additionally, multi-unit (MU) activity of stable neurons from the primary motor cortex and single-unit activity of identified pyramidal tract neurons (PTNs) were recorded during task performance.
Our results indicate that the monkeys were able to move their thumb and index finger less selectively after one hour of AS, measured by an increased number of errors and decreased performance measures. NAS however decreased error numbers and led to increased performances. The difference of the performance change between the AS and NAS intervention was significant for both monkeys. A linear discriminant analysis of MU activity revealed a reduced ability to decode which digit moved from cell activity after AS. This effect was seen in the majority of recorded MUs. By contrast, coding of finger movement was largely unchanged after NAS. The same trends could be seen in the linear discriminant analysis of PTN activity. Our analysis suggests that cortical representations of thumb and index finger became less distinguishable after AS. This diminished ability of the cortex to code movement of the two digits may have led to behavioural consequences, as indicated by the decreased performance measures. Our results are in line with previous findings which demonstrated that motor-cortical representations of the synchronously stimulated muscles extend and overlap after AS. Paired nerve stimulation can thus be used to induce long-term changes in cortical representations, which could have potential in rehabilitation and treatment of neurological disorders with maladaptive neuroplasticity like focal hand dystonia.

Disclosures: **M. Germann:** None. **B. Habekost:** None. **S.N. Baker:** None.

Poster

759. Motor Impairment and Recovery

Location: Hall A

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Program #/Poster #: 759.05/K30

Topic: E.04. Voluntary Movements

Support: MINECO/AEI/FEDER-UE (SAF2017-86246-R)
Comunidad de Madrid (2017-T2/BMD-5231)
The Michael J. Fox Foundation (Grant ID 9205)

Title: Cortical excitability and tSMS-induced plasticity in a large sample of patients with Parkinson's disease

Authors: *C. AMMANN[1], M. DILEONE[1,2], C. PAGGE[1], A. OLIVIERO[3], J. A. OBESO[1,4], G. FOFFANI[1,3];
[1]CINAC, Univ. Hosp. HM Puerta del Sur, CEU-San Pablo Univ., Móstoles, Spain; [2]Advanced Neuro-rehabilitation Unit, Hosp. Los Madroños, Brunete, Spain; [3]Sescam, Hosp. Nacional de Parapléjicos, Toledo, Spain; [4]Ciberned, Inst. Carlos III, Madrid, Spain

Abstract: Cortical excitability and plasticity changes measured by transcranial magnetic stimulation (TMS) have been defined in patients with Parkinson's disease (PD). After 30 years of TMS research in PD results are still mixed and most studies present reduced numbers of subjects. Moreover, studies on evolution of cortical changes with disease progression are scarce. Here we aim to dissolve ambiguity of existing results studying a large sample of patients with a wide range of disease stages. We assessed corticospinal and intracortical excitability recording TMS-induced motor evoked potentials (MEP) from a hand muscle in 130 patients. We classified 4 groups: *de novo* levodopa-naïve (n=47), on levodopa medication without (n=36), and with (n=47) levodopa-induced dyskinesias (LIDs), and healthy controls (n=40). A sub-sample of each group (*de novo*/n=21; non-dysk/n=22; dysk/n=22; control/n=20) received 10 min of transcranial static magnetic field stimulation (tSMS) over the motor cortex, which decreases cortical excitability in healthy subjects (Oliviero et al, 2011). Thus, we assessed cortical plasticity through MEP amplitude changes recorded before and after tSMS. All patients were studied off medication. We confirmed a reduction of intracortical inhibition first observed for the more affected side in *de novo* patients and bilaterally impaired once the disease progresses. No significant alterations were found for intracortical facilitation. PD resting motor threshold values showed a decreasing trend compared to controls. Surprisingly, a significant increase from early on (also less affected side) of MEP variability compared to controls has been observed with a high area under the receiver operating characteristic curve (ROC) comparing less and more affected side of *de novo* patients with healthy subjects. Regarding plasticity changes, we observed a loss of tSMS-induced plasticity in *de novo* and non-dyskinetic patients turning into a

paradoxical MEP potentiation in dyskinetic patients compared to decreased MEP amplitude in healthy subjects. We conclude that cortical excitability is altered in PD expressed early on by changes in corticospinal excitability and intracortical inhibition as the disease progresses. Once altered, excitability abnormalities remain unchanged with PD evolution. We suggest that the decreased inhibition is not due to increased intracortical facilitation. Moreover, MEP variability could present a valuable diagnostic measure for PD in early stages. Finally, we propose that the motor cortex plays an active role in LID pathophysiology rather than being just a 'passive integrator' of subcortical and corticocortical abnormalities.

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Poster

759. Motor Impairment and Recovery

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 759.06/K31

Topic: E.04. Voluntary Movements

Title: Cerebellar tDCS improves performance of a timing-based video game more than M1 tDCS or practice alone

Authors: M. E. WOLFE[1], J. PEREZ[1], A. W. MEEK[2], B. J. POSTON[3], ***Z. A. RILEY**[4]; [1]IUPUI, Indianapolis, IN; [2]Dept. of Kinesiology, Indiana University-Purdue Univ. Indianapolis, Indianapolis, IN; [3]Kinesiology and Nutr. Sci., Univ. of Nevada Las Vegas, Las Vegas, NV; [4]Indiana Univ. Purdue Univ. at Indianapolis, Indianapolis, IN

Abstract: Transcranial direct current stimulation (tDCS) is a brain stimulation technique that has been applied to the motor cortex (M1) to facilitate learning of skilled, dexterous hand tasks. However, when there is a timing component to the motor skill, tDCS is usually applied to the cerebellum (CB). The purpose of this study was to compare M1 tDCS and CB tDCS to determine which resulted in better performance and timing accuracy of a video game involving dexterous finger movements and timing. 100 healthy adults (age: 18-33 yrs ± 3.1) were randomized into M1 anodal (n=25), CB anodal (n=25), CB cathodal (n=25), or CB sham (n=25) stimulation groups. The task used the Step Mania video game that is timing-based and involves pressing the correct arrow keys on a keyboard at specific times when scrolling icons overlapped on a computer screen. Each subject practiced the task at least two times to obtain a pre-practice score. Each key press corresponded to a time relative to the optimal key pressing time. Scores for each trial were an average these numbers. Each subject completed ~2 minutes of practice

followed by ~2 minutes of rest and repeated this 5 times for 20 total minutes of practice. Post-test scores were obtained 5 and 10 minutes following practice. During practice, tDCS was delivered at 2mA in accordance to the condition the subject was randomized to (M1 anodal, CB anodal, CB cathodal, sham). There was a significant main effect for time ($p<0.001$) for changes in timing accuracy but no interaction for time*condition ($p=0.270$). Improvements in timing accuracy occurred faster (trial 1—5 minute post-test) for the M1 anodal ($p=0.004$) and CB cathodal ($p=0.001$) conditions. Timing accuracy did not significantly improve until the 10-minute post-test for the CB anodal ($p=0.003$) and sham ($p=0.009$). Error scores resulted in a significant effect of time ($P<0.001$) but not a significant effect for time*condition ($p=0.173$). Both the M1 anodal ($p=0.008$) and CB cathodal ($p=0.013$) had significant improvements error scores at the 10-minute posttest. In the context of motor learning, these results show that M1 anodal and CB cathodal stimulation conditions both accelerate the learning of a timing-based video game faster than either CB anodal stimulation, or simply practice alone.

Disclosures: M.E. Wolfe: None. **J. Perez:** None. **A.W. Meek:** None. **B.J. Poston:** None. **Z.A. Riley:** None.

Poster

759. Motor Impairment and Recovery

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Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 759.07/K32

Topic: E.04. Voluntary Movements

Support: NIH Grant 2R25GM109432

Title: Variant target effects on motor learning through tDCS

Authors: *J. PEREZ, C. L. LASHER, K. J. HARBISON, Z. A. RILEY;
Indiana University-Purdue Univ. Indianapolis, Indianapolis, IN

Abstract: Transcranial direct current stimulation (tDCS) is a form of non-invasive brain stimulation that has been utilized to stimulate the motor cortex (M1) to accelerate motor learning. The tasks most commonly studied with tDCS of M1 are sequential finger tapping and visual isometric pinch force tasks, though these tasks do not require changing endpoints based on the target. Other tasks with changing endpoints, such as reaching and pointing, require motor adaptive responses from error signals to continually update and improve the movements, usually driven by the cerebellum (Orban de Xivry and Shadmehr, 2014). The purpose of the present study was to determine if tDCS to M1 would still be effective at accelerating motor learning when throwing darts at different targets, even if motor adaptation is primarily mediated through a different brain region. To examine this, participants were randomized into a sham (n=32) or anodal (n=34) tDCS conditions and completed a dart throwing task in which they performed one

pre-test, five practice rounds, and one post-test. In the pre-test, participants aimed to hit the bull's eye. During practice, participants threw at 8-bull eye's sized targets evenly positioned around the dartboard (each 16.5cm from center bull's eye) while receiving either anodal or sham stimulation. Those in the anodal tDCS group received 2mA of stimulation over M1 for 20 minutes. Those in the sham condition only received 30 seconds of stimulation before the machine shut off; but completed the same number of throws as those in the anodal group. Participants repeated the pretest procedures directly after practice, 1-hour after practice, and 24-hours after practice. Results indicated that both groups improved on the task significantly over time ($p \leq 0.001$) and that the variability in their throws decreased significantly ($p \leq 0.001$), though there was no interaction ($p = 0.34$), indicating the stimulation did not have an overall effect on performance. Stimulation of M1 did not appear to be effective at accelerating learning of throwing darts at variable targets beyond what normal practice provides. It is certainly possible that this is due to the learning changes being mediated through the cerebellum, where motor adaptation occurs, and not M1 where movements are simply carried out.

Disclosures: J. Perez: None. **C.L. Lasher:** None. **K.J. Harbison:** None. **Z.A. Riley:** None.

Poster

759. Motor Impairment and Recovery

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 759.08/K33

Topic: E.04. Voluntary Movements

Support: A*STAR Singapore NSS(PhD)
NIH NINDS K02
VA Advanced Fellowship in Neuroscience
Burroughs-Wellcome Trust Fund
VA RR&D Merit Reward

Title: Changes in dorsolateral striatum neural dynamics during recovery after motor cortical stroke

Authors: *L. GUO[1], S. KONDAPAVULUR[1], S.-J. WON[2], K. GANGULY[1];
[1]Neurol., UCSF, San Francisco, CA; [2]Neurol., San Francisco VA Med. Ctr., San Francisco, CA

Abstract: Even with present state of the art rehabilitation methods, a substantial number of stroke patients continue to experience chronic upper-limb motor deficits. Current rehabilitation and neuromodulation methods are hampered by a limited understanding of brain reorganization after stroke, especially at the network and neural dynamics level. Past research has focused on the role of the perilesional cortex (PLC), the area of cortex directly adjacent of the stroke site, in motor recovery. However, executing a skilled motor action requires coordinated activity of both

cortical and subcortical motor areas. Particularly, the dorsal lateral striatum (DLS) is involved in motor learning and execution in healthy individuals and loses input projections after a motor cortical stroke. However, its role in motor recovery after stroke remains unknown.
To understand the dynamic changes in the brain during the stroke recovery process, we first trained Long Evans rats on a single-pellet reach-to-grasp task that assesses skilled forelimb motor function. Next, we induced a photothrombotic stroke over the forelimb motor cortex, and then implanted electrodes in both the PLC and DLS. We then recorded single unit and local field potential data while rats underwent physical rehabilitation using the same task.
On average, accuracy (i.e. pellet retrieval success) and speed of movements significantly decreased after stroke. There was a partial restoration of motor performance with rehabilitation training, reaching a plateau that was generally lower than pre-stroke levels. Interestingly, pharmacological inactivation of DLS post-stroke further decreased the accuracy, speed and amplitude of movements, indicating that DLS was still involved in motor performance after stroke recovery. Although the average movement-locked unit firing pattern in DLS did not change during recovery, there was an expansion in the proportion of movement-modulated units in DLS. Strikingly, DLS population neural activity on a trial by trial level became more consistent and coordinated after rehabilitation. These results demonstrated that the DLS, a previously understudied area in the context of stroke, is also functionally affected by a motor cortical stroke and that patterns of neural activity in DLS during motor actions are reorganized with recovery.

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Poster

759. Motor Impairment and Recovery

Location: Hall A

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Topic: E.04. Voluntary Movements

Support: Merck Sharpe & Dohme - Faculté de médecine
FRQS Junior 1 Grant 35012
NSERC Grant RGPIN-2017-06120

Title: Pain induced metaplasticity interferes with motor learning in intact rats

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Abstract: Motor learning and pain are two key components of rehabilitation. Despite being mostly studied independently from each other, important interactions exist between them in the context of spinal cord injury. Ongoing nociceptive activity or recent pain episodes can reduce the

malleability of the spinal motor circuits and prevent motor learning in spinalized rats. In the neurologically intact system, it has been proposed that descending serotoninergic fibers could counter the repressive effect of pain on motor system plasticity. The aim of our study is to verify whether a recent pain episode affects locomotor pattern learning in intact rats.
For this purpose, we trained Long Evans rats to walk on a custom-made horizontal ladder. After a series of initial training sessions, the rats underwent a week-long rest, during which they were randomly assigned to a control group or one out of two pain conditions. Nociceptive stimuli of different duration were induced by capsaicin or Complete Freund's Adjuvant injections, and timed so that the mechanical hypersensitivity had entirely subsided by the end of the resting period. Training then resumed on a modified version of the horizontal ladder. We evaluated the animals' ability to adapt to the modified task by measuring their transit time and paw misplacements for two 30-minutes daily sessions.
Our results show that prior pain episodes do affect motor learning in neurologically intact rats. The motor learning deficits also seem to be influenced by the duration of the pain episode. Rats displayed learning deficits 24h after receiving a subcutaneous injection of capsaicin, even though they did not show signs of mechanical hypersensitivity. Rats previously subjected to a week of inflammatory pain caused by a Complete Freund's Adjuvant injection displayed even more prolonged motor learning deficits. Our results suggest that prior pain episodes can negatively influence motor learning, and that the duration of the impairment relates to the duration of the pain episode. Our results highlight the importance of addressing pain together with motor training. They may have important implications not only for rehabilitation after neurological lesions, but also for performance athletes returning to sports after injury.

Disclosures: M. Huot-Lavoie: None. **W.K. Ting:** None. **M. Demers:** None. **C. Mercier:** None. **C. Ethier:** None.

Poster

759. Motor Impairment and Recovery

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 759.10/K35

Topic: E.04. Voluntary Movements

Support: NSERC RGPIN2015

Title: The influence of glucose on intracortical and corticospinal excitability as assessed using transcranial magnetic stimulation

Authors: *S. L. TOEPP[1], C. V. TURCO[1], C. NICOLINI[1], A. J. NELSON[2];
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Abstract: Experiments using transcranial magnetic stimulation (TMS) to measure corticospinal and intracortical excitability are commonly used in neuroscience research in clinical and basic applications. However, the effect of dietary factors such as glucose consumption on TMS-based measures has received minimal attention despite the potential influence on precision and reliability. The present double-blinded, placebo-controlled study tested the effects of glucose on two standard TMS measures. Short-interval intracortical inhibition (SICI) is a paired-pulse measure thought to reflect $GABA_A$-mediated neurotransmission, while single-pulse motor evoked potential (MEP) recruitment curve is a frequently used indicator of corticospinal excitability and may reflect cortical glutamate levels. For both measures, TMS was delivered over the left motor cortex and MEP responses were recorded using surface EMG over the muscle belly of the first dorsal interosseous muscle of the right hand. Healthy males (n = 17; age = 22.47 +/- 1.29 y) each participated in 4 sessions. Session 1 involved familiarization to TMS, followed by acquisition of an individualized blood glucose response curve. During sessions 2, 3 and 4, dependent measures were taken before (T0), and at two timepoints following (T1 and T2), ingestion of an experimental treatment solution. The solutions contained glucose (75 g), sucralose-sweetened placebo (control for sweetness) or plain water (control for time). The T1 post-drink assessments were started 5 minutes prior to the blood glucose peak observed during Session 1. T2 assessments were started 35 minutes after T1 to coincide with the delayed arrival of glucose in the cerebrospinal fluid. One-way repeated measures ANOVA found a significant time effect on MEP recruitment curve area for sucralose-sweetened placebo ($p < 0.05$) but not plain water or glucose. Post-hoc paired-sample t tests revealed that MEP recruitment curve area was significantly greater than baseline at T1 and T2 ($p < 0.05$ for both timepoints). No effect was detected with respect to SICI for any treatment. This investigation provides important insight concerning the influence of glucose and will strengthen the interpretation and utility of TMS studies in the future.

Disclosures: S.L. Toepp: None. **C.V. Turco:** None. **C. Nicolini:** None. **A.J. Nelson:** None.

Poster

759. Motor Impairment and Recovery

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 759.11/K36

Topic: E.04. Voluntary Movements

Title: Dexterous timing-based video game performance with complementary transcranial direct current stimulation of the primary motor cortex and cerebellum

Authors: *A. W. MEEK[1], J. PEREZ[1], M. WOLFE[1], A. BOCKELMAN[1], K. HARBISON[1], C. LASHER[1], B. J. POSTON[2], Z. A. RILEY[1];

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Abstract: Transcranial direct current stimulation (tDCS) applied to the primary motor cortex (M1) and cerebellum (CB), can facilitate learning of dexterous motor skills. Although the motor cortex and cerebellum work together to execute movements, stimulation of each site independently can influence motor learning through different mechanisms. It is unknown whether complementary stimulation of both sites simultaneously will influence motor learning. The purpose of this study was to determine if complementary stimulation of M1 and CB would facilitate learning of a video game requiring well timed dexterous finger movements compared to practice without stimulation. Forty-nine adults were randomized into an active stimulation (n=25) or sham (n=24) control group. Step Mania is a timing-based video game that involves pressing arrow keys on a keyboard at specific times when scrolling icons overlap stationary targets on a computer screen. Each key stroke corresponded to a time relative to the optimal key pressing time, putting key strokes into bins corresponding to an accuracy score. Optimal keystrokes received a score of 1, and this score decreased as they were further away from the target (0.8, 0.6, 0.4, 0.2 or 0 points for misses) Subject performance was assessed by timing accuracy (i.e. optimal keystroke timing) and movement errors (i.e. incorrect key strikes). Each subject practiced the task twice to obtain a pre-practice score. Subjects completed 5 practice trials with ~2 minutes of rest after each trial for 20 total minutes of practice. Post-test scores were obtained 5 and 10 minutes after practice. During practice, separate stimulators applied 2 mA anodal tDCS to M1 and 2mA cathodal tDCS to CB. Timing and error data were analyzed with 8 (time) x 2 (condition) mixed ANOVAs. Non-normal movement error data were transformed with a square root transformation. The stimulation group had significantly higher timing scores for each practice trial ($p < 0.001$ to $p = 0.008$) and both the 5 ($p = 0.002$) and 10 minute ($p = 0.001$) post-tests ($p = 0.04$). The stimulation group had significantly fewer movement errors in the first 3 practice trials ($p = 0.036$ to $p = 0.044$) and the 5 minute post-test ($p = 0.044$) compared to sham. These results suggest that complementary M1 and CB tDCS can lead to greater performance gains after 20 minutes of practice compared to normal practice alone. This appears to primarily be due to an effect on timing accuracy which persists after practice. The improved timing accuracy after practicing with stimulation may be facilitated, at least in part, by more practice with correct keystrokes during early practice trials.

Disclosures: **A.W. Meek:** None. **J. Perez:** None. **A. Bockelman:** None. **K. Harbison:** None. **C. Lasher:** None. **B.J. Poston:** None. **Z.A. Riley:** None. **M. Wolfe:** None.

Poster

759. Motor Impairment and Recovery

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Program #/Poster #: 759.12/K37

Topic: E.04. Voluntary Movements

Support: Fondazione Roma (NCDS-2013-00000349)
D1 Funds Università Cattolica

Title: Transcranial direct current stimulation promotes motor recovery in a mouse model of stroke by affecting key molecular players of neuroplasticity

Authors: V. LONGO[1], A. RE[1], S. A. BARBATI[1], M. G. DI DONNA[1], *L. LEONE[1], C. GRASSI[2], M. V. PODDA[2];
[1]Univ. Cattolica del Sacro Cuore, Roma, Italy; [2]Fondazione Policlinico Universitario A. Gemelli IRCCS, Roma, Italy

Abstract: No effective treatments have been identified so far to restore motor function after stroke. The most recent approaches aim to promote brain cortex plasticity and, in this context, transcranial direct current stimulation (tDCS) has become one of the most promising tools, although the mechanisms underlying its effect are not fully understood yet. The purpose of this study is to examine tDCS effects on functional recovery of the paretic limb in a mouse model of stroke and to identify the underlying molecular mechanisms. Focal infarct of forelimb motor cortex area was induced by phototrombosis in 5/6-week-old C57BL/6 mice using the photochemical dye, Rose Bengal, and after 72 hours mice were subjected to tDCS or sham stimulation. TDCS (35.4 A/m^2 for 20 min) was applied once per day for 3 consecutive days (3×tDCS) using a bipolar montage (anode over stroked motor cortex and cathode over the undamaged one). Motor recovery was assessed by grip strength test and single pellet reaching task. Molecular analyses were performed by Western immunoblotting, qRT-PCR, dot blot and ELISA. Results showed that 3×tDCS enhanced forelimb motor recovery after stroke. Indeed, 24 hours after tDCS, mice showed a significant enhancement of neuromuscular strength (+40.0±8.7%; n=11; p=0.0001) and of the success rate in the single pellet reaching task (0.18±0.05; n=12; p=0.04) compared to post-stroke values assessed before stimulation. In contrast, sham stimulated stroked-mice exhibited no significant improvement in strength and success rate (strength: n=8, p=0.7; success rate: n=11, p=0.15).Of note, epigenetic analysis showed that functional improvement in 3×tDCS mice was associated with reduced levels of 5-hydroxymethylcytosine (5hmC), which could be considered a novel outcome measure of functional recovery. Interestingly, our molecular analyses revealed that 3×tDCS modulated key players of neuroplasticity in the motor cortex. Specifically, 3×tDCS mice displayed enhanced levels of Bdnf mRNA (4.55±0.08 fold increase *vs.* sham; p=0.004) and the activated forms of proteins ERK1/2 ($pERK^{Thr204}$; 1.81±0.13 fold increase *vs.* sham; p=0.001) and MEF2C ($pMEF2C^{Ser387}$; 3.09±0.24 fold increase *vs.* sham; p=0.0004). Altogether, our data unveil molecular determinants of neuroplasticity that are affected by tDCS and support the use of this non-invasive brain stimulation technique in clinical settings to promote recovery of motor function after stroke.

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Poster

759. Motor Impairment and Recovery

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 759.13/K38

Topic: E.04. Voluntary Movements

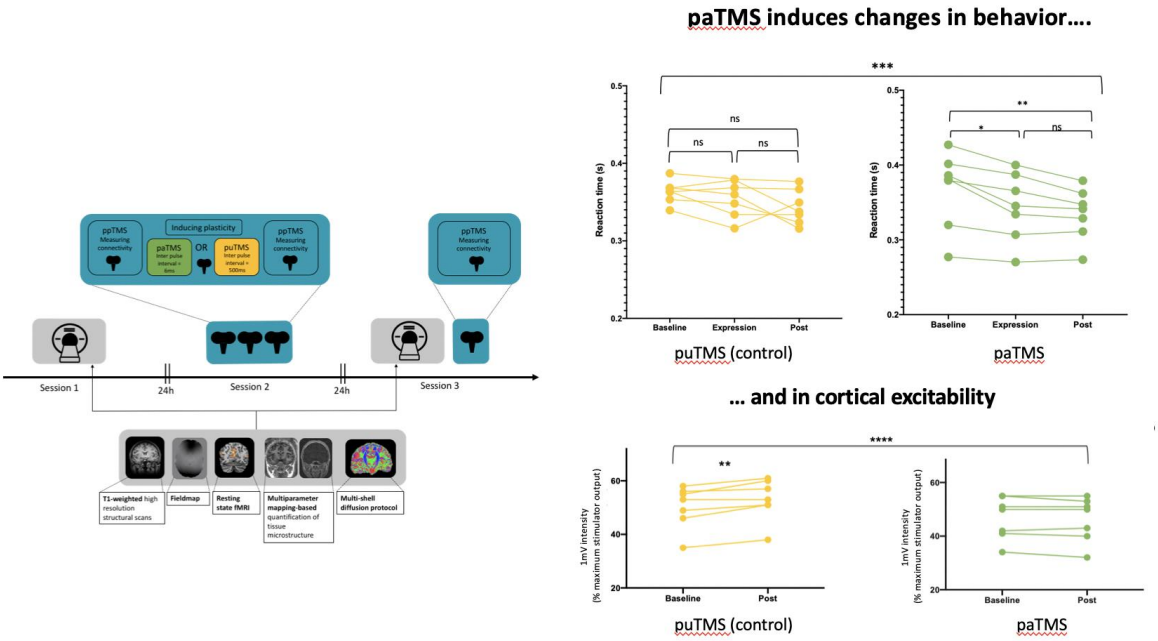
Support: Wellcome Trust 4-year PhD studentship 109062/Z/15/Z

Title: Inducing associative plasticity in a premotor-motor circuit in humans: A randomised-controlled evaluation

Authors: *A. LAZARI[1], L. VERHAGEN[2], P. SALVAN[1], D. PAPP[1], O. VAN DER WERF[1], B. GAVINE[1], M. COTTAAR[1], C. STAGG[1], M. F. RUSHWORTH[3], H. JOHANSEN-BERG[4]; [2]WIN, Dept. of Exptl. Psychology, [1]Univ. of Oxford, Oxford, United Kingdom; [3]Univ. Oxford, Oxford, United Kingdom; [4]Univ. Oxford, Oxford, United Kingdom

Abstract: Methods to induce plasticity in the human brain *in vivo* are still in their infancy. Much of the literature has focussed on targeting individual brain regions, but there is an increasing understanding that connectivity between areas, rather than activity of single regions, may be a key driver of brain function and behaviour.
In recent years, paired associative TMS (paTMS) has emerged as a brain stimulation protocol to potentiate the pathways connecting distant brain areas by activating them in conjunction. Previous evidence suggests paTMS can be used flexibly in many different neuroanatomical domains to induce physiological and behavioural effects. However, this has not been tested in a randomised controlled fashion yet. Moreover, it is unclear how long the paTMS effects last for, and whether they lead to structural reorganisation in the stimulated pathways.
Here, we carry out a randomised-controlled assessment of paTMS where 32 subjects are allocated to paTMS or a control protocol consisting of an equal amount of pulses, but delivered at an interval known not to induce plasticity effects. To characterise paTMS-induced plasticity, effects of paTMS on a set of behavioural, physiological, and MR-based structural and functional markers were assessed. Behavioural testing consisted of an action reprogramming task, while physiological testing consisted of TMS-based metrics of connectivity and overall cortical excitability. DWI, qMRI and rs-fMRI scans were collected before and 24h after paTMS or control.
Preliminary results show that participants receiving paTMS become faster at action execution compared to controls (mixed ANOVA significant group by time interaction, $F(6,14)=23$, $p < 0.0001$). Moreover, changes in cortical excitability across time were also different between paTMS and control (mixed ANOVA significant group by time interaction, $F(1,7)=53$, $p = 0.0002$).
These results corroborate previous findings on the efficacy of paTMS and show that paTMS can

be used to potentiate long-range circuits in humans *in vivo*, and can do so more lastingly than previously thought.



Disclosures: **A. Lazari:** None. **L. Verhagen:** None. **P. Salvan:** None. **D. Papp:** None. **O. van der Werf:** None. **B. Gavine:** None. **M. Cottaar:** None. **C. Stagg:** None. **M.F. Rushworth:** None. **H. Johansen-Berg:** None.

Poster

759. Motor Impairment and Recovery

Location: Hall A

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Program #/Poster #: 759.14/K39

Topic: E.04. Voluntary Movements

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DARPA ElectRx Agreement No. N66001-15-2-4057
DARPA TNT Pacific Grant/Contract No. N66001-17-2-4011

Title: Investigating the interaction of vagus nerve stimulation intensity and interval on motor cortex plasticity

Authors: ***R. A. MORRISON**[1], T. DANAPHONGSE[2], S. T. ABE[3], M. STEVENS[3], K. S. ADCOCK[1], M. P. KILGARD[1], S. A. HAYS[4];

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Abstract: Vagus nerve stimulation (VNS) has recently emerged as a method of enhancing rehabilitation for a wide range of neurological disorders including stroke, traumatic brain injury, and spinal cord injury. Recovery is associated with plasticity in central networks after injury, and VNS promotes recovery by inducing plasticity in networks activated during rehabilitation. Thus, increasing the amount of VNS-mediated plasticity could lead to enhanced recovery.
A number of stimulation parameters influence the magnitude of plasticity driven by VNS. Increasing the current intensity of VNS yields an inverted-U effect on plasticity, where moderate intensities drive the most plasticity while low and high intensities have little effect. The interval between stimulations also affects the magnitude of plasticity. However, it is unknown whether these parameters interact to affect the degree of VNS-mediated plasticity.
Here, we sought to investigate the interaction between interstimulation interval (ISI) and VNS intensity and their effects on plasticity. Rats performed a motor task in which VNS was paired with rhythmic jaw movement during chewing with an ISI of 8 or 32 seconds and an intensity of either 0.4 or 1.2 mA. After five days of VNS pairing during behavioral training, intracortical microstimulation (ICMS) was used to document movement representations in the motor cortex, and motor cortex area eliciting jaw movement was compared between groups.

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Poster

759. Motor Impairment and Recovery

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Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 759.15/K40

Topic: E.04. Voluntary Movements

Support: GNT1097397
GNT1102272

Title: Daily activity composition is associated with c-TBS induced neuroplasticity in the human motor cortex in older adults

Authors: *A. E. SMITH[1], M. R. GOLDSWORTHY[2], L. GRAETZ[2], N. THORNTON[2], N. HODYL[2], M. C. RIDDING[2];
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Abstract: Aging is associated with a reduced capacity of the human brain to re-organise the strength of its connections (called neuroplasticity). Regular engagement in physical activities may enhance this capacity. Surprisingly, however, little is known about the relationship between daily activity compositions (incorporating physical activity, sedentary behaviour and sleep) and neuroplasticity in older adults. The purpose of this study was to determine the association between habitual activity and motor cortical neuroplasticity by measuring motor evoked potential amplitudes (MEPs) elicited after a single, and paired continuous theta burst stimulation (cTBS) paradigm, targeting the primary motor cortex. Twenty-seven (66.5 ±4.6 yrs, 13 women) older adults participated in the study. MEPs were recorded from the right first dorsal interosseous muscle before, between and at 0, 10, 20, 40 and 60 min after paired cTBS separated by 10 min. Habitual activity was assessed objectively for 24 h/day over 7-days. Average time spent in sleep, sedentary behaviour, light physical activity and moderate-to-vigorous physical activity were calculated using pre-defined cut-points (COBRA software, UniSA). When accounting for age and sex, time spent in light physical activity was correlated with a greater neuroplasticity response after paired cTBS (r=-.507, P= 0.007). There was also a trend for greater engagement in sedentary behaviour to be correlated with a reduced neuroplasticity response. Compositional data analysis revealed more time spent in light physical activity at the equal expense of sleep, sedentary behaviour and moderate-to-vigorous physical activity was associated with greater motor cortical neuroplasticity (P= 0.02). These findings provide the first evidence that engaging in light physical activity promotes motor cortical neuroplasticity in older adults.

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Poster

759. Motor Impairment and Recovery

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Program #/Poster #: 759.16/L1

Topic: E.04. Voluntary Movements

Support: NIH P41EB018783
VA MERIT I01CX001812

Title: Operant conditioning of the flexor carpi radialis: Current results and simultaneous EEG recording

Authors: J. J. S. NORTON[1,2], A. EFTEKHAR[1], S. HECKMAN[1,2], A. M. CUTRONE[1,2], *T. M. VAUGHAN[1,2], T. FAKE[1,3], A. K. THOMPSON[1,4], J. R. WOLPAW[1,2];
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Abstract: Operant conditioning of the largely monosynaptic H-reflex is a targeted and non-invasive therapeutic intervention for people with motor dysfunction after spinal cord injury and possibly stroke. It can be used in conjunction with other therapies and has no known adverse side effects (Norton and Wolpaw, COBS, 2018). Here, we report on continued work to extend H-reflex conditioning to the upper extremity (i.e., flexor carpi radialis [FCR]). The conditioning protocol is similar to the one of Thompson, Chen, and Wolpaw (2009): 30 (six baseline and 24 conditioning) sessions over 10 weeks with 245 (20 control and 225 baseline/training) trials/session. In conditioning trials, the participant is asked to either increase (up-condition [UC]) or decrease (down-condition [DC]) H-reflex size. In each trial: the participant maintains a fixed level of background electromyography (EMG); the H-reflex is elicited by a stimulus that produces an M-wave of fixed size; H-reflex size is measured; and, in the conditioning trials only, immediate visual feedback shows the person whether H-reflex size satisfied a criterion. In previous studies of soleus H-reflex conditioning, the H-reflex of most participants gradually changed in the instructed direction over the 24 conditioning sessions. To date, 5 participants have completed the FCR H-reflex conditioning protocol. Four (3 UC and 1 DC) changed FCR H-reflex size in the instructed direction (average change from baseline was 24%). This average H-reflex change is slightly less than previously reported for the soleus H-reflex (~31%; Thompson, Chen, and Wolpaw, J Neurosci, 2009) for reflex conditioning of the lower extremity. The difference may reflect the challenges of working with the upper extremity (e.g., smaller muscle size, maintaining participant posture across sessions). To address these issues, we are working to minimize intra- and/or inter-session variations in key factors (e.g., Mmax, Hmax, Mtarget error). As a result, the coefficient of variation of the H-reflex for the control trials of the baseline sessions is less for the 3 participants currently completing the protocol (0.24) than it was for the first 3 participants (0.35). Finally, because the corticospinal tract is essential for H-reflex conditioning, we have begun to collect electroencephalography (EEG) data every 6th session. Analysis of EEG features (e.g., sensorimotor rhythms) immediately prior to H-reflex elicitation should provide insight into the neural mechanisms responsible for the reflex changes and may lead to protocol modifications that enhance the reliability, rapidity, and magnitude of reflex conditioning.

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Poster

759. Motor Impairment and Recovery

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Topic: E.04. Voluntary Movements

Support: NIH NINDS 2R44NS065545-03A1
NIH P41EB018783
VA Merit I01CX001812

Title: Spinal reflex conditioning system for enhancing motor function recovery after incomplete spinal cord injury

Authors: J. NORTON[1], T. M. VAUGHAN[1], *A. EFTEKHAR[1], A. K. THOMPSON[2], A. HARRISON[3], M. SONNTAG[3], A. M. MELEHAN[3], E. BROWN[3], K. LUU[1], S. DEVETZOGLOU-TOLIOU[1], I. P. CLEMENTS[3], J. R. WOLPAW[1];
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Abstract: Spinal Cord Injury (SCI) affects ~300,000 people in the US, with 11,000 new cases per year. After SCI, spinal reflex function becomes abnormal, contributing to motor impairments and spasticity that affects 65-78% of people with SCI. Current therapies are only moderately successful; motor function often does not return to useful, let alone pre-injury levels. Prior research resulted in a novel, non-invasive therapy that targets beneficial change to specific spinal reflex pathways. The patient learns, through operant conditioning, to modify the brain's control over the reflex pathway. In animals and people with SCI, spinal reflex conditioning reduces spasticity, eliminates limping, and increases walking speed. Clinical translation of spinal reflex conditioning techniques would be facilitated by improved technology for robust, precise, and turnkey implementation. Towards this end, we describe the development and validation of a non-invasive multielectrode array-based platform for spinal reflex conditioning. The system facilitates precise, array-based measurement of H-reflex via integrated hardware and software able to detect and interpret EMG signals, optimize neural stimulation, and provide real-time patient feedback. Practical implementation of spinal reflex conditioning therapies will improve recovery for patients who have reflex-mediated spasticity arising from conditions such as spinal cord injury and stroke.

Disclosures: J. Norton: None. **T.M. Vaughan:** None. **A. Eftekhar:** None. **A.K. Thompson:** None. **A. Harrison:** A. Employment/Salary (full or part-time):; BioCircuit Technologies. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BioCircuit Technologies. **M. Sonntag:** A. Employment/Salary (full or part-time):; BioCircuit Technologies. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BioCircuit Technologies. **A.M. Melehan:** A. Employment/Salary (full or part-time):; BioCircuit Technologies. **E. Brown:** A. Employment/Salary (full or part-time):; BioCircuit Techologies. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BioCircuit Technologies. **K. Luu:** None. **S. Devetzoglou-Toliou:** None. **I.P. Clements:** A. Employment/Salary (full or part-time):; BioCircuit Technologies. E. Ownership Interest (stock,

stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BioCircuit Technologies. **J.R. Wolpaw:** None.

Poster

759. Motor Impairment and Recovery

Location: Hall A

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Program #/Poster #: 759.18/L3

Topic: E.04. Voluntary Movements

Support: VA P01 HD32
NIH HD36020
NS22189
NS061823
HD032571
NICHD/P41EB018783

Title: Impact of globus pallidus or sensorimotor cortex ablation on spinal motoneuron GAD67 and KCC2 and on ventral horn interneuron GLUR2/3: Implications for the mechanisms of spinal reflex operant conditioning

Authors: *Y. WANG[1], L. CHEN[1], J. R. WOLPAW[1,2], X. Y. CHEN[1];
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Abstract: Operant conditioning of the H-reflex (HR) produces a hierarchy of plasticity in brain and spinal cord (Neuroscientist 16:532-49, 2010). HR down-conditioning increases GABAergic input to spinal motoneurons (MNs) that may account for the HR decrease (Eur J Neurosci 23: 141-150, 2006; J Neurophysiol 108: 2668-2678, 2012). Down-conditioning is prevented by corticospinal tract transection, sensorimotor cortex (SMC) ablation, or bilateral globus pallidus (GP) ablation. This study explored the impact of SMC or GP ablation on: GABAergic input to the MNs; potassium-chloride cotransporter (KCC2) in the MNs; and glutamate receptors in ventral horn spinal interneurons (INs). BY affecting chloride balance, KCC2 down regulation impairs GABAergic inhibition and may produce GABAergic excitation (Nat Med 16:302-308, 2010; J Neurosci 33:15488-503, 2013).
Ten anesthetized Sprague-Dawley rats were implanted with EMG electrodes in right soleus (SOL) and a stimulating cuff on right posterior tibial nerve; the left SMC hindlimb area (SMC rats, n=4) or the GP bilaterally (GP rats, n=6) was ablated. Thirty days later, each was exposed to SOL HR down-conditioning. The rat was then injected in right SOL with CTB-Fluor 647, and perfused 3 days later. Five weight-matched naïve control (NC) rats were similarly injected and perfused. Lumbar 4-5 spinal cord was blocked and cut into 16-μm sections for anti-GAD67, anti-KCC2, or anti-GluR2/3 immunohistochemistry labeling. Three-D image stacks were analyzed in

a blinded manner with the Fiji-image J program. Immunoreactivity (IR) in GP and SMC rats was expressed in % of NC values and assessed with one-way ANOVA.
In SMC and GP rats, GAD_{67}-IR on SOL MNs was 81(±6 SEM)% and 92(±3)%, respectively, of the NC value (p=0.03 & 0.08 vs. NC; LSMeans contrast). Number of GABAergic terminals/MN in SMC and GP rats was 13(±1) and 15(±1), respectively; both were decreased ($p<0.01$) vs NC (17(±1)). MN KCC2-IR in SMC and GP rats was 85(±4)% and 89(±3)%, respectively (p=0.001 & 0.03 vs. NC). MN GluR2/3-IR of SMC and GP rats was 109(±6)% and 96(±2)%, respectively, in MNs (p=0.104 & 0.28); it was 122(±2)% and 106(±1)% in ventral horn INs ($p<0.001$ for both).
These initial results indicate that SMC or GP ablation decreases spinal MN GABAergic input and may impair GABAergic inhibition, and increases glutamate in ventral horn INs. Because SMC or GP ablation prevents HR down-conditioning, the GABA and KCC2 effects are consistent with the hypothesis that the spinal GABAergic impact of down-conditioning underlies the HR decrease. The relevance of the increased IN glutamate to the impact of SMC or GP ablation on down-conditioning is at present unclear.

Disclosures: **Y. Wang:** None. **L. Chen:** None. **J.R. Wolpaw:** None. **X.Y. Chen:** None.

Poster

759. Motor Impairment and Recovery

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 759.19/L4

Topic: E.04. Voluntary Movements

Support: DFG 2112280105
DFG LA 3442/3-1
DFG LA 3442/5-1
European Union's Horizon 2020 research and innovation program and Euratom research and training program 2014–2018 (under grant agreement No. 670118)
EU Grant 720270, HBP SGA1 & SGA2
Einstein Stiftung

Title: Tracking of whisking into target zones using a closed-loop, real-time feedback system

Authors: *K. SEHARA[1], V. BAHR[2], B. MITCHINSON[3], M. STAAB[1], S. E. DOMINIAK[1], M. J. PEARSON[4], M. E. LARKUM[1], R. N. S. SACHDEV[1];
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Abstract: One of the principal functions of the brain is to control movement and rapidly adapt behavior to a changing external environment. Over the last decades our ability to monitor activity in the brain, manipulate it while also manipulating the environment the animal moves through, has been tackled with increasing sophistication. Yet, our ability to track the movement of the animal in real time has not kept pace. Here we use a Dynamic Vision Sensor (DVS) based event-driven neuromorphic camera system to implement real-time tracking of a single whisker that mice can move at ~ 25 Hz. The customized DVS-system used here converts whisker motion into a series of events that can be used to estimate the position of the whisker and to trigger a position-based output within 2 milliseconds. Here we interactively set a virtual target region in front of the mouse and generated fast sensory feedback when mice moved their whisker into the target zone. Mice were trained to move a whisker to a target zone, a location varied in the course of a session. We show that mice learn to position their whiskers to the target zones, and change their whisking to match the changing location of the target. The methods developed here are being used to examine the phase and context dependent effects of sensory and motor cortical activation and inactivation on changes in set point / whisking into and out of the target zone.

Disclosures: **K. Sehara:** None. **V. Bahr:** None. **B. Mitchinson:** None. **M. Staab:** None. **S.E. Dominiak:** None. **M.J. Pearson:** None. **M.E. Larkum:** None. **R.N.S. Sachdev:** None.

Poster

759. Motor Impairment and Recovery

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 759.20/L5

Topic: E.04. Voluntary Movements

Support: DFG, 2112280105
DFG, LA 3442/3-1
DFG, LA 3442/5-1
ERC, No. 670118
HBP, EU Grant 720270,

Title: Coordination of behavior in an Air Track maze: Sequential movement of whiskers, the maze and eyes

Authors: R. BERGMANN[1], S. DOMINIAK[1], V. BAHR[4], J. KREMKOW[5], M. A. NASHAAT[6], H. ORABY[6], K. SEHARA[2], M. E. LARKUM[1], *R. N. SACHDEV[3];
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Abstract: The Air-track is a floating “real-world” environment that mice propel around themselves. It has walls that mice contact as they navigate the plus maze shaped platform for reward. Our previous work shows that as mice navigate the maze, they move their whiskers in a stereotyped manner: every trial shows the same pattern of whisking even though the duration of the trials varies widely. Our work has also shown that side to side asymmetry in whisker position, set point of whiskers and whisking frequency are behavioral state dependent and that together these parameters of whisker motion are sufficient to determine “where” the mouse is in the maze and “what” the mouse is doing in the maze. While whiskers are informative about mouse behavior in the maze, mice have little difficulty performing the task even when whiskers have been trimmed. Here we considered the possibility that mice use vision, perhaps they even move their eyes as they navigate the maze. Indeed, while mice push and pull a maze around themselves, they do move their eyes bilaterally, in concert with the movement of the platform. We find that mice first indicate their intent to move the platform by moving their whiskers, then they begin to move the platform, and finally once the platform begins to move, mice move their eyes conjointly. We are examining in particular how and when the eyes move in relationship to the looming and diminishing appearance of objects, i.e. as walls appear and disappear from the animal’s view. We are also examining the role of cortical control in eye movement and whisker positioning.

Disclosures: R. Bergmann: None. **S. Dominiak:** None. **V. Bahr:** None. **J. Kremkow:** None. **M.A. Nashaat:** None. **H. Oraby:** None. **K. Sehara:** None. **M.E. Larkum:** None. **R.N. Sachdev:** None.

Poster

759. Motor Impairment and Recovery

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 759.21/L6

Topic: E.04. Voluntary Movements

Support: VA P01 HD32
NIH HD36020
NS22189
NS061823
HD032571
NICHD/1P41EB018783

Title: Combining H-reflex conditioning and locomotor training enhances locomotor recovery in rates with incomplete spinal cord injury

Authors: *J. R. WOLPAW[1,2], L. CHEN[1], X. YANG[1], Y. CHEN[1], X. Y. CHEN[1];
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Abstract: Operant conditioning of the spinal stretch reflex or its electrical analog, the H-reflex (HR), changes brain and spinal cord (Curr Opin Behav Sci 20:138-144, 2018 for review). In rats and humans with incomplete spinal cord injury (SCI), appropriate reflex conditioning improves locomotion (J Neurosci 26:12537-12543, 2006 & 33:2365-2375, 2013). We are exploring in rats the impact of combining H-reflex conditioning with locomotor training (an established therapy) after SCI.

Under anesthesia, Sprague-Dawley rats were implanted with EMG recording and nerve stimulating electrodes, and received a right SCI at T9. Twenty days later, each rat was exposed to a 60-day intervention of either right soleus HR up-conditioning combined with 5 days/wk locomotor training (CB rats, n=9), or locomotor training alone (LT rats, n=7). Locomotor EMG and HRs, and horizontal ladder crossing were assessed before and after SCI, and at the end of the 60-day treatment.

In rats with SCI, CB treatment increased the protocol HR (the HR during the conditioning protocol) ($p<0.001$, paired t-test); LT treatment did not affect the protocol HR ($p=0.54$). Final HR averaged 210(±19 SE)% of pre-treatment value in the 9 CB rats and 97(±5)% in the 7 LT rats ($p<0.001$ CB vs LT by t-test). In CB rats, the protocol HR appeared to increase more quickly and more than in normal rats exposed to up-conditioning alone. CB, but not LT, treatment also increased the locomotor HR (the HR during locomotion) ($p=0.02$ & 0.31, respectively). Final soleus locomotor HR averaged 273(±57)% of pre-treatment value in CB rats and 106(±5)% in LT rats ($p=0.024$). Both CB and LT treatments were associated with moderate increases in the soleus locomotor burst (120(±5)% and 115(±9)% of pre-treatment value, respectively).

Before SCI, footfalls (i.e., misses) in horizontal ladder crossing were 0.11(±0.08SE)/crossing for CB rats and 0.24(±0.10)/crossing for LT rats ($p=0.32$ CB vs LT by t-test). After SCI and before treatment, they were 6.24(±0.82)/crossing for CB rats and 5.34(±0.58)/crossing for LT rats ($p=0.41$). After treatment, they were 1.80(±0.51)/crossing in CB rats and 5.14(±0.57)/crossing in LT rats ($p<0.001$).

These initial results indicate that, in rats with right SCI, the combination of right soleus H-reflex up-conditioning and locomotor training produces locomotor recovery in SCI rats superior to that produced by locomotor training alone. Further assessment of locomotor kinematics and of the persistence of the superior recovery is underway. If confirmed, these results should lead to human studies exploring the ability of this combined therapy to enhance recovery after SCI beyond that achieved by either therapy alone.

Disclosures: J.R. Wolpaw: None. **L. Chen:** None. **X. Yang:** None. **Y. Chen:** None. **X.Y. Chen:** None.

Poster

759. Motor Impairment and Recovery

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 759.22/L7

Topic: E.04. Voluntary Movements

Support: DFG 2112280105
DFG LA 3442/3-1
DFG LA 3442/5-1
HUZ 670118
HBP 720270

Title: Coordination of whiskers and nose in a go-cue task and the role of motor cortex

Authors: *M. STAAB[1], K. SEHARA[2], S. DOMINIAK[1], M. E. LARKUM[1], R. N. SACHDEV[1]; [2]Inst. of Biol., [1]Humboldt Univ. zu Berlin, Berlin, Germany

Abstract: Rodents move their whiskers to map the external space around their face, and they move their nose to sample the odor field. The motion of these two active sensing elements is often coordinated, to the extent that whisker motion and breathing / sniffing have been linked to the same CPG in the brainstem. Here, in a simple go-cue triggered-whisking to touch task, we monitored the movement of C1 and C2 whiskers bilaterally, while also monitoring the movement of the nose. In preliminary experiments we also performed optogenetic inactivation of the motor cortex to examine whether coordination of whisker movement on one side of the face, coordination of whisker movement bilaterally, or whisker-nose motion coordination were altered. We find that: 1) Each mouse has distinct patterns of whisker motion, with distinct pattern of coordination between whiskers and coordination of whisker-nose motion; 2) Whiskers on one side of the face don't move together: the spread between adjacent whiskers changes, and the speed of adjacent whiskers varies in the course of each trial; 3) the nose moves on every trial, with large movement just before or just after whiskers hit the contact sensor; 4) Inactivation of motor cortex in Vgat-cre;FLEX-Chr2 mice affects performance - success rate decreases, and affects the coordination between whiskers, between whiskers and nose motion, and alters the frequency components in whisking.

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Poster

759. Motor Impairment and Recovery

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 759.23/L8

Topic: E.04. Voluntary Movements

Support: NIH P41EB018783
VA MERIT I01CX001812

Title: An epidermal electronic system (EES) grid electrode for measuring electromyography (EMG) during operant conditioning of human flexor carpi radialis H-reflex

Authors: J. J. S. NORTON[1,2], Y. T. KWON[3], A. EFTEKHAR[1], **T. FAKE**[1,4], *A. M. CUTRONE[1,2], J. R. WOLPAW[1,2], W. YEO[3];
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Abstract: Operant conditioning of the flexor carpi radialis (FCR) H-reflex may provide a non-invasive and targeted therapeutic intervention for people with motor dysfunction in the upper extremity following stroke (Norton and Wolpaw, COBS, 2018). In the conditioning protocol, an FCR H-reflex is elicited with surface electrical stimulation and measured with electromyography (EMG). After collection of baseline data, participants are asked to either increase or decrease their H-reflex size. Guided by visual feedback, the participants learn to change H-reflex size after multiple sessions. Here, we report initial development of a flexible and conformal grid of EMG electrodes using an epidermal electronic system (EES; Herbert et al., Materials, 2018). In contrast to traditional EMG electrodes, the EES device conforms to the skin and does not require electrolytic gel. The initial design of the EES device consists of a 4 x 4 grid of electrodes; each electrode measures 0.4 x 0.6 cm with an inter-electrode distance of 1.0 x 1.4 cm. The individual electrodes are made of circular pads connected by serpentine mesh. In two pilot experiments, we are collecting data to demonstrate that the newly designed EES device can measure reflex responses from the FCR. Experiment 1 is comparing the H/M ratios measured (during recruitment curves [RCs]) with a traditional electrode to those measured with an EES device. Initial results show small differences between the H/M ratios recorded from the two devices which may be due to minor differences in the recording conditions (e.g., electrode size and time of day). Experiment 2 is evaluating inter-session variability in reflex measurements using RCs; the EES device provides stable Hmax and Mmax values despite variations in placement between sessions. With further evaluation and refinement of methods, the EES device may increase the stability and comprehensiveness of EMG recording during H-reflex conditioning sessions, and may thereby enhance the consistency and effectiveness of reflex conditioning protocols.

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Poster

759. Motor Impairment and Recovery

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 759.24/L9

Topic: E.04. Voluntary Movements

Support: NIH/NIBIB 1P41EB018783

Title: The effect of perturbation-based training on the soleus H-reflex

Authors: ***J. H. BARNES**[1,2], E. W. GREENBERG[1], S. M. HECKMAN[1], J. R. CRENSHAW[2], J. R. WOLPAW[1,3];
[1]Natl. Ctr. for Adaptive Neurotechnologies, Wadsworth Center, NY State Dept. of Hlth., Albany, NY; [2]Univ. of Delaware, Newark, DE; [3]Stratton VA Med. Ctr., Albany, NY

Abstract: Perturbation-based training (PBT) protocols, in which participants repeatedly attempt to recover from rapid surface translations, seek to improve the reactive response needed to maintain upright balance during external disturbances. While this type of training has been shown to reduce the likelihood of falls in some at-risk populations, the neuroplasticity underlying it is unknown. To begin addressing this gap in knowledge we investigated the effect of PBT on the soleus H-reflex, bilaterally. Six participants (3 men) aged 28-48 years completed a six-session PBT protocol. Perturbations, consisting of brief (600-700ms) rapid posterior surface translations, were delivered during standing via a computer-controlled treadmill and custom software. Each participant experienced ~75 perturbations/session; perturbation difficulty level, defined by the acceleration/deceleration rate of the treadmill belts, was adjusted on a trial by trial basis according to a progressive practice training model. Before each trial, the participant was instructed to “try not to step.” To determine the effect of this training on the soleus H-reflex, soleus H-reflex/M-wave recruitment curves and soleus H-reflex control trials (i.e., H-reflex responses elicited while background EMG and M-wave size are constant) were recorded bilaterally during standing before training began and after completion of the six training sessions. Over the course of training, all participants improved in their reactive abilities, successfully responding to faster and larger perturbations without stepping. For four participants, this improvement was associated with an increase in soleus H-reflex size in the leg used most often for stepping during unsuccessful trials; the H-reflex in the other leg did not change. For two participants, soleus H-reflex size decreased approximately equally in their stepping leg and their stance leg. Study of additional individuals is being conducted and analyses of electromyographic activity, kinematics, and ground reaction forces are ongoing to explore their functional relevance.

Disclosures: **J.H. Barnes:** None. **E.W. Greenberg:** None. **S.M. Heckman:** None. **J.R. Crenshaw:** None. **J.R. Wolpaw:** None.

Poster

759. Motor Impairment and Recovery

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 759.25/L10

Topic: E.04. Voluntary Movements

Support: NSF Award #1701049
NIH Grant # P41EB018783 (NIBIB)

Title: The relationship between sensorimotor cortex activity and H-reflex size in human flexor carpi radialis: Toward enhancing the therapeutic efficacy of spinal reflex operant conditioning

Authors: *L. M. MCCANE[1], J. R. WOLPAW[1], A. EFTEKHAR[1], A. K. THOMPSON[2], D. J. MCFARLAND[1], W. G. BESIO[3];
[1]Natl. Ctr. for Adaptive Neurotechnologies, Wadsworth Center, NY State Dept. of Hlth., Albany, NY; [2]Dept. of Hlth. Sci. and Research, Col. of Hlth. Professions, Med. Univ. of South Carolina, Charleston, SC; [3]Electrical Computer and Biomed. Engin. Dept., Univ. of Rhode Island, West Kingston, RI

Abstract: Operant conditioning of the H-reflex (electrical analog of the spinal stretch reflex) in the soleus muscle can trigger wider beneficial plasticity that improves walking in animals or people with incomplete spinal cord injury (Thompson & Wolpaw 2014). Animal studies show that H-reflex conditioning requires sensorimotor cortex (SMC). Furthermore, in both animals and people, H-reflex size correlates with SMC sensorimotor rhythm (SMR) amplitudes immediately before H-reflex elicitation (Boulay CB et. al. 2015, Thompson AK et. al. 2018). Taken together, these findings suggest that brain-computer interface (BCI)-based SMR training could improve the consistency, rapidity, and magnitude of H-reflex conditioning and thereby enhance its clinical efficacy and practicality. To evaluate this possibility, we are recording EEG from the scalp over SMC during flexor carpi radialis (FCR) H-reflex elicitation. The goal is to define the normal relationship of H-reflex size to preceding SMR activity and to the concurrent somatosensory evoked potential (SEP). We hypothesize that H-reflex size will correlate with preceding SMR amplitudes in β and γ frequency bands and with amplitudes of components of the SEP produced by the stimulus that elicits the H-reflex. The relatively large and EEG-accessible arm region of human SMC should facilitate this analysis. The study is approved by the New York State Dept Health IRB. Neurologically healthy people are seated with the right arm extended in a neutral position. EMG is collected from 8 arm muscles (bipolar, 2 kHz) while the person keeps FCR EMG at ~10% maximum voluntary contraction (guided by visual feedback). Median nerve stimulation (1-ms biphasic) is delivered in 6 blocks of 50 trials each (1 trial every

4-6 sec). Stimulus amplitude (initially selected from the ascending limb of the person's H-reflex recruitment curve) is continually adjusted to maintain a small stable M-wave. Sixteen channels of scalp EEG and tEEG (Koka K et.al., 2007) are recorded (1200 Hz) over left SMC. BCI2000 software records EEG and EMG, controls the stimulus, and provides visual feedback. Ten people have been studied to date. Data analysis is: assessing the degree to which SMR β and γ band amplitudes predict H-reflex size; delineating SEP components and their correlations with H-reflex size and SMR amplitudes; comparing results for EEG and tEEG data; and defining inter-person variations in EMG across the 8 muscles. The results should guide future studies seeking to improve the clinical efficacy and practicality of spinal reflex conditioning (e.g., by training SMR amplitude and/or using SMR amplitude to trigger H-reflex elicitation).

Disclosures: L.M. McCane: None. **J.R. Wolpaw:** None. **A. Eftekhar:** None. **A.K. Thompson:** None. **D.J. McFarland:** None. **W.G. Besio:** A. Employment/Salary (full or part-time):; CRE Medical. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); CRE Medical.

Poster

760. Brain-Computer Interface: Extracranial

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 760.01/L11

Topic: E.05. Brain-Machine Interface

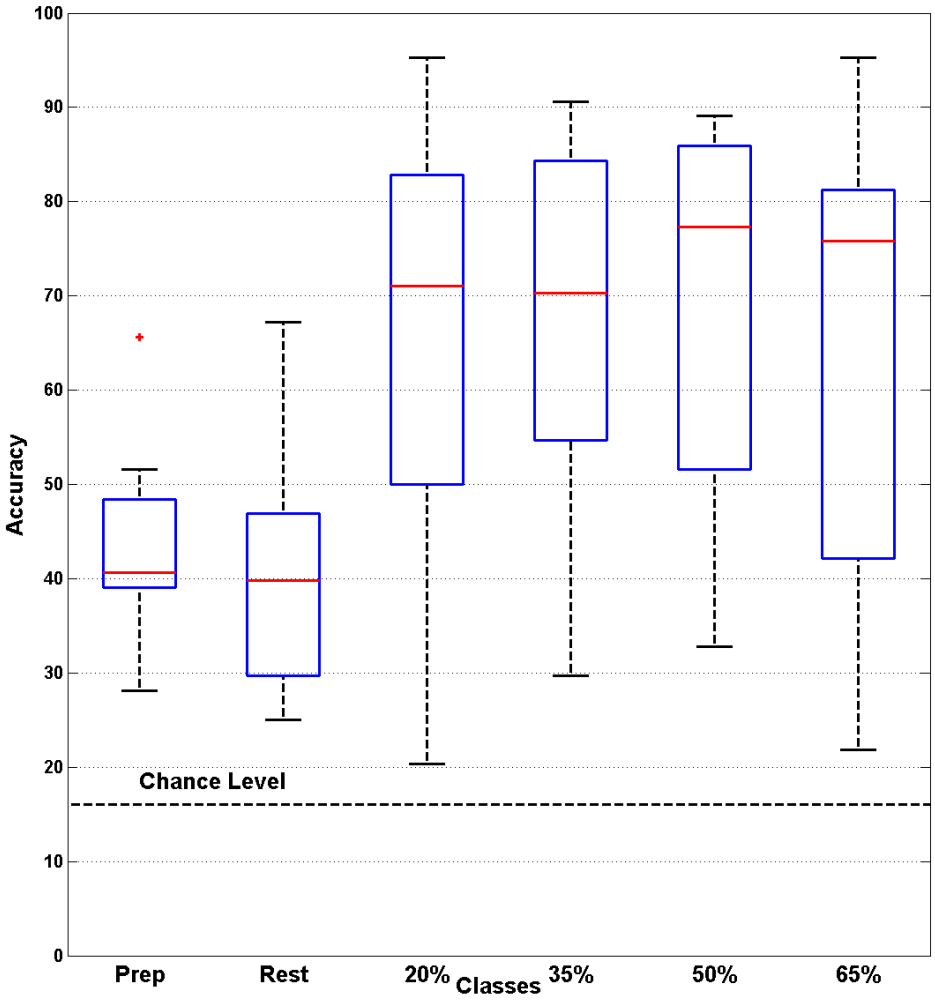
Support: and National Science Foundation Grant 1539068

Title: Neural correlates of graded movement for brain-computer interfaces

Authors: *C. HADDIX, A. AL-BAKRI, S. SUNDERAM;
Univ. of Kentucky, Lexington, KY

Abstract: Brain-computer interfaces (BCI) are often designed to detect and act on changes in brain signals, termed event-related potentials (ERP), associated with attempted or imagined movement for instance. The number of commands available for BCI operation is limited by the number of distinct mental tasks the user can perform (e.g. right hand, left hand, foot movement, etc.). As an alternative, we propose to predict and use, from the electroencephalogram (EEG), the degree of effort in a specific movement task to generate multiple command signals out of one. In an IRB-approved study, ten healthy subjects participated in a handgrip task in which they were required to control the force applied on a hand dynamometer to match a target value based on visual feedback provided by means of a digital display. Target forces were specified as a percentage of the subject's maximum voluntary contraction force (MVC) - 20%, 35%, 50%, 65% -- and used as a measure of their effort in the task. A neural network was trained to classify the EEG associated with these force targets and tested using 4-fold cross validation on each subject

individually. Preliminary results indicate that EEG features related to modulation of the sensorimotor rhythm (SMR) are separable for different degrees of effort. Pooled accuracies for the four classes, with a baseline resting condition and pre-movement preparation also considered as classes, ranged from 64-69%, well above the level expected from chance of 16%. The results of this study highlight the potential for expanding the degrees of freedom associated with simple control signals intended for use with a BCI. Further development of the effort prediction model, with dynamic feedback to the subject on their intended level of effort as predicted from the EEG, may find utility in rehabilitative protocols for those afflicted with neuromuscular impairments.



Disclosures: **C. Haddix:** None. **A. Al-Bakri:** None. **S. Sunderam:** None.

Poster

760. Brain-Computer Interface: Extracranial

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 760.02/L12

Topic: E.05. Brain-Machine Interface

Support: NIH Grant TL1TR002344
NIH Grant R21NS102696-01A1

Title: Resting state functional connectivity alterations associated with chronic stroke recovery via a brain-computer interface

Authors: *J. B. HUMPHRIES[1], A. SCOTT[2], M. OLUFAWO[2], K. Y. PARK[3], A. G. S. DANIEL[1], K. RYBCZYNSKI[2], T. NOTESTINE[2], A. R. CARTER[4], E. C. LEUTHARDT[2]; [1]Biomed. Engin., [2]Neurosurg., [3]Radiology, [4]Neurol., Washington Univ. in St. Louis, St. Louis, MO

Abstract: *Background:* Stroke is a leading cause of adult disability. Approximately 77% of stroke survivors experience a loss or reduction of upper extremity motor function known as hemiparesis, and 65% of hemiparetic stroke patients do not regain motor function 6 months after stroke. Recently, upper motor therapy for chronic stroke survivors with a brain-computer interface (BCI) controlled with motor cortical signals from the non-lesioned hemisphere was found to be effective for restoring motor function in the chronic stage of stroke. However, the effects of this therapy method on the function and organization of the brain are not yet well understood. *Methods:* To understand how the functional organization of the brain changes during chronic stroke recovery with a contralesional BCI, a cohort of chronic stroke patients underwent resting-state functional MRI (rs-fMRI) scans and motor function evaluations before and after receiving 12 weeks of contralesional BCI therapy at home. Patients were asked to perform a cued motor imagery task for an hour per day, 5 days per week by using an BCI hand orthosis controlled with noninvasive EEG signals. EEG signals were processed in real time. Motor imagery detection was translated into a command for motors to open the hand orthosis. Functional connectivity was calculated from rs-fMRI data by computing the pairwise correlations among regions of interest in preprocessed data. Preprocessing included image coregistration and alignment, normalization to atlas space, smoothing, and nuisance regression. *Results:* This study is still ongoing; however, preliminary analysis of rs-fMRI data has revealed interesting trends. The change in functional connectivity over the course of therapy was calculated for 3 patients, 2 of which achieved clinically significant recovery defined as an increase of greater than 6 points on the Upper Extremity portion of the Fugl-Meyer Assessment. Intra-region and interhemispheric functional connectivity of cortical somatomotor network (SMN) voxels increased in the patients who achieved clinically significant recovery and

decreased in the patient who did not. Examples of these cortical areas include Primary Motor and Sensory Cortex and Premotor Area. *Conclusions:* A longitudinal change in SMN connectivity corresponding to motor recovery may indicate a reorganization of motor-related function induced by contralesional BCI therapy. This result also informs the role of the contralesional hemisphere in stroke recovery by showing that bilateral motor function changes can benefit motor recovery in a chronic stroke population. We expect these results to become more robust as we recruit and analyze more patients.

Disclosures: **J.B. Humphries:** None. **A. Scott:** None. **M. Olufawo:** None. **K.Y. Park:** None. **A.G.S. Daniel:** None. **K. Rybczynski:** None. **T. Notestine:** None. **A.R. Carter:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Neurolutions, Inc. **E.C. Leuthardt:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Neurolutions, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neurolutions, Inc..

Poster

760. Brain-Computer Interface: Extracranial

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 760.03/L13

Topic: E.05. Brain-Machine Interface

Title: Bispectral feature extraction improves brain-computer interface performance

Authors: *D. SYED[1], C. K. KOVACH[2], P. E. GANDER[2], C. G. REDDY[3], B. F. SNOAD[2], M. A. HOWARD, III[2];
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Abstract: Brain-computer interfaces (BCIs) allow a computer to interpret and act on its user's intentions, without need of the peripheral nervous system. BCIs classify brain states by extracting relevant features from electrode data through the application of machine learning techniques. Time-varying signal power recovered by bandpass filtering within pre-selected frequency bands, or by more comprehensive time-frequency decompositions, often provide the input to such classifiers. But because the power spectrum discards phase information, these techniques are insensitive to properties of the signal related to spectral phase, such as any information encoded in cross-frequency interactions, notably phase-amplitude coupling. This information is preserved in so-called higher-order spectra, which are related to time-shift invariant higher moments (Nikias and Raghuveer 1987, Kovach et al. 2018). We have recently developed a novel approach to recovering information from higher-order spectra using an application of the bispectrum (Kovach et al. 2018, Kovach and Howard, preprint), in the form of

filters optimized for the detection of characteristic recurring features within a signal. Here, we investigated whether this bispectral approach to feature extraction could improve the performance of an electrocorticographic (ECoG) BCI. We trained a support vector machine classifier to discriminate two mental task conditions (in which a human subject was instructed to "imagine the tune of 'Jingle Bells'" or "imagine feeling very angry"), using both bandpass power in standard EEG frequency divisions and the output of bispectral feature extraction. The trained classifier was used offline to simulate driving a robot in real time. Our bispectral/bandpass classifier performed with higher accuracy than either technique alone. Additionally, the combined classifier performed comparably to band power alone using fewer channels. Our findings suggest that feature identification with higher-order spectra may improve ECoG BCI performance while minimizing implant size.

Disclosures: D. Syed: None. **C.K. Kovach:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Methods described in this work are the subject of U.S. Provisional Patent Application No: 62/695,586. **P.E. Gander:** None. **C.G. Reddy:** None. **B.F. Snoad:** None. **M.A. Howard:** None.

Poster

760. Brain-Computer Interface: Extracranial

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 760.04/L14

Topic: E.05. Brain-Machine Interface

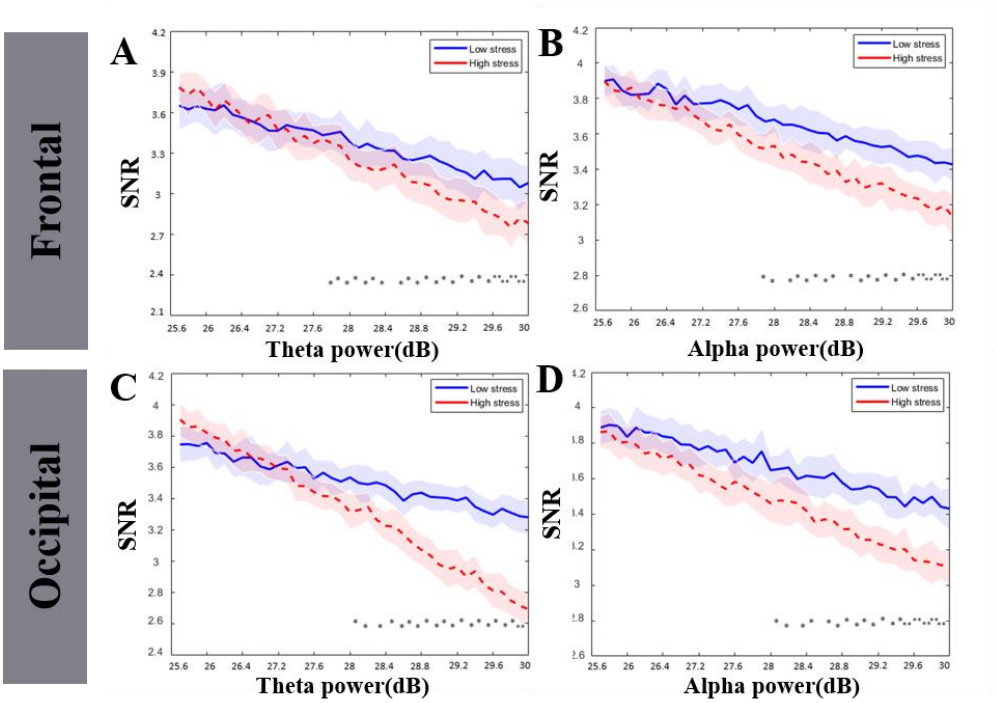
Support: MOST 107-2221-E-009 -150

Title: Resting and pre-stimulus EEG spectra predict SNR of EEG and BCI performance

Authors: *L.-W. KO[1], H.-Y. CHANG[1], T.-P. JUNG[2];
[1]Inst. of Bioinformatics and Systems Biol., Natl. Chiao Tung Univ., Hsinchu, Taiwan; [2]Swartz Ctr. for Computat. Neuroscience, Inst. for Neural Computation, Univ. of California San Diego, La Jolla, CA

Abstract: Most research in Brain-Computer-Interfaces (BCI) focuses on technologies to improve accuracy and speed. Little has been done on the effects of user state changes on BCI performance. For example, stress, arousal, motivation, and fatigue can all affect the EEG signals used by a BCI, which in turn impacts performance. To systematically explore the factors affecting BCI performance, this study embeds a Steady State Visually Evoked Potential (SSVEP) based BCI into a "game with a purpose" (GWAP) to obtain data over significant lengths of time under both high and low stress conditions. Ten healthy volunteers played a GWAP that resembles popular match-three games, such as Jewel game, Zoo, or Candy Crush. We recorded the target search time, target search accuracy, and EEG signals during gameplay to

investigate the impacts of stress on EEG signals and BCI performance. We used Canonical Correlation Analysis (CCA) to determine whether the subject had found and attended to the correct target.The experimental results show that SSVEP accuracy is reduced by stress. We also found a negative correlation between EEG spectra and the SNR of EEG in the frontal and occipital regions during gameplay, with a larger negative correlation for the high-stress conditions. Furthermore, CCA also showed that when the EEG alpha and theta power increased, the target search accuracy decreased, and the spectral amplitude drop was more evident under the high-stress situation. These results provide new, valuable insights into research on how to improve the robustness of BCIs in real-world applications.



Disclosures: **L. Ko:** None. **H. Chang:** None. **T. Jung:** None.

Poster

760. Brain-Computer Interface: Extracranial

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 760.05/L15

Topic: E.05. Brain-Machine Interface

Support: Wallace H. Coulter Center for Translational Research

Title: Development and application of mild therapeutic hypothermia to reduce cortical inflammation associated with Utah microelectrode array implantation in the rat

Authors: *E. A. DUGAN[1], I. TAMAMES[2], C. BENNETT[2], A. PRASAD[3], W. DIETRICH, III[5], S. RAJGURU[4];
[1]Biomed. Engin., [2]Univ. of Miami, Miami, FL; [3]Biomed. Engin., [4]Biomed. Engin. and Otolaryngology, Univ. of Miami, Coral Gables, FL; [5]Neurol Surgery, Univ. of Miami Sch. of Med., Miami, FL

Abstract: Neuroprosthetics hold tremendous promise to advance our understanding of the nervous system through basic research, and to restore lost sensory inputs and motor outputs through brain-computer interfaced (BCI) devices. Maintaining high quality neuronal signals for long periods of time are key challenges that must be thoroughly addressed to develop clinical applications for neuroprosthetics. Previous studies have shown that acute and chronic inflammation, oxidative stress, and BBB disruption are likely factors that contribute towards inconsistent chronic electrode performance. Methods to reduce the host response is essential to the development of clinically effective BCI devices and may be achieved with mild therapeutic hypothermia (mTH). The therapeutic benefits of mild hypothermia for some neurological conditions include a reduction in inflammatory processes and restoration of the blood brain barrier (BBB). To examine the benefits of mTH during electrode implantation, our laboratory has designed a custom device to deliver controlled mTH to the implant site without requiring any modifications to the current surgical approach. In vivo cortical temperature measurements were compared to theoretical 3D modeling to determine a cooling profile and protocol. Once developed, male Sprague-Dawley rats (250-300g; n=20) were implanted with custom-made, non-functional Utah Microelectrodes Array (UMEA) consisting of 4 x 4 grid of 1.5mm long parylene-coated silicon shanks. mTH was applied to the implant site (n=10) prior to surgical implantation. The temperature of the implant site was slowly lowered by 3-4 degrees (cooling phase: 10 mins), the UMEA was inserted, and cooling continued for 120 minutes (maintenance phase) followed by a slow rewarming phase (10 mins). We compared mRNA expression levels for genes associated with apoptosis, inflammation and the blood brain barrier (BBB) at 48 hours, 72 hours, 7 days and 14 days post implantation between normothermic and hypothermic groups. We show significant beneficial molecular responses to therapeutic hypothermia and demonstrates the efficacy of hypothermia in reducing inflammation and altering molecular activity that may benefit restoration of the functional properties of the BBB following UMEA implantation.

Disclosures: E.A. Dugan: None. **I. Tamames:** None. **C. Bennett:** None. **A. Prasad:** None. **W. Dietrich:** None. **S. Rajguru:** None.

Poster

760. Brain-Computer Interface: Extracranial

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 760.06/L16

Topic: E.05. Brain-Machine Interface

Title: Decoding of arm movements from electroencephalogram using convolutional neural network

Authors: *M. KATO, S. SHIMADA;
Meiji Univ., Kawasaki, Japan

Abstract: In the present study, we measured electroencephalogram (EEG) when an individual performed reaching movements with his right arm. We made a CNN model that can decode four directions of reaching motion of the right arm from EEG data. Two healthy right-handed male subjects (aged 23) with written informed consent took part in this study. The trials of experiment were conducted by operating the avatar's right arm displayed on the screen using a joystick. Trials began by placing the avatar arm on the base position, which was shown as a 12×12 cm^2 square located at the center of the screen. The avatar arm had to keep inside of a base position for a random interval of 0.4 to 1 s. After this hold, a target appeared on the screen. The target was a circle with a diameter of 12 cm appeared at the distance of 20 cm either front, back, left, or right of the base position. When the avatar arm reached to the target and 1 s passed, the base position re-appeared. The experiment consisted of 2 sessions. The session included 8 blocks and one block included 150 trials. EEG signals were sampled at 1200 Hz from 60 channels. EEG data from 0.5 s before the target onset to 3.25 s (3.2 s for Subject2) after the onset was defined as a trial. Each trial was classified into 4 classes (front, back, left, right). The input data was created by extracting the EEG data with a time window of 2 s and a slide width of 0.04 s in each trial. The input data was divided into training data, validation data, and test data at 8: 1: 1. We constructed a CNN model to classify arm movements from EEG with four convolutional layers and one softmax classification layer. The result showed that the CNN model can classify the four types of movements of the right arm with accuracy of 78% (front: 77%, back: 54%, left: 90%, right: 90%) for Subject1 and 57% (front: 85%, back: 38%, left: 60%, right: 44%) for Subject2. The classification accuracy of Subject 2 was lower than Subject 1, mainly due to measurement noise. Also, the accuracy of the back was the lowest for both subjects, though still higher than the chance level, possibly because the movement to pull back the arm is rather small. The result demonstrated that the CNN model is possible to classify four types of movements of the right arm from EEG data.

Disclosures: M. Kato: None. **S. Shimada:** None.

Poster

760. Brain-Computer Interface: Extracranial

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 760.07/L17

Topic: E.05. Brain-Machine Interface

Support: Chuck Noll Foundation

Title: Novel electrodes for reliable EEG recordings on coarse and curly hair

Authors: *A. ETIENNE[1], H. WEIGLE[1], T. LAROIA[1], A. AFELIN[2], A. KRISHNAN[1], S. KELLY[1], P. GROVER[1];
[1]Carnegie Mellon Univ., Pittsburgh, PA; [2]Wesleyan Univ., Middletown, CT

Abstract: EEG is a powerful and affordable brain imaging tool used for the diagnosis of neurological disorders (e.g. epilepsy), brain computer interfacing, and understanding how the brain functions. Unfortunately, existing EEG electrodes and systems are not designed to accommodate a large fraction of the population. Specifically, existing EEG systems work best with individuals with short, straight hair. That leaves most of the population (including a large fraction of women) at a disadvantage, and leaves a smaller subset of people (those with long and curly or kinky hair) with an experience that can range from uncomfortable to emotionally taxing, and in the worst case, still does not yield high-quality measurements. Bringing human-centered design to EEG, we design EEG recording systems, "goEEG systems," including hair preparation and electrodes, specifically aimed at accommodating coarse and curly hair.

The study applied our goEEG system to individuals with coarse and curly hair, comparing the results with classical approaches used in the field. We performed experiments for quantifying advantages of our electrodes over classical ones with braided hair, as well as classical electrodes on unbraided hair. On the left side of the head, we cornrowed hair according to the 10-20 system. Next, we placed two industry standard gold cup electrodes and two of our electrodes on the braided side. We repeated the placement on the right hemisphere where the hair was left free and not cornrowed. The proposed electrodes, in conjunction with our recently proposed EEG-compatible braiding techniques [Etienne et al., EBMC'17], were observed to have an order of magnitude lower impedance than conventional systems.

Our novel electrodes and braiding goEEG solution provides a lower impedance than traditional systems used clinically and neuroscientifically for EEG recordings. Lower impedance not only provides higher SNR recordings, it also implies improved electrodes-skin contact. Thus, it is likely that goEEG electrodes will offer longer term recordings because they will maintain contact longer.

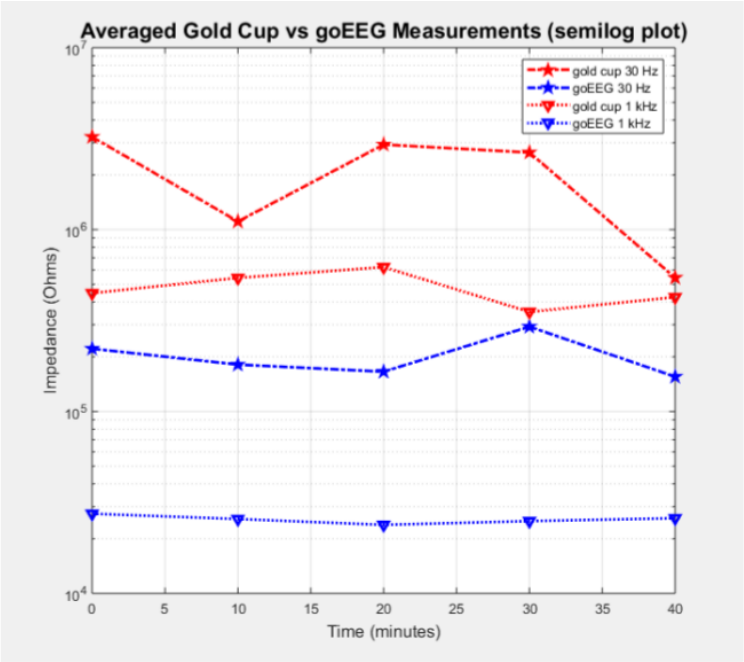


Figure 1: Shown above are the average measured impedances over time of the Gold Cup (industry standard) electrodes and the goEEG electrodes, depicted at both 30 Hz and 1 kHz, with the y axis on a logarithmic scale. We can see that the impedances for the goEEG electrodes are, on average, an order of magnitude lower than the Gold Cup electrodes for each respective frequency.

Disclosures: **A. Etienne:** None. **H. Weigle:** None. **T. Laroia:** None. **A. Afelin:** None. **A. Krishnan:** None. **S. Kelly:** None. **P. Grover:** None.

Poster

760. Brain-Computer Interface: Extracranial

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 760.08/L18

Topic: E.05. Brain-Machine Interface

Title: Effects of training on electroencephalogram about motor imaginary tasks pertaining to the lower limbs

Authors: ***M. S. SHIBATA**[1], K. HOSHINO[1], A. ISHIYAMA[1], Y. ONO[2];
[1]Electrical Engin. and Biosci., Waseda Univ., Tokyo, Japan; [2]Meiji Univ., Kanagawa, Japan

Abstract: We measured electroencephalography (EEG) activity related to motor imaginary of the lower limbs. The purpose of this study is to confirm if training strengthens event-related

desynchronization (ERD) or event-related synchronization (ERS) in motor area for the lower limbs. Four healthy young adult (all men) participated in the study. First, the participants performed the motor imaginary tasks pertaining bending movements of both knees for two seconds before training while their EEG responses were measured. After that, the participants were trained. In the training, the participants watched the video of the person moving the leg in the first-person view and performed the motor imaginary as directed by the video. The training was conducted three times on different days, and the motor imagery EEG was measured after the training. Also, the participants actually bend both knees and their EEG responses were measured at this time. The experiment is conducted to compare the EEG when they actually move the legs with the EEG that appeared by training of motor imaginary of both knees bending. The EEG of pre-training and that of post-training were compared. The electrical signals were acquired from the Cz electrodes according to the International 10-20 system which corresponds to the motor field of the legs. Blink-related artifacts were removed and the power spectrum intensity was calculated by time-frequency analysis. Spectrum powers for the alpha wave band (7 - 14 [Hz]) and the beta wave band (15-30 [Hz]) were determined. Training-related change in alpha wave region showed two different tendencies of enhanced ERD or ERS. That in beta wave region showed no remarkable change in ERD and ERS. The power spectrum intensity of both of the EEG frequency was examined in the same manner as before. The participant who could enhance ERD approximately by 50% by training showed ERD approximately 50% during actually moving. Similarly, those who could enhance ERS showed ERS during actually moving. These results suggest that motor imagery training could strengthen motor-related activity and there is the possibility that the motor imagery EEG after training and the actually moving EEG are similar.

Disclosures: **M.S. Shibata:** None. **K. Hoshino:** None. **A. Ishiyama:** None. **Y. Ono:** None.

Poster

760. Brain-Computer Interface: Extracranial

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 760.09/L19

Topic: E.05. Brain-Machine Interface

Support: CHART

Title: A computational model and brain-computer interface technology that uses virtual reality to measure anxiety induced disruption to motor function in biological systems

Authors: *R. MEACHAM, M. E. HERNANDEZ, S. M. LAVALLE, R. B. SOWERS, A. YERSHOVA;
Univ. of Illinois Urbana-Champaign, Urbana-Champaign, IL

Abstract: We propose a new approach that unites both machine learning and experimental methods to measure and predict cognitive states such as anxiety, based on physiological signals and computer vision, with regard to biological systems at the neuronal level. Our study examines the effect of virtual reality scenes with differing levels of anxiety-inducing stimuli to persons with or without a fear of falling. The experiments used the HTC Vive to show subjects custom-built animated virtual reality (VR) simulations of a local neighborhood park using Unity. Different versions of the VR simulation were generated, each with a varying level of anxiety-inducing stimuli, in order to show the walking paths with high, low, and moderate levels of risk for falling. EEG, EOG, and heart rate were measured as subjects participated in these virtual experiences. Using a machine learning model for emotional expressions, we also measured emotional engagement with specific anxiety inducing segments of the stimuli. Our results suggest that frontal alpha and beta frequencies may provide salient neural features for detection of anxiety, in high versus low anxiety trials. There are no noticeable desynchronous characteristics in these datasets, however this may simply be due to the limited sample size or differences in stimuli between VR conditions. The results from our preliminary research suggest promise for VR and brain-computer interface technology as a promising rehabilitation tool and behavioral training technique. VR provides the sensation of presence in an imaginary world, which opens up the possibility of rehabilitation from anxiety disorders such as fear of falling, fear of flying, and post-traumatic stress disorder. Given prior findings that suggest that individuals who have high emotional engagement (high anxiety) at the beginning of exposure and gradual habituation (decrease in anxiety) have the most successful recoveries, future work will examine individual changes in anxiety during the exposure to anxiety-inducing VR simulations.

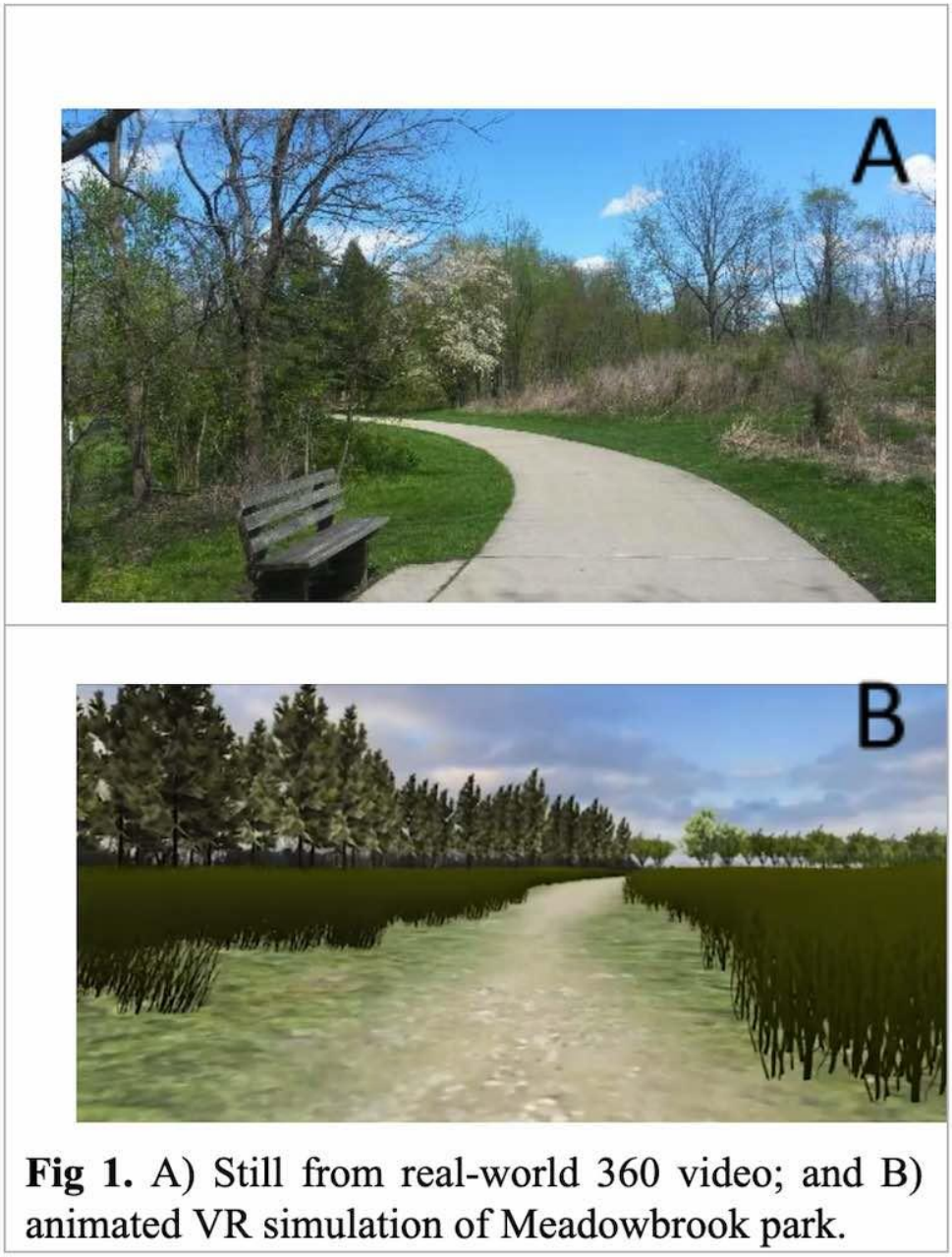


Fig 1. A) Still from real-world 360 video; and B) animated VR simulation of Meadowbrook park.

Disclosures: R. Meacham: None. **M.E. Hernandez:** None. **S.M. LaValle:** None. **R.B. Sowers:** None. **A. Yershova:** None.

Poster

760. Brain-Computer Interface: Extracranial

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 760.10/L20

Topic: E.05. Brain-Machine Interface

Support: ICT R&D program of MSIP/IITP (2017-0-01724)

Title: Electrocortical activity while standing, walking, and recovery after unpredictable trip perturbations

Authors: *J. AN, D. YOO, B.-C. LEE;
Univ. of Houston, Houston, TX

Abstract: Although the balance-recovery reactions from unexpected gait perturbations (e.g., trips and slips) are relatively well-understood in musculoskeletal and biomechanical perspectives, little is known about how the brain's electrophysiological activities are dynamically changed during balance recovery after unpredictable gait perturbations. In this study, 128-channel non-invasive electroencephalography (EEG) signals were collected from healthy young adults during quiet standing, normal walking, and recovery following trip perturbations induced by a programmable split-belt treadmill. The programmable split-belt treadmill produced an unpredictable trip perturbation by quickly stopping the treadmill's left belt. The stopped left belt returned to the pre-perturbation walking speed after the first heel strike of the compensatory limb (i.e., non-tripped limb). We analyzed electrocortical activity during three different periods (i.e., standing, walking, and recovery following the trip perturbation). Power spectral analysis was computed using Welch's method from two different clusters of electrodes in the primary sensorimotor cortex (SMC) and posterior parietal cortex (PPC). The results showed that alpha (8-13 Hz) spectral power was significantly decreased during the recovery period compared to the walking and standing periods in both SMC and PPC. These findings may inform improvements of gait perturbation paradigms intended for fall reduction and prevention.

Disclosures: J. An: None. **D. Yoo:** None. **B. Lee:** None.

Poster

760. Brain-Computer Interface: Extracranial

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 760.11/DP10/L21

ControlExtraData.DynamicPosterDisplay:
Dynamic Poster

Topic: E.05. Brain-Machine Interface

Support: DFG BI 195/77-1
BMBF 16SV7701 CoMiCon
LUMINOUS-H2020-FETOPEN-2014-2015-RIA (686764)
Wyss Center for Bio and Neuroengineering, Geneva

Title: Brain computer interface based communication for individuals in locked-in state without gaze fixation

Authors: *A. TONIN[1], A. JARAMILLO-GONZALEZ[1], A. RANA[1], M. KHALILI ARDALI[1], N. BIRBAUMER[2,1], U. CHAUDHARY[1,2];
[1]Univ. of Tübingen, Tübingen, Germany; [2]Wyss Ctr. for Bio and Neuroengineering, Geneve, Switzerland

Abstract: Several neuronal disorders, such as amyotrophic lateral sclerosis (ALS), severely impairs the communication capacity of an individual. Commercial eye tracker-based communication devices along with several other brain computer interfaces (BCIs) have been developed to provide a means of communication to individuals in locked-in state (LIS), i.e., individuals who can reliably move their eyes and fixate their gaze. Once the individuals lose the gaze fixation ability none of the available devices function. Therefore, patients who can still open and close their eyes albeit with difficulties but cannot fixate their gaze and without intact eye movement control are left without any means of communication. To provide such individuals with a means of communication an electroencephalogram (EEG)- and electrooculogram (EOG)-based auditory BCI communication system was developed, which enabled such individuals to auditorily form sentences.
The BCI communication system is based on a binary yes/no classification that allows individuals to select letter. This study was performed with four individuals with ALS in transition from the locked-in state to completely locked-in state but unable to use eye trackers for communication. The signal was recorded using both EEG and EOG electrodes and the individuals were asked to auditorily select or discard a word, a letter or a group of letters by thinking yes/no and moving or not-moving their eyes.
The developed system has been tested in total 45 times and all the four individuals successfully performed at least one copy spelling session, selecting a test sentence, and one free spelling session, freely selecting a sentence. The speller worked with an information transfer rate of 5.664±0.25 bits/min and attained a typing speed of 0.551±0.049 char/min. The signal analyses show that the developed system can even work using only two EOG electrodes, which needs to be tested by performing more BCI sessions with these individuals.
The developed auditory speller system has the potential to provide a means of communication to individuals without gaze fixation ability and with invisible but miniature eye-movements. The complete auditory implementation implies a slow typing speed but assure the usability of the system by patients with non-intact sight.

Disclosures: **A. Tonin:** None. **A. Jaramillo-Gonzalez:** None. **A. Rana:** None. **M. Khalili Ardali:** None. **N. Birbaumer:** None. **U. Chaudhary:** None.

Poster

760. Brain-Computer Interface: Extracranial

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 760.12/L22

Topic: E.05. Brain-Machine Interface

Title: Differences in event related desynchronization of mu rhythms between three types of motor imagery during action observation of leg movement

Authors: *K. HOSHINO[1], M. SHIBATA[1], A. ISHIYAMA[1], Y. ONO[2];
[1]Electrical engineering and Biosci., Waseda Univ., Tokyo, Japan; [2]Meiji Univ., Kanagawa, Japan

Abstract: Brain-machine interface based on Electroencephalography (EEG-BMI) can be used to recover motor function by re-establishing motor pathway, and this method has been increasingly applied to the rehabilitation of stroke patients in recent years. However, the analysis of EEG for legs movements is less advanced than it is for hands, making it more difficult to apply to rehabilitation at present. In this study, we analyzed event-related desynchronization (ERD) of mu rhythms in EEG of motor imagery during action observation of three types of lower limb movement, with the aim of suggesting an effective rehabilitation system. Six healthy men participated in the study, which comprised two experiments: (1) motor imagery of foot movement (MI experiment), and (2) motor imagery during action observation of three types of foot movements (MI-AO experiment). During both experiments, all participants were seated in front of a computer screen with their legs stretched out, parallel to the floor, on footrests. In the MI experiment, they were instructed to perform motor imagery of both knees bending for two seconds according to a cue presented on the screen, for 10 times. In the MI-AO experiment, they were asked to perform motor imagery of both knees, the right knee, and the left knee while watching a leg-action video on the screen, with 20 trials performed for each of the types of movement. ERD power and occurrence rate were evaluated in both experiments. The MI-AO experiment shows that the ERD power was significantly increased for the MI-AO of both legs compared to the right and the left individually. There was no significant difference in the occurrence rate of ERD between the three types of leg movement with the rate being approximately 50% in all cases. No differences in the power and occurrence rate of ERD were observed between MI and MI-AO. These results suggest that movement of both legs is desirable for patients with difficulty in detecting ERD power when they start their motor imagery training. There was no difference in ERD power and occurrence between MI and MI-AO, suggesting that observation of movements that are unfamiliar to the participants might not contribute to enhance ERD strength. Therefore, visual and proprioceptive neurofeedback on top of MI or MI-AO might be better rehabilitation method.

Disclosures: **K. Hoshino:** None. **M. Shibata:** None. **A. Ishiyama:** None. **Y. Ono:** None.

Poster

760. Brain-Computer Interface: Extracranial

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 760.13/L23

Topic: E.05. Brain-Machine Interface

Support: NIH BRAIN Grant U01NS099724
T&C Chen Brain-machine Interface Center at Caltech
The Boswell Foundation

Title: Decoding movement intentions from posterior parietal cortex using functional ultrasound neuroimaging

Authors: *S. L. NORMAN[1], V. N. CHRISTOPOULOS[1], D. MARESCA[1], C. DEMENÉ[2], T. DEFFIEUX[3], M. TANTER[4], M. G. SHAPIRO[1], R. A. ANDERSEN[5];
[1]Caltech, Pasadena, CA; [2]CNRS UMR 7587, INSERM U979, ESPCI Paris, PSL Res. Univ., Inst. Langevin, Paris, France; [3]Physmed / Inserm U1273, Paris, France; [4]INSERM, Paris, France; [5]BBE, Calif Inst. of Technol., Pasadena, CA

Abstract: Advanced neural interfaces have the potential to impact neuroscience from bench to bedside. Recently, functional ultrasound (fUS) was introduced as a revolutionary hemodynamic imaging technique with excellent spatiotemporal resolution (e.g. 100 μm,10 ms), field of view (e.g. 15mm) and sensitivity [Mace et al, Nature Methods, 2011]. In addition, it is portable and potentially noninvasive. As a result, fUS is rapidly gaining popularity in neuroscience methodology for its ability to record high-quality neurovascular function in awake, behaving animals. Brain-machine interfaces (BMIs) are devices that use neurophysiological signals from the brain to control external devices. In addition to their clinical applications, BMIs are powerful tools for investigating brain function [Zhang et al., Neuron, 2017]. Here, we utilize fUS as a recording technique in an offline brain-machine interface (BMI) paradigm to investigate movement intention in the posterior parietal cortex of a non-human primate (NHP).Specifically, we trained the NHP to perform memory-guided saccades and reaches (acquired via joystick) to targets presented in left or right visual fields. During the task, we acquired fUS images at 1 Hz over the intraparietal sulcus (IPS) to capture the lateral intraparietal area (LIP) - an area associated with planning eye movements - and the parietal reach region (PRR) - an area associated with planning reaching movements. Using hemodynamic fUS signal during movement planning, we classified left-cued vs. right-cued eye and hand movements. Cross-validated decode accuracies ranged from 61.5% (binomial test vs. chance level, $p=0.012$) to 100% ($p<0.001$) on a given day (average across days: 80%, $p<0.001$).Finally, we leveraged the BMI decoders to elucidate spatiotemporal patterns of information content and propagation through posterior parietal brain regions. Specifically, we found highly localized patches of

activity tuned to contralateral movement intention in LIP, VIP, and PRR. We also identified patches of activity in medial parietal area (PM), located within PGm, consistent with electrophysiological (Thier et al., Journal of Neurophysiology, 1998) and histological (Passarelli et al., Cerebral Cortex, 2018) findings, but not previously reported in studies using noninvasive techniques such as MRI.These findings suggest that 1) fUS is capable of decoding single-trial movement intention and is therefore a viable neural interface for online BMI control, and 2) multiple brain areas within PPC, previously only detectable by more invasive methods, play critical roles in planning eye and hand movements.

Disclosures: S.L. Norman: None. **V.N. Christopoulos:** None. **D. Maresca:** None. **C. Demené:** None. **T. Deffieux:** None. **M. Tanter:** None. **M.G. Shapiro:** None. **R.A. Andersen:** None.

Poster

760. Brain-Computer Interface: Extracranial

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 760.14/L24

Topic: E.05. Brain-Machine Interface

Support: Funding for this work was provided by Ball Aerospace under contract to the U.S. Air Force.

Title: Longitudinal observation of event-related potentials commonly used in brain-computer interfaces

Authors: *J. R. ESTEPP[1,3], A. M. PIASECKI[4], K. E. ALEXANDER[1], C. L. WINTERMUTE[1], S. M. ELBASIOUNY[2,1];
[1]Dept. of Biomedical, Industrial, and Human Factors Engin., [2]Dept. of Neuroscience, Cell Biology, and Physiol., Wright State Univ., Dayton, OH; [3]US Air Force Res. Lab., Wright-Patterson AFB, OH; [4]Ball Aerospace, Fairborn, OH

Abstract: Electroencephalography (EEG) data are often referred to as being non-stationary, but it is rarely ever the case that this non-stationarity is explicitly defined, and its effect in use cases such as brain-computer interfaces (BCIs) is not well understood. BCIs often make use of the brain's phase-locked response to stimuli, as measured by EEG, as an alternate control pathway to infer and actuate motor intent when the primary motor pathway is unavailable. These so-called event-related potentials (ERPs) can be decoded in either single- or multiple-trial (e.g., averaged) paradigms such that a specific selection in a fixed-choice problem can be decoded from the cortical response. While there are many examples of test-retest reliability of ERPs in literature, it is also often reported that these decoders need to be retrained to the fixed-choice problem due to an observed decay in performance, which has sometimes been attributed to the non-stationarity

effect in EEG without direct evidence. There seems to be dissonance between these two findings; if the ERPs can be reliably evoked, then why do the decoders ever need to be retrained? The goal of this work is to observe test-retest reliability of common ERPs used in BCIs in a longitudinal study consisting of weekly sessions spanning approximately 3 months' time. To achieve this, dense-array EEG was recorded from participants while they observed open-loop versions of common ERP-inducing stimuli (both active and reactive) in a within-subjects, repeated measures design. The hypothesis is that that other factors affecting single-trial response data that are not observable in average ERPs over a large number of trials must be affecting the generalization of the decoder, thereby unifying test-retest reliability of ERPs and decoder instability claims. Regarding non-stationary, this hypothesis can be restated by saying that the ERP itself is parametrically stationary, whereas other processes influencing the recorded voltage waveform are driving non-stationarity in the single-trial response. While these factors could be numerous and difficult to control for in well-designed experiments, it is expected that an initial observation of high test-retest reliability for the average ERP is important knowledge with which to begin to realize the possibility of decoder generalization. These findings will significantly contribute to our understanding of the dynamics of the cortical signals being mapped by these decoders and allow for decoder training and validation strategies to be developed from these data in future work.

Disclosures: **J.R. Estepp:** None. **A.M. Piasecki:** None. **K.E. Alexander:** None. **C.L. Wintermute:** None. **S.M. Elbasiouny:** None.

Poster

760. Brain-Computer Interface: Extracranial

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 760.15/L25

Topic: E.05. Brain-Machine Interface

Support: EPSRC CDT HiPEDS EP/L016796/1
EPSRC capital equipment support grant

Title: Deep learning time-resolves fNIRS cortical activation asymmetries during a force tracking task evoking non-stationary haemodynamic responses

Authors: *P. ORTEGA, A. FAISAL;
Computing, Imperial Col., London, United Kingdom

Abstract: Functional near-infrared spectroscopy (fNIRS) is a wearable, non-invasive brain imaging technique that offers a new window for the brain's motor control study in less constrained environments. However, the slow dynamics of the hemodynamic response (HR) and the interference of pulse, breathing and sensor movement artifacts limit our ability to time-

resolve cortical activation differences for different motor behaviors. While standard methods require simplifying assumptions on the HR model and systemic noise interference that do not hold for all experimental conditions, we address the cortical response decoding problem from a data-driven perspective. We propose a convolutional neural network architecture, hemCNN, that learns easy-to-interpret filters in three fNIRS dimensions: oxy/deoxy-hemoglobin, channel and hemisphere. Our architecture is trained to classify fNIRS signals as belonging to left or right-hand use during a 1 Hz paced hand-grip force-tracking task performed by 12 people. Our method resolves per-trial and intra-stimuli hemispheric differences in time under non-stationary conditions for both hands. All tests are conducted in unseen subjects confirming the inter-subject stability of the models. Additionally, recorded systemic signals (breath and pulse) are discarded as sources of information for the classification task, further supporting the functionality of the features. In the oxy/deoxy-hemoglobin dimension, the convolutional filters learn features mostly related to oxy/deoxy-hemoglobin over-crossing points. In the channel and hemisphere dimensions, the convolutional filters reveal an early contralateral activation followed by an ipsilateral activation around central channels. Our approach reduces some unrealistic strong assumptions on the nature of the signal and extracts more suitable features based on the raw data, enabling new findings that support previous evidence from similar but less dynamic tasks that could not be resolved using standard methods. The absence of baseline correction and the invariance of the convolution operation to time translations of our method could help to unlock fNIRS for a variety of real-time and continuous fNIRS streaming tasks with applications from mobile brain imaging to brain-machine interfacing.

Disclosures: P. Ortega: None. **A. Faisal:** None.

Poster

760. Brain-Computer Interface: Extracranial

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 760.16/L26

Topic: E.05. Brain-Machine Interface

Support: AMED Grant 18dk0310062j0003
AMED Grant 19dk0310096j0001

Title: A web-based BCI application with interactive customizing tool for severe paralysis patients and their caregivers

Authors: *T. KOMATSU, K. TAKANO, K. NAKAMURA;
Systems Neurosci. Section, Dept. of Rehabil. for Brain Functions, Res. Inst. of Natl. Rehabil. Ctr. for Persons with Disabilities, Tokorozawa, Saitama, Japan

Abstract: We have developed the efficacious brain-computer interface (BCI) system for late-stage amyotrophic lateral sclerosis (ALS) patients including completely locked-in state. The system recorded steady-state visual evoked potentials (SSVEPs) induced by flickering green/blue LEDs using non-invasive solid-gel electrodes. To downsize this, we introduce a web-application approach to the BCI system. This has similar advantages to the traditional modularly configured BCI platform connected by TCP/UDP, except that its GUI is rendered by WebGL on the modern browser rather than the native application. The BCI application server constantly pushes EEG or its classified signals to the browser through WebSocket. Though the original system has kept applicative accuracy for over 27 months, we had to learn a lot through the operation. The optimal content and resolution for the user (ALS patient) and operator (nurse, occupational therapist, home-care worker, etc.) GUIs differed in most cases. Also, the researcher wanted to observe the raw or processed EEG. If a BCI-GUI is provided as a web application, they can use the terminal, even though their personal iOS/Android tablet, without having to install any GUI processes. So our BCI web server provides different URIs to render GUIs for users, operators, researchers and developers. Severe paralysis users were able to call the on-screen functional icons, or large buttons, corresponding to each of the green/blue flickering LEDs as a Yes/No communication board or a remote control switch to kick something APIs. In a progressive paralysis, the number of LEDs that effectively induced SSVEPs tended to decrease with paralysis progresses. For practical use, it is necessary to customize the function and number of LEDs and their state transitions, such as a simple loop or a hierarchical tree structure, in the field. The BCI web server also provides URIs for GUI edit tools that allow general caregivers to resolve these problems as easily as drag and drop. To update and downsize our efficacious SSVEP-based BCI system for late-stage ALS patients, we replace its native GUI application with the web application using WebSocket and WebGL. Severe paralysis users are able to control this with the same input accuracy as the original. Caregivers operate and customize the BCI-GUI for daily communication and kicking environmental APIs well. This source code and architecture will release under a suitable open-license.

Disclosures: **T. Komatsu:** None. **K. Takano:** None. **K. Nakamura:** None.

Poster

760. Brain-Computer Interface: Extracranial

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 760.17/L27

Topic: E.05. Brain-Machine Interface

Support: Wyss center for Bio and neuro engineering, Geneva, Switzerland

Title: Sleep in the completely locked-in state (CLIS)

Authors: *U. CHAUDHARY[1,2], A. MALEKSHAHI[3], A.-J. GONZALEZ[3], A. TONIN[1], A. RANA[4], N. BIRBAUMER[1,2];
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Abstract: Persons in the completely locked in state (CLIS) suffering from amyotrophic lateral sclerosis (ALS) are deprived of many Zeitgebers of the circadian rhythm: While cognitively intact, they are completely paralyzed, eyes mostly closed, with artificial ventilation and artificial nutrition, and social communication extremely restricted or absent. Polysomnographic recordings in 8 patients in CLIS however revealed the presence of regular episodes of deep sleep during night time in all patients. It was also possible to distinguish an alpha-like state and a wake-like state. Classification of REM sleep is difficult because of absent eye movements and absent muscular activity. 4 out of 8 patients did not show any sleep spindles. Those who have spindles also show K-complexes and thus regular phases of sleep stage 2. Thus, despite some irregularities we found a surprisingly healthy sleep pattern in these patients concordant with positive quality of life reports.

Disclosures: U. Chaudhary: None. **A. Malekshahi:** None. **A. Gonzalez:** None. **A. Tonin:** None. **A. Rana:** None. **N. Birbaumer:** None.

Poster

760. Brain-Computer Interface: Extracranial

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 760.18/L28

Topic: E.05. Brain-Machine Interface

Support: Chuck Noll Foundation for Brain Injury Research

Title: Hydrophilic conductive sponge electrodes for EEG monitoring

Authors: *A. KRISHNAN, K. ROZYLOWICZ, H. WEIGLE, S. K. KELLY, P. GROVER; Carnegie Mellon Univ., Pittsburgh, PA

Abstract: Objective and Rationale: Despite being almost 100 years old and being widely used clinically, there are several limitations in today's EEG technology, including: (i) a large setup time, about 45 minutes per patient for 16-32 electrodes; (ii) drying of gels which increases electrode-skin impedance, lowering quality of recordings; (iii) sticky gels and electrodes that do not sit well with hair on the scalp. These issues are addressed in this work, where we have developed a novel hydrophilic conductive sponge-based electrode. Current clinical techniques

use a gold cup that holds an electrolytic gel against the scalp to create a low-impedance electrode. A key factor that makes a low impedance bio-signal sensor is the ionic interface between the metal connector and the skin. Sponge electrodes are useful in this regard, and those have been used in neuroscience experiments thus far are non-conductive, and are ineffective when they dry. Clinical settings require long periods of monitoring. Our earlier work [Krishnan et al., EMBC'17] considered the use of conductive polymer materials made of biocompatible polydimethylsiloxane (PDMS), however, these polymers are hydrophobic and do not support an ionic medium for an extended amount of time. To ensure easy application and retention of saline solution in the electrode-interface, we developed a methodology to use a hydrophilic polymer material to create a conductive sponge that ensures that the electrode remains conductive even as it is drying, providing a graceful degradation of impedance which can be rehydrated when required.
Methods and Results: Our conductive sponge material was developed by using a commercial pre-polymer compound of diisocyanate and a polyol. A surfactant was added to allow for water absorption and carbon nanofibers were used for conductivity. On mixing the pre-polymer with water, the curing process results in a foam due to the generation of carbon dioxide. Once cured, the samples were tested for impedance and hydrophilicity. Dry electrode impedance was under 30kΩ (@1kHz) with the time for water absorption at about 20 seconds. On the other hand, damp electrode impedances were under 10kΩ and showed instantaneous water absorption. Usability of the electrodes was tested by performing EEG experiments on humans and we were able to observe alpha wave activity in the brain.
Conclusion: Our hydrophilic conductive sponges provide a low-cost, low-impedance and fast-installation solution for EEG recordings. Additionally, they are non-magnetic and can be used in conjunction with MRIs enabling measurement of brain activity at a high spatial as well as high temporal resolution.

Disclosures: A. Krishnan: None. **K. Rozylowicz:** None. **H. Weigle:** None. **S.K. Kelly:** None. **P. Grover:** None.

Poster

760. Brain-Computer Interface: Extracranial

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 760.19/L29

Topic: E.05. Brain-Machine Interface

Support: NIH R21HD054697
NIDRR H133G090005
NSF DGE0718128

Title: Evidence of latency variation in the P3 speller brain computer interface

Authors: *D. E. THOMPSON[1], M. MOWLA[1], J. E. HUGGINS[2];
[1]Electrical and Computer Engin., Kansas State Univ., Manhattan, KS; [2]Physical Med. and Rehabilitation; Biomed. Engin., Univ. of Michigan, Ann Arbor, MI

Abstract: The P3 event-related potential is a notoriously variable brain response, yet it has been used successfully for brain-computer interfaces (BCIs) for over thirty years. Our prior investigations [1] indicated a possible causative link between P3 latency jitter and poor BCI performance. That relationship has been investigated by other groups, e.g. [2]. However, some have argued [3] that latency jitter in people with amyotrophic lateral sclerosis (ALS) has yet to be demonstrated.

We approached this question through an offline analysis of an existing dataset of 40 people operating a BCI, 25 men (age: 45±21 years, mean±std.) and 15 women (age: 42±20 years). Of these, 12 had ALS and 6 had muscular dystrophy. We used the first visit by each person, with N>=69 characters.

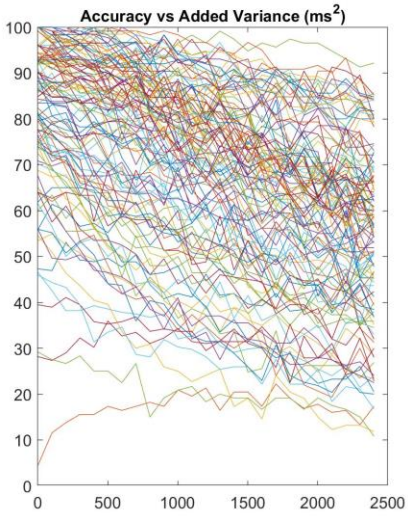
We added normally-distributed latency jitter to the brain responses. Our method [1] gave an estimate for the endogenous latency. We compared two models for BCI performance, one based on added jitter and one based on the sum of added and endogenous jitter.

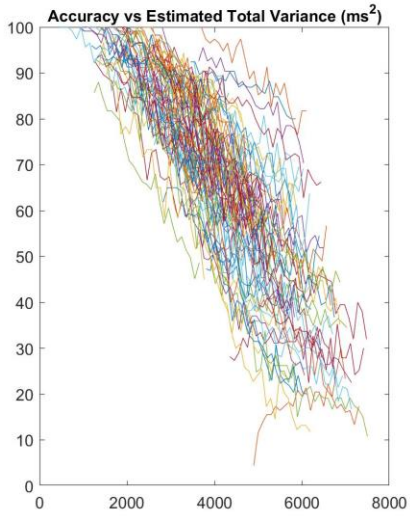
As seen in the figure, total estimated jitter has a clear relationship between jitter and performance. Further, the slope from the artificial jitter is nearly equivalent to the slope calculated from between-sentence comparisons of endogenous latency jitter. Taken together, these two pieces of evidence support the claim that our method is measuring endogenous latency jitter.

[1] D. E. Thompson, S. Warschausky, and J. E. Huggins, “Classifier-based latency estimation: a novel way to estimate and predict BCI accuracy,” *J. Neural Eng.*, vol. 10, no. 1, p. 016006, Feb. 2013.

[2] P. Aricò, F. Aloise, F. Schettini, S. Salinari, D. Mattia, and F. Cincotti, “Influence of P300 latency jitter on event related potential-based brain-computer interface performance,” *J. Neural Eng.*, vol. 11, no. 3, p. 035008, May 2014.

[3] A. Riccio *et al.*, “On the relationship between attention processing and P300-based Brain Computer Interface control in Amyotrophic Lateral Sclerosis,” *Front. Hum. Neurosci.*, vol. 12, 2018.





Disclosures: **D.E. Thompson:** None. **M. Mowla:** None. **J.E. Huggins:** None.

Poster

760. Brain-Computer Interface: Extracranial

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 760.20/L30

Topic: E.05. Brain-Machine Interface

Title: Assessment of high-frequency and multi-color visual stimulus using dry electrodes for BCI applications

Authors: ***Y.-T. WANG**, S. JENNINGS, R. VIAJAR, M. A. CHEVILLET;
Facebook, Menlo Park, CA

Abstract: Steady-state visual evoked potential (SSVEP) brain-computer interface (BCI) has attracted much attention as it requires less training time and provides a high information transfer rate. However, the use of wet (gel) electrodes and flashing visual stimuli severely limit its relevance to real-world applications. We assessed the feasibility of combining (1) wireless EEG system with dry electrodes, (2) over-critical-fusion-frequency visual stimuli, and (3) training-free decoding algorithms. A customized headband provided partial coverage of the occipital cortex using 6 dry electrodes, and SSVEPs were induced using an iso-luminance visual stimulus consisted of red and green colors flashing at 50 Hz. Finally, two training-free decoding algorithms - canonical correlation analysis (CCA) and filter bank CCA (FBCCA) - were applied to evaluate decoding accuracy.
The study was approved by an external Institutional Review Board, and 20 participants were

provided written informed consent form before the participating. Six dry “Flex” electrodes (Cognionics, Inc.) were positioned over region Oz and data were collected at 500 Hz sampling rate. Ground and reference electrodes were attached on the forehead. Participants were presented with two different visual stimuli: a circle alternating between black and white at 10 Hz, and a circle alternating between red and green at 50 Hz. Both visual stimuli covered ~5 degree field of view, and data were recorded during 2 one-minute sessions for each visual stimulus. Data were epoched into 3-second trials after applying a band-stop filter (59-61 Hz).
Trials with blinks and an absolute value over 25 micro-volts were rejected.
The mean decoding accuracy of black-white stimulus using 3-seconds of SSVEP response time was 0.9739±0.0811 for CCA and 0.9524±0.1129 for FBCCA. In contrast, the mean decoding accuracy of the red-green stimulus using 3-second data was 0.4454±0.1627 for CCA and 0.7507 ± 0.2276 for FBCCA. The difference between CCA and FBCCA was not significant for the black-white 10 Hz stimulus (p= 0.1729), but was significant for the red-green 50 Hz stimulus (p<0.01).
Notably, the decoding accuracy using FBCCA was better than CCA when using more than 1.8 seconds of the SSVEP response. These results suggest that it is feasible to detect SSVEPs using dry electrodes and over-critical-fusion-frequency stimulus, and that FBCCA can improve decoding accuracy in high-frequency SSVEP-based BCI.

Disclosures: **Y. Wang:** None. **S. Jennings:** None. **R. Viajar:** None. **M.A. Chevillet:** None.

Poster

760. Brain-Computer Interface: Extracranial

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 760.21/L31

Topic: E.05. Brain-Machine Interface

Support: DFG BI 195/77-1
BMBF 16SV7701 CoMiCon
LUMINOUS-H2020-FETOPEN-2014-2015-RIA (686764)
Wyss Center for Bio and Neuroengineering, Geneva

Title: Bimodal electroencephalography (EEG) and functional near-infrared spectroscopy (fNIRS) brain-computer interface (BCI) for communication by individuals in completed locked-in state (CLIS)

Authors: *A. JARAMILLO-GONZALEZ[1], A. TONIN[1], M. KHALILI ARDALI[1], A. RANA[1], N. BIRBAUMER[1,2], U. CHAUDHARY[1,2];
[1]Inst. for Med. Psychology and Behavioural Neurobio., Univ. of Tuebingen, Tuebingen, Germany; [2]Wyss-Center for Bio- and Neuro-Engineering, Geneva, Switzerland

Abstract: Individuals in completely locked-in state (CLIS), due to amyotrophic lateral sclerosis (ALS), are left without a means of communication. A recent functional near-infrared spectroscopy (fNIRS) based brain-computer interface (BCI) demonstrated classification of "yes" and "no" answer by individuals in CLIS with up to 70% accuracy. Such a low classification accuracy and high error rate limit the performance of the BCI system. Hence there is a need to explore other approaches to improve the classification and thereby the performance of the BCI system. Several multimodal Brain-Computer Interfaces (BCI) have proven successful in recent years, therefore multimodal BCI that exploit the complementary information from multiple data sources is a potential path for improvement. Here we propose the use of a bimodal EEG-fNIRS hybrid BCI (hBCI), taking advantage of the synergistic effect of both signals, improving the spatiotemporal resolution and increasing the reliability of the engineered features. Available data set of different days and sessions from six individuals in CLIS, recorded with simultaneous 7 EEG and a set of 8 fNIRS source-detectors (20 channels), acquired during a "yes" and "no" questions' paradigm, will be analyzed. A supervised modality integration using 1) General Linear Model (GLM) obtained from extracting EEG features and correlating them with the fNIRS data, and 2) a symmetric approach by analyzing both EEG and fNIRS data series with Mutual Information will be performed. Along with this, an unsupervised approach by means of Principal Component Analysis (PCA) will also be performed. The results obtained from these analyses will be compared to determine the methodology to be implemented to improve the classification of "yes" and "no" answer by individuals in CLIS, thereby improving the performance of the BCI-based communication.

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Poster

760. Brain-Computer Interface: Extracranial

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 760.22/L32

Topic: E.05. Brain-Machine Interface

Support: EU ERC-Consolidator Grant Feel Your Reach (681231)
EU Horizon 2020 MoreGrasp (643955)

Title: Towards non-invasive decoding of cortical patterns: Goal directed movements, movement trajectories, error potentials, hand movement attempts and artificial sensory feedback in humans

Authors: *G. R. MUELLER-PUTZ, J. PEREIRA, R. KOBLER, C. LOPES DIAS, L. HEHENBERGER, A. SCHWARZ, P. OFNER, A. I. SBURLEA;
Graz Univ. of Technol., Graz, Austria

Abstract: In Europe estimated 300,000 people are suffering from a spinal cord injury (SCI) where 40% are tetraplegics. With the help of motor neuroprostheses (NP), grasping and elbow function can be substantially improved. A natural solution for controlling a robotic arm or a NP would be to record motor commands from the corresponding cortical areas and convert them into control signals with the help of brain-computer interface (BCI) technology [1]. We showed the control of a motor neuroprosthesis in individuals with SCI using electroencephalography (EEG) [2, 3]; however, the control strategy is not yet intuitive enough. The objective of FeelYourReach project is to develop a novel EEG-based control framework that incorporates goal-directed movement intention, movement decoding, error processing and delivery of sensory feedback for a more intuitive control of a robotic arm. Our findings in these areas show that goal-directed movements have different neural correlates than movements that are not directed towards a target [4]. Moreover, we found differences between the neural correlates of externally and internally-driven target selection [5]. Progress was made in the decoding of 2D/3D arm movement trajectories [6]. We also explored the relation between neural, muscle and kinematic correlates of a large variety of hand movements [7]. Next, we showed the asynchronous detection of erroneous potentials in a task that involved continuous control and feedback [8]. During the MoreGrasp project [9], we developed a novel NP which allows an end-user to regain control of the lost hand-function by either using a shoulder position sensor, instrumented objects, the neural correlates of movement attempt, or a combination of them. Currently, a clinical study is ongoing and preliminary results on 15 end users will be shown. Our current findings suggest that with these approaches an end-user will be able to intuitively control a NP with his/her mind only. [1] Müller-Putz et al. Prog in Brain Res 2016 [2] Rupp et al. Proc IEEE 2015 [3] Müller-Putz et al. Neurosci Let 2005 [4] Pereira et al. Neuroimage 2017 [5] Pereira et al. SciRep 2018 [6] Kobler et al. SciRep 2018 [7] Sburlea and Müller-Putz, SciRep 2018 [8] Lopes-Dias et al. JNE 2018 [9] Müller-Putz et al. IEEE EMBC 2019

Disclosures: **G.R. Mueller-Putz:** None. **J. Pereira:** None. **R. Kobler:** None. **C. Lopes Dias:** None. **L. Hehenberger:** None. **A. Schwarz:** None. **P. Ofner:** None. **A.I. Sburlea:** None.

Poster

760. Brain-Computer Interface: Extracranial

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 760.23/L33

Topic: E.05. Brain-Machine Interface

Support: Horizon 2020 ERC-Consolidator Grant Feel Your Reach (681231)

Title: Relating neural, muscle and kinematic grasping correlates during movement observation and execution

Authors: *A. I. SBURLEA[1], N. BUTTURINI[2], G. R. MUELLER-PUTZ[1];
[1]Inst. of Neural Engineering, TUGraz, Graz, Austria; [2]Univ. of Padova, Padova, Italy

Abstract: Electromyographic and kinematic information have been proposed as candidates for the neural representation of hand control. However, it remains unclear how these movement covariates are reflected in electroencephalographic (EEG) activity during different stages of grasping movements, such as hand-preshaping, reaching the final grasping posture and holding. In this exploratory study, we simultaneously acquired EEG, kinematic and electromyographic signals in 31 human subjects while observing 33 different pictures of hand-object interaction and executing the different types of grasps previously observed. Our study aims were three-fold. First, we investigated the relation between EEG movement covariates and the behavioral covariates associated with the movement execution phase. Using representational similarity analysis, we found that EEG activity reflected different movement covariates in different stages of grasping. During the pre-shaping stage, centro-parietal EEG in the lower beta frequency band reflected the object's shape and size, whereas during the finalization and holding stages, contralateral parietal EEG in the mu frequency band reflected muscle activity. Second, we asked how the EEG patterns of static grasping observation relate with the behavioral covariates of movement execution. We found that the EEG representation of the observation phase in the mu and low beta frequency bands was correlated with the muscle representation during the execution, most strongly in the movement holding phase. This similarity indicates that when visually processing the hand-object interaction, we focus on the final grasping posture. Furthermore, we found that contralateral and central parietal and occipital regions in the mu and beta frequency bands of the EEG representation of movement observation reflected the object's shape and size. Third, we investigated whether the muscle envelope of different grasping movements can be continuously predicted from low frequency EEG amplitudes using a filtering approach. We achieved higher prediction accuracy for intermediate grasps compared to power or precision grasps. These findings contribute to the understanding of the temporal organization of neural grasping patterns, and could inform the design of noninvasive neuroprosthetics and brain-computer interfaces. Moreover, these findings allow us to gain a joint understanding of the relation between movement observation and execution and a mean to facilitate an intuitive control of neuroprostheses in motor impaired individuals.

Disclosures: A.I. Sburlea: None. **G.R. Mueller-Putz:** None. **N. Butturini:** None.

Poster

760. Brain-Computer Interface: Extracranial

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 760.24/L34

Topic: E.05. Brain-Machine Interface

Support: ERC Consolidator Grant 681231 'Feel Your Reach'

Title: Using ErrPs to improve continuous BCIs

Authors: *C. LOPES-DIAS, A. I. SBURLEA, G. R. MUELLER-PUTZ;
Inst. of Neural Engin., Graz Univ. of Technol., Graz, Austria

Abstract: Brain-computer interfaces (BCIs) convert brain activity of a user into actions of an external device and are a valuable tool for people with severe motor disabilities. However, BCIs' performance is not optimal and, sometimes, unintended actions are executed.
The recognition that a mistake has been committed is associated with a neural pattern named error-related potential (ErrP). The use of ErrPs is an intuitive strategy to improve BCIs by allowing to identify (and correct) unintended commands.
The existence and detection of ErrPs in discrete BCIs (in which actions occur in a discrete manner) is well established, but BCIs are developing to provide users continuous control. In this situation, the user's awareness that the BCI performed an unintended action can occur at any moment. Therefore, such BCIs require an asynchronous decoding of ErrPs. We try to address the asynchronous decoding of ErrPs during continuous control and feedback.
In our first experiment, the EEG of 15 able-bodied participants was measured while they controlled a cursor on a screen towards a target using a joystick. In 30% of the trials, the participants lost control over the cursor and this deviated into an unintended direction. Evaluating the data offline, in a simulated online scenario, we obtained an average TNR (percentage of correct trials in which no ErrP detection occurred) of 84% and an average TPR (percentage of error trials in which no ErrP detection occurred before the error onset and at least one ErrP detection occurred after the error onset) of 65%.
In our second experiment, we measured the EEG of 15 able-bodied participants while they controlled a robotic arm towards a target using their right hand. In 30% of the calibration trials, the robot made an 'error' during the trajectory and participants lost control over the robot. The experiment was divided in calibration and testing phases. The calibration phase was used to train an ErrP classifier. In the testing (online) phase, participants could regain the robot's control if an ErrP was detected after the error occurred. In the testing phase, we obtained an average TNR of 87% and an average TPR of 70%.
We also investigated the use of generic ErrP classifiers. For that, we used the calibration data from our second experiment and tested the performance of generic classifiers (trained with the data of 14 participants and tested in the remaining participant). We obtained an average TNR of 82% and an average TPR of 54%.
These results indicate that asynchronous detection of ErrPs is reliable even in an online scenario and that a generic classifier could be used as a strategy to eliminate calibration, serving as a starting point for an adaptive classifier.

Disclosures: C. Lopes-Dias: None. **A.I. Sburlea:** None. **G.R. Mueller-Putz:** None.

Poster

760. Brain-Computer Interface: Extracranial

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Program #/Poster #: 760.25/L35

Topic: E.05. Brain-Machine Interface

Title: Visuo-spatial complexity and object-relatedness impact brain activity during motor imagery

Authors: *S. C. WRIESSNEGGER, J. PEREIRA, A. SCHWARZ, G. MUELLER-PUTZ; Inst. of Neural Engin., Graz Univ. of Technol., Graz, Austria

Abstract: Motor Imagery (MI) is a task which has been used for driving brain plasticity and motor learning in several fields including sports, motor rehabilitation and brain-computer interface (BCI) research. In the past, many studies have shown that changes in brain activity associated with MI can serve as useful control signals for BCIs. Most studies focus on improving signal processing feature extraction and classification methods, but the performance of a BCI can also be improved by optimizing the user's control strategies. That is, using more vivid and engaging mental tasks for control instead of simple hand/finger tapping tasks. We performed several neuroimaging studies measuring electrical and hemodynamic brain activity during different types of MI. We investigated imagining a more complex action, such as playing tennis or football, which incorporates not only motor-related processing but also visuo-spatial imagery which is refelected in fronto-parietal network activation [1]. In another study using functional near infrared spectroscopy (fNIRS) we investigated MI including emotion-laden objects. Twenty right-handed healthy participants performed motor imagery of squeezing different types of affective objects, like a sticky ball, a cactus or a rotten apple. The results showed that affective MI compared to neutral MI lead to increased oxy-hemoglobin [oxy-Hb] concentration changes. Brain regions located contralateral frontal and also parietal show higher [oxy-Hb] increases [2]. A follow up study with the same paradigm but by means of electroencephalography (EEG) was performed with 15 right-handed healthy participants. We found a stronger left parietal event related desynchronization [ERD] during the imagery of squeezing a cactus in the beta frequency band. Summarizing, our studies indicated a more distinctive brain activity in a broader network of brain areas during the performance of more complex MI tasks when compared to simple tasks. Therefore we surmise that visuo-spatial cognition and action affordances play a significant role in MI eliciting distinctive brain patterns suggested to improve the performance of future BCI systems.

[1] Wriessnegger, S. C., Brunner, C., & Müller-Putz, G. R. (2018). Frequency Specific Cortical Dynamics During Motor Imagery Are Influenced by Prior Physical Activity. Frontiers in Psychology, 9.

[2] Wriessnegger, S. C., Bauernfeind, G., Kurz, E. M., Raggam, P., & Müller-Putz, G. R. (2018).

Imagine squeezing a cactus: Cortical activation during affective motor imagery measured by functional near-infrared spectroscopy. Brain and cognition, 126, 13-22.

Disclosures: S.C. Wriessnegger: None. **J. Pereira:** None. **A. Schwarz:** None. **G. Mueller-Putz:** None.

Poster

760. Brain-Computer Interface: Extracranial

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 760.26/L36

Topic: E.05. Brain-Machine Interface

Support: FeelYourReach - European Research Council Consolidator Grant ERC-681231
MoreGrasp - European ICT Programme Project H2020-643955

Title: Investigating goal-directed movement planning and intention using electroencephalography

Authors: *J. PEREIRA, A. I. SBURLEA, P. OFNER, A. SCHWARZ, G. MÜLLER-PUTZ; Graz Univ. of Technol., Graz, Austria

Abstract: Investigating the neural correlates of goal-directed actions, including the movement planning phase, is of interest for the development of brain-computer interfaces (BCIs) for control. We use electroencephalography (EEG) to study several aspects of movement planning in execution (ME) and imagination (MI) tasks in subjects without motor disabilities, as first steps towards intuitive BCIs for people with upper-limb motor impairments. In a first study (n=10), we investigated whether the presence of a motor goal could influence the classification performance (of ME vs. rest) during a reach-and-touch task [1]. We show that movement-related cortical potentials (MRCPs) on the goal-directed condition differ from those of the non-goal-directed condition. Moreover, we show that low-frequency time-domain EEG features are suitable for classification of movement intention, and that the classification performance is affected by the goal-directedness of the movement. Highest accuracies are achieved on the goal-directed condition (accuracy=79%), rising above chance-level before movement onset for all subjects (and for 6 subjects on the non-goal-directed condition). The classifier patterns attributed these differences to premotor and primary motor areas, as well as to the posterior parietal cortex. On a second study (n=15), we focused on the goal-directed MI of a grasp, to study the differences between externally-cued or internally-driven target selection processes - which are related to the definition of the motor goal itself [2]. For that purpose, we developed a paradigm that allowed the separation between target selection and the actual MI. We found out that the late event-related cortical potentials encode differences between both conditions - which reflect the perceptual and cognitive processes prior to the MI. Additionally, we could estimate a reliable MI

onset that enabled us to train for the first time a classifier of self-paced MI vs. rest, leading to an offline performance significantly higher than chance-level for both time-locked and asynchronous classification scenarios. We believe that these findings contribute to the development of intuitive BCIs in which movement targets are defined internally and the goal-directed movements are self-paced.
[1] Pereira et al. Neuroimage 2017 [2] Pereira et al. Scientific Reports 2018

Disclosures: **J. Pereira:** None. **A.I. Sburlea:** None. **P. Ofner:** None. **A. Schwarz:** None. **G. Müller-Putz:** None.

Poster

760. Brain-Computer Interface: Extracranial

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 760.27/L37

Topic: E.05. Brain-Machine Interface

Support: ERC Consolidator Grant Feel Your Reach (681231)
R&D of technologies for high-speed wireless comm. from inside to outside of the body and large-scale data analyses of brain information and their app. for BMI from the NICT, Japan

Title: Expression of kinematic information in EEG and MEG signals during visuomotor tasks

Authors: ***R. J. KOBLER**[1,2], A. I. SBURLEA[1], V. MONDINI[3], E. KOLESNICHENKO[4], H. HASHIMOTO[2], M. HIRATA[2], G. R. MUELLER-PUTZ[1];
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Abstract: Electroencephalographic (EEG) and magnetoencephalographic (MEG) signals carry information about upper-limb kinematics. Their expression in M/EEG signals is potentially influenced by many factors. We believe that vision and movement type (i.e., discrete vs continuous) are key factors. To identify their effects, we investigated visuomotor tasks in several studies.
In a first EEG study (15 healthy subjects), we investigated the influence of vision during goal-directed upper-limb movements [1]. Our paradigm implemented a center-out task (COT) followed by a pursuit tracking task (PTT). It involved two visual stimuli (target and cursor) in two conditions. In one condition (exe), subjects controlled the cursor with their right hand. In the second condition (obs), subjects observed a computer controlled cursor. Regarding the PTT, our findings indicate that premotor and primary sensorimotor areas carried significant information

about cursor velocity in the exe condition, whereas parieto-occipital areas carried significant directional information in either condition. Regarding the COT, we could classify condition (exe vs obs) and direction (left, up, right and down) above significance level. The two classifiers relied on different cortical areas. Contra-lateral pre- and primary motor areas predicted condition, while parieto-occipital areas predicted direction in both conditions.
In a second EEG study (10 healthy subjects), we investigated how the results of the PTT translate to an online control scenario. In both conditions (hand movement based control, EEG based control) the kinematics could be decoded above the significance level, with parieto-occipital areas carrying significant information about end-effector velocity. We observed an amplitude-scaling mismatch between the decoded and actual kinematics, which resulted in declined tracking quality in the EEG based control condition.
To address the amplitude-scaling mismatch, we conducted an MEG study (20 healthy subjects), where we investigated a similar PTT as in the first EEG study. In this study, the subjects controlled the cursor with their right index finger [2]. We found that the MEG signals carried not only significant information about velocity, but also about speed in primary-sensorimotor areas. We believe that our findings can aid to a new generation of non-invasive brain-computer interfaces.
[1] Kobler RJ et al. Sci.Rep. 2018 [2] Kobler RJ et al. Proc. 8thGBCIC. 2019(accepted)

Disclosures: **R.J. Kobler:** None. **A.I. Sburlea:** None. **V. Mondini:** None. **E. Kolesnichenko:** None. **H. Hashimoto:** None. **M. Hirata:** None. **G.R. Mueller-Putz:** None.

Poster

760. Brain-Computer Interface: Extracranial

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 760.28/L38

Topic: E.05. Brain-Machine Interface

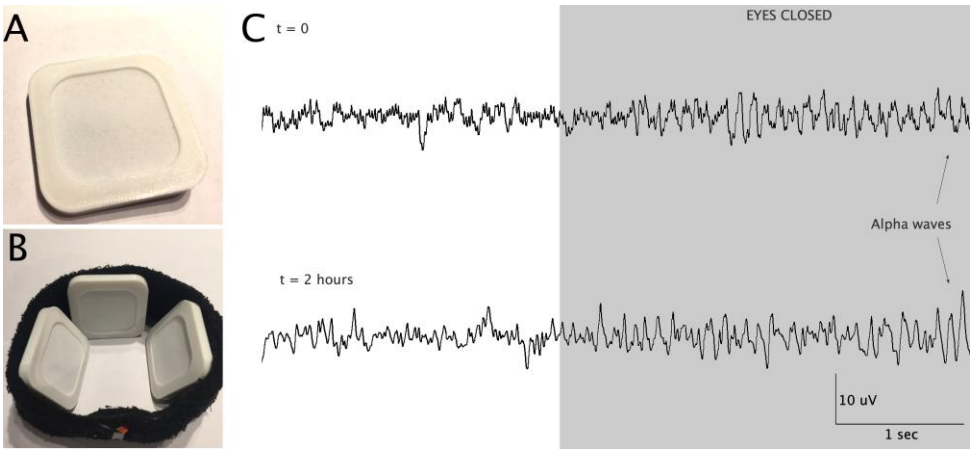
Title: Low impedance, low cost electrodes for long-term electroencephalography and non-invasive electrical brain stimulation

Authors: *N. VYSOKOV[1], I. TARASENKO[1], A. TARASENKO[2], M. OGANESYAN[1]; [1]BrainPatch, London, United Kingdom; [2]Univ. Col. London, London, United Kingdom

Abstract: Combining non-invasive recording of electrical brain activity (electroencephalography or EEG) with non-invasive electrical brain stimulation (NIBS) is a challenge in many aspects. Currently electrodes suitable for EEG and NIBS require cumbersome procedures of gel or special paste application prior to the electrode set up; saline-soaked sponges may also be used but their EEG performance may be inconsistent.
We have developed electrodes that can be used for EEG recordings as well as for NIBS; below we present the results of the tests performed. The electrode assembly consists of a layer of

medical-grade highly absorbent foam saturated with saline solution, and a thin interface of conductive material, all held together by soft non-conductive polymer that prevents leakage and evaporation (A). Thus, when the electrodes come in contact with the scalp or hair, the liquid interface is created which in turn results in the electrode impedance in the sub 5 kOhm range over the forehead (Fp1-Fp2) and over the hair (T3-T4). Due such low impedance we could obtain high signal-to-noise ratio for EEG recordings over a period of at least 2 hours (C). The data acquired is of sufficient quality to detect changes in conventional parameters (e.g. see alpha waves in panel C), but also for processing by more sophisticated machine learning algorithms. The observed change in impedance was in the range of +/- 10%, the quality of the recorded signal was comparable and voltage (4.5-6 V) required to reach the same current (1 mA) for tDCS/tACS didn't differ significantly.

Most importantly, these electrodes can be used in a headband so that they are easy to apply (B), do not cause discomfort and are relatively inexpensive. This makes them potentially suitable for a wide variety of clinical and medical applications as well as home use. The ability to record EEG and deliver the stimulation without the need to change the electrode set up opens up the potential avenues for further research on closed-loop electrical NIBS.



Disclosures: **N. Vysokov:** A. Employment/Salary (full or part-time):; BrainPatch. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BrainPatch. **I. Tarasenko:** A. Employment/Salary (full or part-time):; BrainPatch. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BrainPatch. **M. Oganesyan:** A. Employment/Salary (full or part-time):; BrainPatch. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BrainPatch. **A. Tarasenko:** None.

Poster

760. Brain-Computer Interface: Extracranial

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 760.29/L39

Topic: E.05. Brain-Machine Interface

Title: Open Phantom: A freely available phantom device for use in EEG testing and validation

Authors: A. B. YU[1], S. E. BOTTOMLEY[1], C. G. SINKS[2], M. W. NONTE[3,1], ***W. HAIRSTON**[4];
[1]CCDC Army Res. Lab., Aberdeen Proving Ground, MD; [2]CCDC US Army Res. Lab., Aberdeen Proving Ground, MD; [3]DCS Corp., Alexandria, VA; [4]CCDC .Army Res. Lab., Aberdeen Proving Ground, MD

Abstract: Despite electroencephalography (EEG) being commonly used for decades in medicine and as the basis for a myriad of neuroimaging research, the EEG community as a whole has yet to adopt a single device or approach for calibrating and validating EEG data acquisition equipment or related algorithms. While so-called phantom devices are used in MRI, CT, PET, and other imaging devices for testing and calibration, to date no such device has been widely adopted for EEG. To be useful, such a device would need to be (1) electrically conductive in a manner roughly analogous to the human scalp, (2) consistent and predictable, and (3) relatively cost-effective in order to be accessible across the community. A major challenge to all three of these has been finding a suitable material which can satisfy all of these needs. We propose that a suitable phantom head device can be easily fabricated using ballistics or similar gelatins, in order to meet all of the above criteria (inexpensive, easy to mold, and has conductively tunable). Here, we discuss an ongoing project developing such phantoms, their general design, and suitability for different applications, with designs that are freely available. An MRI was used to create a realistic size/shape head model, which was then used to design an inverse mold based on pouring gelatinous fluid in from the top. In one design, the internal brain capsule contains multiple internal dipole sources, while another uses a rigid skull formation to simulate the rigidity and poor conductivity of skull. Designs can be 3-D printed and easily fabricated within a day, and researchers are invited to modify designs and provide their own modifications back to the community. Once fabricated, phantoms can be used for a variety of applications, with differing designs specific to each. For example, models can be used for characterizing the size and origin of motion-related artifacts in EEG, testing the efficacy of different noise removal techniques, evaluating the SNR of different electrodes or other DAQ approaches, or even predicting the noise associated with a particular environment.

Disclosures: **A.B. Yu:** None. **C.G. Sinks:** None. **M.W. Nonte:** None. **W. Hairston:** None. **S.E. Bottomley:** None.

Poster

760. Brain-Computer Interface: Extracranial

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 760.30/L40

Topic: E.05. Brain-Machine Interface

Support: DARPA N3

Title: Fabrication of tunable electrical skull phantom from carbon nanofiber-doped PDMS

Authors: T. X. CAI[1], ***M. FORSSELL**[2], A. KRISHNAN[2], J. W. REDDY[2], P. GROVER[2], M. CHAMANZAR[2];
[1]Biomed. Engin., [2]Electrical and Computer Engin., Carnegie Mellon Univ., Pittsburgh, PA

Abstract: Objective:
Novel neural stimulation and recording techniques can be better developed and validated on tissue phantoms that mimic specific properties of brain tissue, scalp and skull. The properties of these artificial samples can sometimes more accurately match live tissue, and offer better control, than excised biological samples, enabling calibration of stimulation and recording techniques under different conditions. The electrical properties of the brain are often approximated by saline solutions and agar gels. However, investigations on transcranial brain interfacing also benefit from the use of skull phantoms, for which no standard exists. The study presented here reports a versatile method to fabricate skull-like electrical phantoms using carbon nanofiber (CNF)-doped polydimethylsiloxane (PDMS).

Methods and results:
The skull phantom must have low conductivity matching that of the skull, which ranges from 10 to 100 mS/m. In order to be used in electrophysiological experiments, e.g. to test or study noninvasive techniques, the skull phantom must also be biocompatible as well as stable in contact with cerebrospinal fluid (CSF). Agar-based tissue phantoms absorb water and ions, resulting in variable conductivities that change over time.
Conductive PDMS phantoms can be fabricated by mixing conductive particles with the monomer before curing. However, clustering leads to an inhomogeneous material in which the overall conductivity is dominated by low conductivity regions, in particular for samples in which the overall conductivity is low. Our method consists of incorporating CNFs (PR-24-XT-HHT, Pyrograph) into the PDMS matrix before curing. The CNF is first dispersed in isopropyl alcohol (IPA), then mixed with methyl-terminated PDMS monomer before mixing with a regular PDMS monomer (Sylgard 184, Dow Corning). The methyl-termination aligns the CNFs and results in a greater homogeneity of the CNF dispersion, and therefore a greater homogeneity of the conductivity in the sample. After sonication, the solvent is evaporated and then the CNF-PDMS sample is cured.
Conclusion:
The resistivity of the samples is characterized as a function of the mixing ratio of CNF in PDMS, displaying an inverse relationship. A resistivity of 12Ωm is obtained at 1.7% CNF in weight. The degree of homogeneity of the phantoms is characterized by fabricating 1 cm-thick samples and measuring the conductivity of individual 1 mm-thick slices. Edge effects result in lower conductivity along the top and bottom of the sample, as expected. At depths between 3 mm and 9 mm, the conductivity is measured to be 12.3±3.5 Ωm (n=17 slices over 3 samples).

Disclosures: T.X. Cai: None. **M. Forssell:** None. **A. Krishnan:** None. **J.W. Reddy:** None. **P. Grover:** None. **M. Chamanzar:** None.

Poster

761. Brain-Computer Interface: Stimulation for Sensation

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 761.01/L41

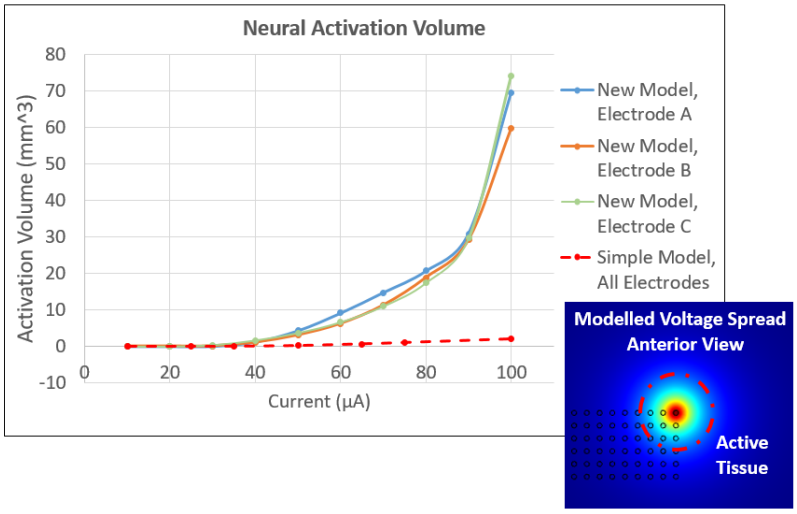
Topic: E.05. Brain-Machine Interface

Support: NEI EY022931
EY007003
Research to Prevent Blindness

Title: A computational framework for the Argus II implant: Factors influencing neural activation volume

Authors: *K. E. FINN[1], H. J. ZANDER[1], S. F. LEMPKA[2], J. D. WEILAND[3];
[1]Biomed. Engin., [2]Biomed. Engineering, Anesthesiol., [3]Biomed. Engineering, Ophthalmology and Visual Sci., Univ. of Michigan, Ann Arbor, MI

Abstract: Electrical stimulation of retinal tissue via the Argus II implant induces visual percepts in blind people. Percepts are consistent trial to trial for single electrodes but vary across subjects and electrodes (Luo 2016). We hypothesize that computational models can predict variation caused by device placement and disease progression. Previous models have neglected these effects, simplifying the retina as a slab of homogenous tissue and using an idealized microelectrode array (MEA) at uniform distance from the retina (Loizos 2018, Esler 2018, Abramian 2015). The purpose of this exploratory research was to quantify the benefit of an anatomically accurate eye model with realistic implant placement.
We created a 3D COMSOL model to integrate eye shape, electrode array curvature and device position in and around the eye. Based on the physical model of device and eye, we generated finite element electric field solutions. For comparison, we implemented a simple literature-based model with an idealized ground and MEA, using the same tissue thicknesses, conductivities, and electrode size. Neural activation volume was defined as retinal tissue exceeding a certain voltage during an applied stimulus. The voltage threshold (13 mV) was found using a biophysical retinal ganglion cell model and standard pulse (biphasic, 0.45 msec, 20 Hz) (Fohlmeister 1997). We applied current in the clinical range (0-100 µA) to single electrodes and quantified neural activation volume in mm^3. Higher activation volume implies larger visual percepts.
Results for both models are shown below. All electrodes in the simple model activated equal volume, which increased linearly with current. The new model had great activation volume at currents above 70 µA and up to 24% variation between electrodes. Our results suggest that curvature dependent electrode-retina distance, implant details, and ground position have substantial effects on electric field shape. Including these factors represents an improvement over previous retinal stimulation models.



Disclosures: **K.E. Finn:** Other; Second Sight Medical Products Inc. **J.D. Weiland:** Other; Second Sight Medical Products Inc..

Poster

761. Brain-Computer Interface: Stimulation for Sensation

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 761.02/L42

Topic: E.05. Brain-Machine Interface

Support: EY022931
EY007003
Research to Prevent Blindness

Title: Studying the effect of order and duration ratio of pulse polarities on perception thresholds with Argus II retinal prosthesis

Authors: *D. HAJI GHAFFARI[1], K. E. FINN[1], V. E. JEGANATHAN[1], J. D. WEILAND[1,2]; [1]Biomed. Engin., [2]Ophthalmology, Univ. of Michigan, Ann Arbor, MI

Abstract: Retinal prosthetic implants have helped improve vision in blind patients with retinitis pigmentosa (RP) and age-related macular degeneration (AMD), two of the common retinal diseases that lead to loss of photoreceptors and eventual blindness. Although patients with retinal implants have reported improvement in light perception and performing visual tasks, their ability to perceive shapes and letters is currently limited due to the low precision of retinal activation. A clinical trial reported that among 30 implanted patients, about half of the electrodes have thresholds above the acute stimulation safety limit. To allow safe stimulation, such electrodes are used in unison with neighboring electrodes, effectively creating a larger electrode, which further decreases the resolution. Thus, threshold reduction remains an important topic.
A previous *in vitro* mouse retina study in our lab (Chang et al. 2018) used calcium imaging to measure responses to electrical stimulation. Based on this study, we hypothesize that asymmetric anodic-first stimulation with duration ratios greater than 10 reduces the retinal ganglion cell (RGC) activation threshold, versus a standard cathodic-first biphasic pulse. Patch clamp recordings of RGCs verified this result. We are currently performing human subjects testing to further examine the effect of asymmetric anodic-first pulses on perception thresholds. In one Argus II retinal prosthesis subject, we measured responses to asymmetric anodic-first (AAF), symmetric cathodic-first (CF), symmetric anodic-first (AF), and symmetric cathodic-first stimulation with an interphase gap (ICF).
Subject 1 demonstrated a significant increase in perception probability with AAF pulses of 0.07, 0.1, and 0.2 ms duration compared to CF and AF, with an average increase of 94.07 % and 94.17 % respectively. Perception probability for the AAF decreased after adding a ICF with an interphase gap of 1.01 ms to the trial. ICF resulted in a perception probability 35% greater than that of the AAF, indicating that the ICF is either more effective than the AAF in decreasing perception thresholds or it results in brighter phosphenes. Post-test interview revealed that this

subject's criteria for perception was to only report the brightest percepts. The subject had few false positives, but likely underreported dim percepts. Thus, the percentages above are interpreted as indicating relative brightness amongst different stimulus types. The qualitative results from this subject are consistent with measurements from *in vitro* mouse retina.

Disclosures: **D. Haji Ghaffari:** Other; Second Sight Medical. **K.E. Finn:** Other; Second Sight Medical. **V.E. Jeganathan:** Other; Second Sight Medical. **J.D. Weiland:** Other; Second Sight Medical.

Poster

761. Brain-Computer Interface: Stimulation for Sensation

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 761.03/L43

Topic: E.05. Brain-Machine Interface

Support: Second Sight Medical Products

Title: Effectiveness of the Orion visual cortical prosthesis for the performance of simple visually guided behaviors

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[1]Neurosurg., Baylor Col. of Med., Houston, TX; [2]Second Sight Med. Products, Inc., Sylmar, CA; [3]Scientific Res., Second Sight Med. Products, Sylmar, CA; [4]Second Sight Med. Prod, Sylmar, CA; [5]Baylor Col. Med., Houston, TX

Abstract: Electrical stimulation of visual cortex produces perception of small flashes of light known as phosphenes. It has long been recognized that this could provide the basis for a visual cortical prosthesis, a device that could restore partial vision to blind subjects. Currently, an early feasibility trial is underway for the Orion Visual Cortical Prosthesis produced by Second Sight Medical Products. The device includes a camera, a visual processing unit, a transmitter, wireless transmission of signals to an implanted receiving coil, and an array of 60 cortical surface electrodes. The array is placed over the primary visual cortex and surrounding areas. This device has been implanted in four subjects at UCLA and two at BCM. In this abstract, we report on initial results from the two subjects at BCM. Subject 1 (M; age 34; age at onset of blindness 9) was implanted ~1 year ago. Initial testing was conducted by using a laptop computer rather than the camera to drive electrical stimulation (direct mode). After implantation, 58 electrodes were available for electrical stimulation, and 58 produced phosphenes when stimulated with currents <7.5 mA at 20 Hz (threshold = 4.95 +/- 1.14 mA, mean +/- stdev). Following this initial testing phase, the system was then connected to the camera (video mode). Using the system in video mode, the subject could perform a square localization task on a computer touchscreen with high

accuracy (mean error with system on = 3.2 cm, mean error with system off = 12.3 cm). In addition, the subject could locate items placed on a table in front of him, and could use the system for basic navigation tasks, for example to find hallways within buildings, or to identify sidewalks. Subject 2 (M; age 57; age at onset of blindness 45) has been implanted for ~4 months. After surgery 59 electrodes were available for electrical stimulation, and 55 produced phosphenes when stimulated with <7.5 mA (mean threshold 3.71 +/- 1.19 mA). We obtained highly reliable phosphene mapping in this subject, and he is in the process of video mode testing at this time. At the meeting we will present quantitative data from visual function testing of both subjects, and videos demonstrating the performance of the subjects in visually guided behaviors.

Disclosures: **W.H. Bosking:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Second Sight Medical Products. **D.N. Oswalt:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Second Sight Medical Products. **P. Sun:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Second Sight MEdical Products. **U.K. Patel:** A. Employment/Salary (full or part-time):; Second Sight Medical Products. **M. Armenta Salas:** A. Employment/Salary (full or part-time):; Second Sight Medical Products. **C. Cruz:** A. Employment/Salary (full or part-time):; Second Sight Medical Products. **A. Fazio:** A. Employment/Salary (full or part-time):; Second Sight Medical Products. **J.D. Dorn:** A. Employment/Salary (full or part-time):; Second Sight Medical Products. **D. Yoshor:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Second Sight Medical Products.

Poster

761. Brain-Computer Interface: Stimulation for Sensation

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 761.04/L44

Topic: E.05. Brain-Machine Interface

Support: NIH Grant UH3NS103442

Title: Early feasibility study for the Orion cortical visual cortical prosthesis: From thresholds to visual function

Authors: ***U. K. PATEL**[1], M. ARMENTA SALAS[1], S. NIKETEGHAD[2], W. H. BOSKING[3], V. WUYYURU[1], M. P. BARRY[1], D. YOSHOR[3], J. D. DORN[1], N. POURATIAN[2]; [1]Second Sight Med. Products, Inc., Sylmar, CA; [2]Dept. of Neurosurg., UCLA, Los Angeles, CA; [3]Dept. of Neurosurg., Baylor Col. of Med., Houston, TX

Abstract: Stimulation of human visual cortex is known to elicit visual perceptions that could potentially be used for creating artificial vision for individuals who have lost their vision due to non-cortical etiologies. Although there have been attempts to build brain stimulators for the

visual cortex in the past, fully implanted, chronic cortical visual prostheses have remained theoretical until recently. The Orion Visual Cortical Prosthesis System, which is currently being tested in a five-year early feasibility study (NCT03344848), is a new device that is intended to restore some functional vision to blind patients. There are currently six subjects enrolled between two study centers. Average age at time of implant was 50.3 years. All subjects had bare or no light perception due to non-cortical etiology at the time of implant, but were previously sighted. The Orion System comprises an implant (consisting of an electronics package, receiving antenna, and an electrode array with 60 non-penetrating electrodes with 2mm diameter); glasses with a video camera; headwear containing a transmitting antenna; and a video processing unit (VPU). The video camera collects real-time visual information, which is then processed by the VPU and converted to stimulation patterns on the electrode array. The Orion implant drives each electrode with current-controlled, charge-balanced square waves. A radio frequency link between the transmitting and receiving antenna sends data and power to the implant.
Phosphene thresholds are a primary input to the individualized program that converts visual information into stimulation patterns. Bounded by device capability and safety limits, thresholds were found for over 97% of electrodes. Average thresholds ranged from 1.6 mA - 3.7 mA across subjects at first measurement and were mostly stable over time. The interplay among threshold results, waveform parameters, and safety and performance constraints of the implant will be discussed with regards to strategies for stimulation of real-time visual information. As of May 1, 2019, average implant duration was 11.1 months (range 3.4 - 15.0 months). One serious adverse device event (seizure) has been reported. At six months post-implant, 3 of 5 subjects performed significantly better with the system on than off on a light localization task; 2 subjects performed better on a direction of motion task, and no subjects had measurable visual acuity. All 5 subjects were rated as receiving “positive” or “mild positive” benefit on a functional vision assessment.

Disclosures: **U.K. Patel:** A. Employment/Salary (full or part-time):; Second Sight Medical Products, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Second Sight Medical Products, Inc. **M. Armenta Salas:** A. Employment/Salary (full or part-time):; Second Sight Medical Products, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Second Sight Medical Products, Inc.. **S. Niketeghad:** None. **W.H. Bosking:** None. **V. Wuyyuru:** A. Employment/Salary (full or part-time):; Second Sight Medical Products, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Second Sight Medical Products, Inc. **M.P. Barry:** A. Employment/Salary (full or part-time):; Second Sight Medical Products, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Second Sight Medical Products, Inc.. **D. Yoshor:** None. **J.D. Dorn:** A. Employment/Salary (full or part-time):; Second Sight Medical Products, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Second Sight Medical Products, Inc.. **N. Pouratian:** None.

Poster

761. Brain-Computer Interface: Stimulation for Sensation

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 761.05/L45

Topic: E.05. Brain-Machine Interface

Support: NEI EY023336

Title: Reliable shifts in phosphene location achieved using current steering in human visual cortex

Authors: *D. OSWALT[1], W. H. BOSKING[2], P. SUN[2], U. K. PATEL[4], M. ARMENTA SALAS[5], J. D. DORN[6], B. L. FOSTER[2], M. BEAUCHAMP[3], D. YOSHOR[7];
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Abstract: Electrical stimulation of early visual cortex is known to elicit visual percepts called phosphenes that can be localized in visual field space to the corresponding part of the retinotopic map. Cortical visual prosthetic devices (CVPs) attempt to use the reliability of spatial relationships between many phosphenes to evoke visual patterns, with more complex patterns theoretically feasible as the number of electrodes increases. While novel phosphene locations have traditionally been limited to the number of electrodes present in cortex, this study proposes creation of virtual electrodes through current steering paradigms to evoke phosphenes in locations distinct from the physical electrode. Current steering uses parallel stimulation on nearby electrodes; the location of a virtual electrode is modulated by the ratio of current applied to each electrode in the pair. This technique has been used in cochlear and retinal implants to improve resolution, but has previously not been evaluated in cortex.Static current steering paradigms were evaluated in one sighted subject (sub1) undergoing clinical epilepsy monitoring and one blind subject (sub2) enrolled in an early feasibility study for a CVP system (NCT03344848). Subjects were asked to fixate during stimulation then indicate phosphene location on a touch screen monitor. Sets of trials with randomized presentation of fixed and virtual electrodes were conducted. In a condition with two fixed and one virtual electrode, each subject reported three phosphene locations. Sub1 reported phosphenes in an intermediary location an average 2.77 deg from either fixed electrode (4.9 deg separation). Sub2 reported an intermediary phosphene location 3.3 deg from fixed electrodes 5.4 deg apart. In a condition with two virtual electrodes, sub2 responded with four phosphene clusters, with an average shift of 2.7 deg between cluster centers, fixed electrodes spaced 6.9 deg.Current steering was also tested with a dynamic stimulation protocol, whereby current was applied in rapid succession at varied ratios to create three virtual locations in addition to the two fixed. Sub2 reported five

phosphenes, with cluster centers shifting an average 1.5±0.4 deg, fixed electrodes spaced 5.5 deg.In each condition phosphene locations reliably shifted with the ratio of applied current. These experiments demonstrate current steering as an effective means to introduce phosphene locations distinct from those generated with physical electrodes. The use of virtual electrode may improve device resolution in a step towards creating more coherent visual sensations and directly translate to improved functional outcomes of CVPs and other BCIs.

Disclosures: **D. Oswalt:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Second Sight Medical Products. **W.H. Bosking:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Second Sight Medical Products. **P. Sun:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Second Sight Medical Products. **U.K. Patel:** A. Employment/Salary (full or part-time):; Second Sight Medical Products. **M. Armenta Salas:** A. Employment/Salary (full or part-time):; Second Sight Medical Products. **J.D. Dorn:** A. Employment/Salary (full or part-time):; Second Sight Medical Products. **M. Beauchamp:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Second Sight Medical Products. **D. Yoshor:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Second Sight Medical Products. **B.L. Foster:** None.

Poster

761. Brain-Computer Interface: Stimulation for Sensation

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 761.06/L46

Topic: E.05. Brain-Machine Interface

Support: UH3NS103442

Title: Characterization and template comparison of phosphene location in blind human subjects with the Orion™ System

Authors: ***M. ARMENTA SALAS**[1], U. K. PATEL[1], S. NIKETEGHAD[2], W. H. BOSKING[3], M. P. BARRY[1], V. WUYYURU[1], J. D. DORN[1], D. YOSHOR[3], N. POURATIAN[2]; [1]Second Sight Med. Products, Inc., Sylmar, CA; [2]Univ. of California Los Angeles, Los Angeles, CA; [3]Baylor Col. of Med., Houston, TX

Abstract: Pioneering work by Dobelle et al (1974) provided key evidence for restoring some artificial vision through cortically-implanted prosthetic devices. Regardless of recent advancements with human BMI systems (Hochberg, 2012; Aflalo, 2015), few have involved sensory areas, specifically cortical areas related to primary visual function (Artificial Vision, 2017). We are interested in developing a cortical prosthetic system that restores a level of artificial functional vision to people living with blindness. To this end, Second Sight is

conducting an Early Feasibility Study with the Orion™ System, a cortical vision prosthesis, at two different clinical sites. The study's primary goal is to demonstrate the safety of the device, and one of its research objectives is to characterize the phosphenes generated with the system. As part of the study, we recruited six subjects who are bilaterally blind with bare or no light perception, due to a non-cortical etiology. A pre-implantation MRI and a post-implantation CT were collected for all subjects. The MRI and CT images were co-registered using tools from FSL (FMRIB Analysis Group, 2019), the electrode locations were determined using image thresholding with MRICron software (NITRC, 2019) and tools from iElectrodes software (Blenkmann et al, 2017). Using the estimated electrode locations, and a recent area and map location template from sighted subjects (Benson et al, 2014), we estimated where the phosphenes would be perceived in each subject's visual field. After initial threshold assessment across the array, we collected empirical spatial map (i.e. phosphene location) data from single electrode stimulation. The spatial data were captured for five of the subjects, across different sessions. When compared against the predicted locations, the subject's responses differed on average 40° (s.d. 6°) in polar angle, and 17° (s.d. 5.7°) in eccentricity, across all tested electrodes. Moreover, we observed that for several electrodes the reported empirical locations followed well the predicted distributions. We have also conducted an initial exploration of shape and size of the phosphenes, finding that for most of the subjects the larger size phosphenes correlate to more eccentric locations. These first assessments provide key insights to understanding the quality and reliability of the visual information we can provide with the current system, and its future functionality.

Disclosures: **M. Armenta Salas:** A. Employment/Salary (full or part-time):; Second Sight Medical Products. **U.K. Patel:** A. Employment/Salary (full or part-time):; Second Sight Medical Products. **S. Niketeghad:** None. **W.H. Bosking:** None. **M.P. Barry:** A. Employment/Salary (full or part-time):; Second Sight Medical Products. **V. Wuyyuru:** A. Employment/Salary (full or part-time):; Second Sight Medical Products. **J.D. Dorn:** A. Employment/Salary (full or part-time):; Second Sight Medical Products. **D. Yoshor:** 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.; Second Sight Medical Products. **N. Pouratian:** F. Consulting Fees (e.g., advisory boards); Second Sight Medical Products.

Poster

761. Brain-Computer Interface: Stimulation for Sensation

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 761.07/M1

Topic: E.05. Brain-Machine Interface

Support: DARPA N66001-16-4006

NIH R01F050920
UM Robotics Fellowship
NSF-GRFP
A. Alfred Taubman Medical Research Institute

Title: Functional prosthesis control using regenerative peripheral nerve interfaces and chronically implanted intramuscular electrodes

Authors: *A. K. VASKOV[1], P. P. VU[2], N. NORTH[3], A. J. DAVIS[4], T. A. KUNG[5], P. S. CEDERNA[5,2], C. A. CHESTEK[2,1,6,7];
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Abstract: Commercial myoelectric prostheses for persons with upper-limb amputations are controlled by residual muscle activity via electromyography (EMG) recorded from the skin surface. These traditional systems are unable to obtain reliable EMG signals for finger-specific motions because the desired signals are either obscured by superficial muscle activity or non-existent due to the level of amputation. Intramuscular recording techniques and Regenerative Peripheral Nerve Interfaces (RPNIs) can potentially resolve each of these issues. RPNIs are created by implanting the end of a severed peripheral nerve into a small free muscle graft and have been demonstrated to produce stable EMG recordings after reinnervation in animal studies (Kung et al., 2014; Vu et al., 2017). To date, two patients with transradial amputations have enrolled in a clinical study where bipolar electrodes were implanted chronically. P1 had RPNIs surgically created on each of the median, ulnar, and radial nerves. P2 had two RPNIs surgically created on the ulnar nerve, which had been subdivided into two fascicles, and one RPNI created on each of the median and radial nerves. Eight pairs of bipolar electrodes (Synapse Biomedical) were implanted into the ulnar and median RPNIs for both subjects as well as six and five residual muscles for P1 and P2, respectively. A Matlab xPC (Mathworks) decoded EMG in real-time and controlled virtual (MuJoCo) and physical prosthetic hands (DEKA, Ossur). We recorded strong motor-specific EMG signals from the implanted electrodes; for example, 2530μV and 650μV mean peak-to-peak motor unit signals from P1 and P2's median RPNIs during thumb flexion trials. Using binned mean absolute value as an input, a Naïve Bayes classifier distinguished 9 individual finger and wrist movements offline with an average accuracy of 92.6% across 50ms time bins. Performance did not greatly improve with additional features or alternate classifiers. P1 and P2 completed an online virtual posture matching task distinguishing all 9 movements and rest with an average success rate of 93.6%. To reduce decoder latency, we implemented a Hidden Markov Model (Kemere et al., 2008) which P1 and P2 used to classify 4 functional grasps and rest with average decoding latencies of 92 and 224ms. P1 also used the DEKA hand to complete a functional reach and place activity requiring multiple grasps. These results indicate that implanted intramuscular electrodes can record high-quality signals from RPNIs and residual muscles to provide users with intuitive multi-grasp control. Future work includes integrating a functional prosthesis for P2 and exploring techniques to add wrist activation to our control scheme.

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Poster

761. Brain-Computer Interface: Stimulation for Sensation

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 761.08/M2

Topic: E.05. Brain-Machine Interface

Support: DARPA BTO SPAWAR Pacific Grant/Contract No. N66001-15-C-4017
National Science Foundation (NSF) Grant NSF/NCS-FO ECCS-1533649
National Science Foundation (NSF) Graduate Research Fellowship Program Award No. 1747505

Title: A chronic neuro-myoelectric sensorimotor interface improves dexterous use of a bionic arm

Authors: *J. A. GEORGE[1], T. S. DAVIS[2], M. R. BRITON[1], M. D. PASKETT[1], C. C. DUNCAN[3], D. T. HUTCHINSON[4], G. A. CLARK[1];
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Abstract: The long-term goal of these studies is to provide amputees with intuitive control of, and natural sensory feedback from, multiarticulate sensorized bionic arms. Here we 1) report on a chronic sensorimotor interface consisting of implanted Utah Slanted Electrode Arrays (USEAs; Blackrock Microsystems) and intramuscular electromyographic recoding leads (iEMG; Ripple LLC); and 2) quantify improved control of bionic arms via an optimized modified Kalman filter (mKF). We implanted 2-3 USEAs and a 32-channel iEMG into the residual arm nerves and forearm muscles of 2 transradial amputees. Amputee S6 received implants 13 years after a traumatic amputation. Amputee S7 received implants during an elective amputation that followed 25 years of prior complex regional pain syndrome (CRPS) and hand disuse. Sensory feedback was evoked by stimulating through USEA electrodes, triggered by the experimenter or by sensors on a bionic arm. Both amputees reported functional proprioceptive and cutaneous percepts. For S7 there was a narrow window between detection and discomfort, hinting at a central contributing mechanism for CRPS. S6 experienced up to 119 different percepts that were localized, well-distributed across the hand, and perceived as enjoyable. Sensory feedback improved grip precision and reduced the coefficient of variation ($p < 0.05$). Sensory percepts were stable within sessions and most were stable (mean: 71%) when retested at 1-to-2-month intervals. After the first month post-implantation, there were no significant changes in median detection thresholds (52 µA) or electrode impedance (64 kΩ). Simultaneous proportional motor control was provided by a mKF using both EMG and neural recordings. EMG provided a robust

measure of motor intent across the 14-month (S6) and 17-month (S7) study durations. For S7, neural recordings further improved control ($p < 0.001$) and were also viable over time, with 26 electrodes providing neural signals (signal-to-noise ratio of 7.69) at 503 days after implantation. Modifications for the mKF (optimized offline) included ad-hoc thresholds that reduced unintended movement ($p < 0.001$) and gains that improved intended movement ($p < 0.001$). The mKF also improved sustained grasping ($p < 0.001$) in real-time and allowed both amputees to successfully complete activities of daily living (e.g., eating, using tools, etc.) with the DEKA "LUKE" arm. S7 also completed a supervised take-home trial with the "LUKE" arm using the mKF deployed onto a portable wireless processor (Brinton et al., SfN 2019), demonstrating the translational impact of and improved dexterity afforded by chronic sensorimotor interfaces and multiarticulate bionic arms.

Disclosures: **J.A. George:** None. **T.S. Davis:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent: WO2018026842A1. **M.R. Briton:** None. **M.D. Paskett:** None. **C.C. Duncan:** None. **D.T. Hutchinson:** None. **G.A. Clark:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent: WO2018026842A1, Patent: WO2018023026A1, Patent: 8359083, Patent: 8639312.

Poster

761. Brain-Computer Interface: Stimulation for Sensation

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 761.09/M3

Topic: E.05. Brain-Machine Interface

Support: DARPA HAPTIX N66001-15-C-4016

Title: Sensory consequences of electrical stimulation of individual fascicles within peripheral nerve

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Abstract: As part of the DARPA HAPTIX program, we are engaged in the development of a bidirectional peripheral nerve interface to provide intuitive motor control and robust sensory feedback for upper extremity prosthetic devices. Electrical stimulation of peripheral nerves can be used to evoke a wide range of sensations. The quality, location, and size of these percepts is dependent on the population of nerve fibers that are activated by a stimulation pulse train. Developing electrodes and methods of selectively activating specific portions of the nerve, so as to maximize the number of distinct stimulation-induced sensory percepts, has been a major focus of peripheral interfacing research.

Our approach involves implanting longitudinal electrode arrays *into* individual fascicles within peripheral nerve and additionally placing cuff electrodes *around* each fascicle. This method is designed to exploit the natural somatotopic organization and functional separation of fibers into fascicular groups within peripheral nerve. Interfacing at both the intra- and extra-fascicular levels also results in a high level of redundancy to mitigate the effects of electrode damage common in chronic peripheral nerve interfaces.
To date, we have implanted chronic electrodes of this design in the forearms of five human subjects with upper extremity amputations. Here we report on the sensory percepts reported by these subjects during stimulation of individual fascicles within the median or ulnar nerve. During the implantation procedure, intraoperative functional testing was used to broadly classify each fascicle of interest as being comprised of primarily sensory, primarily motor, or mixed sensory and motor fibers. Throughout the implant period, stimulation of sensory fascicles primarily produced cutaneous sensations, including light touch, pressure, and vibration. Stimulation of motor fascicles often produced proprioceptive sensations referring to muscle contraction, joint position, or movement. The size and location of these percepts within the hand also varied consistently based on the fiber type contained in the stimulated fascicle.
The ability to form redundant, chronic interfaces with individual fascicles of peripheral nerve provides unique opportunities to selectively activate the nervous system. This methodology has broad application to both stimulation and recording in peripheral and cranial nerves.

Disclosures: C.K. Overstreet: None. **J. Cheng:** None. **E.W. Keefer:** None.

Poster

761. Brain-Computer Interface: Stimulation for Sensation

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 761.10/M4

Topic: E.05. Brain-Machine Interface

Support: NSF Award 1847315

Title: Vns enhances thalamic information transmission through control of noradrenergic and cholinergic systems

Authors: *C. RODENKIRCH, Q. WANG;
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Abstract: Vagus nerve stimulation (VNS) has long been used to modulate brain circuit dynamics to treat seizure and depression in clinical settings. Previous work has also suggested that VNS can facilitate rehabilitation through its effects on neural plasticity. Further, VNS has been shown to enhance memory and learning via its effects on the acetylcholine and locus coeruleus-norepinephrine (LC-NE) systems. However, little is known about the effect of VNS on

sensory processing. Here, we examined the effect of VNS on thalamic feature selectivity and information transmission in the rodent vibrissa system. We recorded single-unit activity in the ventral posteromedial (VPm) nucleus of the thalamus, an early stage of the rat's vibrissa pathway, in response to repeated presentations of a 15 s block of frozen white gaussian noise whisker stimulation. During these recordings, we randomly cycled through varying VNS patterns (off, 30 Hz for 30 seconds followed by 90 seconds off, 30 Hz for 3 seconds followed by 7 seconds off, and 10 Hz continuous). Each stimulation condition period lasted for 180 seconds and was repeated multiple times (2-6 repetitions). 75 seconds of deadtime followed any stimulation condition to allow for the system to reset. The feature selectivity of each recorded neuron was then estimated separately for each of the VNS activation conditions using spike-trigged reverse correlation analysis. Our preliminary data showed that VNS produced similar effects on thalamic sensory processing as the effects we observed with direct LC activation. In particular, VNS caused a dramatic reduction in the occurrence of bursting activity within the VPm, indicating decreased calcium T-channel activity. Using information theory to quantify the information VPm spikes transmit about the absence/presence of features in the received stimulus, we found that VNS dramatically increased both information transmission efficiency (bits/spike) and rate (bits/second). Pharmacological manipulations were performed to tease apart the role of the noradrenergic and cholinergic systems in this VNS-induced enhancement. Taken together, our preliminary results suggest that certain patterns of VNS can be used to improve sensory-related information transmission via optimizing the coding properties of neurons in the early stage of sensory pathways.
The authors would like to thank Kilgard and Kronoer Labs for sharing their VNS electrode design. This project was supported by NSF Award 1847315.

Disclosures: C. Rodenkirch: None. **Q. Wang:** None.

Poster

761. Brain-Computer Interface: Stimulation for Sensation

Location: Hall A

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Program #/Poster #: 761.11/M5

Topic: E.05. Brain-Machine Interface

Support: European Research Council 2017-STG 759998 (FeelAgain)

Title: Biomechanical analysis of data from transfemoral amputees with a bionic leg restoring neural sensory feedback

Authors: *G. VALLE[1,2], F. M. PETRINI[1], T. STIEGLITZ[3], M. BUMBASIREVIC[4], S. RASPOPOVIC[1];
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Biomed. Microtechnology, IMTEK-Dept Microsystems Eng, Univ. of Freiburg, Freiburg, Germany; [4]Orthopaedic Surgery Dept., Sch. of Med. Univ. of Belgrade, Belgrade, Serbia

Abstract: Leg amputation destroys the sensory-motor communication between the central nervous system and the environment during standing and walking. Lower-limb amputees rely on very limited and uncomfortable haptic feedback from the stump-socket interaction to monitor ground and obstacles contact, climb stairs, or walk in uneven terrains. The lack of sensory feedback causes several impairments to patients that risk falls, have decreased mobility, increased cognitive load during walking, do not perceive the prosthesis as part of their body (low embodiment) resulting often in prosthesis rejection. In upper-limb amputees, neural interfaces allowed to restore somatotopic sensations, thanks to the direct nerve stimulation and to the connection between nervous structures and robotic hand prosthesis. Considering the highly-disabling clinical condition of trans-femoral amputees, we decided to translate this approach overcoming many scientific and technological barriers. Indeed, it has never been proved that the neural stimulation by implantable neural interfaces can evoke sensations from missing leg and foot, also exploitable in a bionic leg in real-time. In this work, we developed a lower-limb prosthesis restoring sensory feedback by means of neural stimulation injected through Transversal Intraneural Multichannel Electrodes (TIME) implanted in the sciatic nerve. The stimulation was driven by the readout of pressure sensors positioned under the prosthetic foot in a sensorized insole, and an encoder embedded in the prosthetic knee. Two trans-femoral amputees were involved in this study performing motor tasks where their mobility was investigated. We perform the biomechanical and signal analysis of kinematic and dynamic data acquired with wearable sensors. Very promising results showed the clinical and functional benefits provided by restoring neural sensory feedback to lower limb amputees. Our findings indicate a clear path towards the development of a new sensory-enhanced leg neuroprostheses to improve life of people with amputations.

Disclosures: G. Valle: None. **F.M. Petrini:** None. **T. Stieglitz:** None. **M. Bumbasirevic:** None. **S. Raspopovic:** None.

Poster

761. Brain-Computer Interface: Stimulation for Sensation

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 761.12/M6

Topic: E.05. Brain-Machine Interface

Support: This work was sponsored by the Defense Advanced Research Projects Agency (DARPA) Biological Technologies Office (BTO) HAPTIX program through the Space and Naval Warfare Systems Center, Pacific Contract No. N66001-15-C-4016.

Title: Bi-directional control and sensory restoration solution for amputees

Authors: *E. W. KEEFER, III[1], C. OVERSTREET[1], J. CHENG[2], Q. ZHAO[3], Z. YANG[3]; [1]Nerves Inc., Dallas, TX; [2]Plastic Surgery, UTSW Med. Ctr., Dallas, TX; [3]Univ. of Minnesota Twin Cities, Edina, MN

Abstract: We have accumulated 3+ years of human amputee data from 6 subjects to date in the DARPA HAPTIX program using electrodes surgically targeted to specific fascicles of the ulnar and median nerves. Using our unique electronics and deep learning-based decoding strategy, we have for the first time allowed amputees completely intuitive control of individual prosthetic digits. The amputee-machine interface is truly bi-directional, in that the computer uses the neural signal to interpret the intent of the amputee to move individual fingers or make gestures, and the amputee selects between different AI models to personalize and tune his experience while controlling the prosthetic digits based upon the "feel" of the model response to his movement intent. The major focus of our sensory stimulation work has been to develop methods of providing functionally-relevant feedback of interactions between the prosthesis and the external environment. This is a multi-faceted challenge, requiring innovations in stimulation technique, sensorization of prosthetic devices, and understanding of the psychophysics of artificial sensation. Effective multichannel stimulation is critical for sensory-capable prosthetic hands with multiple degrees of freedom. The sensations induced by interleaved multichannel stimulation can differ wildly from the sum of the sensations evoked by discrete stimulation on a single electrode; however, little attention has previously been devoted to understanding the sensory effects of multichannel stimulation.

We have developed a comprehensive system containing the following interdependent components: (1) Motor control derived from a novel peripheral nervous system (PNS) interface for individual digit control obtained through surgically targeting specific fascicles of forearm nerves. (2) Neural decoding based on a novel machine learning algorithm that critically reduces the amount of patient effort and training time yet provides high decoding performance. (3) Sensory feedback by closed-loop stimulation through selective and specific surgical targeting of neural interfaces to discrete tactile and proprioceptive neural components. The result is a robust, reliable, and intuitive interface for dexterous prosthetic control with tactile and proprioceptive sensory feedback where the human subjects provide cognitive functions, which are supplemented and enhanced by the great computational power provided by the AI. The human subjects adapt to the AI algorithm for better performance, and new data are generated to allow the AI to better support the human subject (true man-machine interactive learning).

Disclosures: E.W. Keefer: A. Employment/Salary (full or part-time):; Nerves Incorporated. **C. Overstreet:** A. Employment/Salary (full or part-time):; Nerves Incorporated. **Z. Yang:** None. **Q. Zhao:** None. **J. Cheng:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Nerves Incorporated.

Poster

761. Brain-Computer Interface: Stimulation for Sensation

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 761.13/M7

Topic: E.05. Brain-Machine Interface

Support: Research was sponsored by the U.S. Army Research Office and the Defense Advanced Research Projects Agency (DARPA) was accomplished under Cooperative Agreement Number W911NF-15-2-0016.

Title: Closed-loop stimulation of cervical spinal cord and dorsal roots in upper-limb amputees to enable sensory discrimination

Authors: *S. CHANDRASEKARAN[1], A. C. NANIVADEKAR[2], D. M. WEIR[1], E. R. HELM[1], M. L. BONINGER[1], J. L. COLLINGER[1], R. A. GAUNT[3], L. E. FISHER[3];
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Abstract: In an effort to provide meaningful sensory feedback in upper-limb amputees, we electrically stimulated the dorsal spinal cord and roots (DSCR) using FDA-cleared spinal cord stimulation (SCS) leads. Three 16-contact SCS leads were placed percutaneously into the lateral epidural space targeting the C6-C8 roots. Stimulation was delivered through the SCS leads using a custom stimulator for up to 4 weeks following implant, after which the electrodes were removed. Here we show the receptive fields, detection thresholds and just-noticeable differences (JNDs) measured using a structured reporting system from two upper-limb amputees. In both subjects, increasing stimulation amplitude and frequency evoked a linear increase in the perceived intensity within the ranges tested (1-6 mA and 20-300 Hz) while increasing pulse width showed an asymptotic change in perceived intensity. JNDs showed a strong dependence on the stimulus amplitude in accordance with Weber's law. We also carried out closed-loop experiments, where the subjects were asked to interact with an object using a sensorized DEKA hand or a virtual hand in MuJoCo and determine its size or compliance. Stimulation amplitude was mapped either linearly or exponentially to force data from the sensorized prosthesis. One subject used a DataGlove worn on her contralateral intact hand to control the prosthesis in a proportional fashion while the other subject used EMG signals from the residual limb to control grasp closing at constant velocity. With DataGlove control, the subject was consistently more adept at determining object size (62% and 74% mean accuracy in the real and virtual world task scenarios, respectively) than object hardness (46% mean accuracy in MuJoCo). With constant velocity myoelectric control, the other subject achieved a higher accuracy level in determining object hardness (72% and 53% mean accuracy in the two scenarios, respectively) but could not perform better than chance (33% accuracy) for determining object size in either of the task scenarios. Thus, DSCR stimulation can provide information for both contact detection and object

compliance but it might be important to design the right control strategy to achieve maximal accuracy in functional tasks. In conclusion, stimulation of the DSCR can evoke sensory percepts in the missing limb which could be utilized with minimal training by the subject for control of a prosthesis.

Disclosures: S. Chandrasekaran: None. **A.C. Nanivadekar:** None. **D.M. Weir:** None. **E.R. Helm:** None. **M.L. Boninger:** None. **J.L. Collinger:** None. **R.A. Gaunt:** None. **L.E. Fisher:** None.

Poster

761. Brain-Computer Interface: Stimulation for Sensation

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 761.14/M8

Topic: E.05. Brain-Machine Interface

Support: WM Keck Foundation Medical Research Program
OHSU-UO Collaborative Seed Grant

Title: Retinal implants with vertically aligned carbon nanotube pillar arrays for *in vivo* retinal studies

Authors: *K. ZAPPITELLI[1], J. STODDARD[2], R. TAYLOR[1], T. MCGILL[2], B. ALEMÁN[1]; [1]Univ. of Oregon, Eugene, OR; [2]Oregon Hlth. and Sci. Univ., Portland, OR

Abstract: Microelectrode array (MEA)-based retinal implants provide a valuable means to counteract vision loss due to retinal degenerative diseases. Penetrating electrodes—micrometer-scale, needle-like electrodes that penetrate deep into the retinal tissue—promise to improve MEA implants because they allow for closer proximity to the target neurons, thereby decreasing the stimulation threshold and alleviating inflammation. Vertically aligned carbon nanotubes (VACNTs) are an attractive material for penetrating electrodes because of their excellent biocompatibility and neural stimulation properties, and their intrinsic ability to form mechanically stable, high-aspect-ratio structures. Despite their promise, retinal implants with VACNTs have not been assessed *in vivo*. A key obstacle to *in vivo* work has been to create implants that simultaneously satisfy the physical size requirements (sub-millimeter) for surgical implantation into rodents and the synthesis constraints of high-aspect-ratio VACNT structures, which, although strong, are also mechanically flexible and delicate. Therefore, many fundamental questions remain about the *in vivo* structural integrity and chemical viability of VACNT electrodes and the corresponding *in vivo* physiological response. In this work, we develop a robust procedure to build passive silicon implants with patterned VACNTs for *in vivo* retinal studies. We make implants with lateral dimensions below a millimeter, and we use high-temperature chemical vapor deposition (CVD) to grow VACNT “forests” (which largely cover

the implant surface) and penetrating electrode structures by patterning VACNT pillar arrays of various heights, diameters, and spacing. We then surgically insert the VACNT and bare silicon control implants into the subretinal space of an anesthetized rat. Post-surgery, we use high-resolution optical coherence tomography to image the fundus to confirm implant placement and lack of adverse surgical events (e.g. subretinal hemorrhaging) and to quantify the degree to which the different VACNT structures remained intact. This work makes the crucial first step towards assessing the viability of VACNTs as an electrode material in MEA-based retinal implants. In the future, we aim to use this approach to identify the optimal pillar penetration depth that simultaneously maximizes electrode stability and minimizes structural reorganization and immune response of the retina post-implantation.

Disclosures: K. Zappitelli: None. **J. Stoddard:** None. **R. Taylor:** None. **T. McGill:** None. **B. Alemán:** None.

Poster

761. Brain-Computer Interface: Stimulation for Sensation

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 761.15/M9

Topic: E.07. Rhythmic Motor Pattern Generation

Support: DARPA N66001-15-C-4038

Title: Neural stimulation eliciting sensation activates reflex pathways in lower-limb amputees

Authors: *H. CHARKHKAR[1,2], K. H. CHENG[1,2], N. S. MAKOWSKI[3,2], R. J. TRIOLO[1,2]; [1]Case Western Reserve Univ., Cleveland, OH; [2]Louis Stokes Cleveland VA Med. Ctr., Cleveland, OH; [3]MetroHealth Med. Ctr., Cleveland, OH

Abstract: Sensory feedback including cutaneous and proprioceptive inputs from the foot and ankle plays an important role in locomotion and stability. Compared to able-bodied individuals, lower-limb amputees (LLAs) have a higher fall risk and exhibit gait abnormalities which may result in part from lack of proper sensory feedback from the missing limb. Electrical stimulation of peripheral nerves in the residual limb elicit sensations referred to the missing limb and could provide LLAs with feedback about plantar pressure of the prosthetic foot. However, it is unknown whether neural stimulation to elicit sensation activates reflex pathways. This study investigated the activation of such pathways by examining changes in activity of selected muscles in the intact and residual limbs during peripheral nerve sensory stimulation in a LLA. Electrical stimulation was delivered via nerve cuff electrodes implanted in the residual limb of a transtibial amputee on pre-branch sciatic and post-branch tibial nerves. Stimulation elicited tactile sensation or proprioception. The reported proprioception included sensation of residual muscle movement or movement at the ankle. Surface electromyograms (EMG) were collected in

both legs from tibialis anterior (TA), medial gastrocnemius (MG), bicep femoris longus (BF), and vastus medialis (VM) muscles. The participant was instructed to either stand straight or flex his knee about 20 degrees to stretch the quadriceps. Each trial consisted of 2s of pre-stimulation baseline followed by 3s of stimulation. EMG signals were amplified, digitized, and then filtered to remove artifacts. EMG Mean absolute value (MAV) was calculated for baseline and stimulation phases of each trial; statistical significance was determined by a two-tailed paired t-test.
Compared to baseline, MAVs for BF and VM on the affected side were increased ($p<0.05$) with no changes in MAV on the intact limb during standing straight. However, when the same stimuli were applied during a flexed stance, EMG decreased for BF and MG on the intact side ($p<0.01$). Findings suggest activation of crossed extensor circuitry during nerve stimulation while quadricep muscles are slightly stretched. Repetition will determine if these results generalize, but preliminary results indicate direct-nerve interface for sensory restoration in a LLA activates reflex circuitry that could bilaterally affect locomotion dynamics.

Disclosures: H. Charkhkar: None. **K.H. Cheng:** None. **N.S. Makowski:** None. **R.J. Triolo:** None.

Poster

762. Posture and Gait II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 762.01/M10

Topic: E.06. Posture and Gait

Support: NSF 1535036
AHA 15SDG25710041

Title: Explicit adjustment of step timing during split-belt walking reveals interdependent recalibration of movements in space and time

Authors: *M. GONZALEZ-RUBIO, N. F. VELASQUEZ, G. TORRES-OVIEDO;
Dept. of Bioengineering, Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Several studies have shown that spatiotemporal features of walking can be adapted by interacting with novel environments, such as walking with the legs moving at different speeds (i.e., split-belt walking). It is unclear the degree to which such recalibration of walking movements in the spatial and temporal domains is interdependent. In this study we aimed to determine the interdependence between the spatial and temporal control of the limbs during walking. We hypothesized that spatial and temporal inter-limb features are controlled independently based on previous studies demonstrating their dissociation. To test this hypothesis, subjects walked on a split-belt treadmill, which requires the adaptation of spatial and temporal

gait features. We further altered the adaptation of one domain and observed the impact on the adaptation of the other domain. We used visual feedback to manipulate either "where" (spatial feedback group) or "when" (temporal feedback group) subjects landed their feet as they walked in the split-belt condition. The steady state during split-belt walking and subsequent after-effects of spatial and temporal features in the feedback groups were contrasted with those of a control group, who walked in the split-belt condition without any specific instruction (n=7 in each group). We computed step time and step position, which are gait parameters known to quantify adaptation and after-effects of the spatial and temporal control of the limb. Separate two-way repeated measures ANOVAs were used to contrast outcome measurements for the control group to each feedback group. We confirmed that explicit adjustments of step position had a domain-specific effect (i.e., reduced steady state: $p<0.01$ and after-effects: $p<0.01$ of step position compared to controls, but not the step time's steady state: $p=0.39$; after-effects: $p=0.9$). Surprisingly, this dissociation was not maintained when step time was explicitly altered. In other words, the temporal feedback group had reduced steady state ($p<0.01$) and after-effects ($p<0.01$) in step position and step time compared to the control group. In sum, we observed that motor adaptation in the spatial domain was susceptible to changes in the temporal domain, whereas motor adaptation in the temporal domain was resilient to adjustments in the spatial domain. Our results suggest a hierarchical organization such that explicit changes to temporal deficits cannot occur without modifying the spatial control of the limb, which informs the treatment of patients with spatial and/or temporal asymmetries.

Disclosures: M. Gonzalez-Rubio: None. **N.F. Velasquez:** None. **G. Torres-Oviedo:** None.

Poster

762. Posture and Gait II

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Topic: E.06. Posture and Gait

Support: NIH T32GM081760
NSF 1535036
PITT STRIVE fellowship

Title: Interaction between healthy aging and walking speed on the generalization of locomotor adaptation

Authors: *D. M. MARISCAL, C. J. SOMBRIC, H. M. HARKER, G. TORRES-OVIEDO; Dept. of Bioengineering, Univ. of Pittsburgh, Pittsburgh, PA

Abstract: We have previously shown that older adults have greater after-effects overground following split-belt walking compared to young individuals (Sombric et al., 2017), suggesting

that healthy aging increases the generalization of recalibrated movements across walking conditions. However, in the aforementioned study old and young participants walked at relatively slow speeds, which could influence the generalization of after-effects overground, as it does on the treadmill (Vasudevan and Bastian, 2010). Thus, in this study we investigated the extent to which healthy aging and walking speed regulated the generalization of adapted movements across different walking situations. We hypothesized that subjects would generalize more if they were adapted around their preferred walking speed. This hypothesis was formulated on the basis that unnatural speeds would be used as context-specific cues that will reduce generalization. To test this hypothesis, we compared the magnitude of after-effects overground following split-belt walking when older (n=16, age: 73.13±5.40 yrs.) and younger (n=16, age: 20.81±6.02 yrs.) adults walked on a split-belt treadmill at either faster or slower speeds than their self-selected speed. All groups experienced a gradual split-belt perturbation (i.e., gradual change from 1:1 to 2:1 speed ratio) because this type of adaptation favors generalization (Torres-Oviedo and Bastian, 2012). To assess generalization subjects walked overground following a split-belt adaptation paradigm. Kinematic data were recorded to characterize the after-effects of step position and step time (Finley et al., 2015), which are spatial and temporal asymmetry measures known to generalize differently (Sombric et al., 2017). Two-way ANOVA was used to compare overground after-effects across groups. We found that older adults generalized more step position (spatial parameter) when they were adapted at slower speeds, whereas young adults generalized more this gait parameter when adapted at faster speeds (interaction: p=0.001). In contrast, in the temporal domain (step time) older adults generalized more than young adults, regardless of the walking speed at which they were adapted (Age: p=0.007). Our results indicated that healthy aging and walking speed affect the generalization of split-belt walking patterns across environments. Therefore, treadmill-assisted rehabilitation would be more effective in older populations if they are adapted at slower speeds, whereas younger adults need to be adapted at faster speeds.

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Poster

762. Posture and Gait II

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Program #/Poster #: 762.03/M12

Topic: E.06. Posture and Gait

Support: NSF BRIGE 1342183
NSF 1535036

Title: Human perception of walking speed asymmetry and its adaptation over the course of split-belt walking

Authors: *P. A. ITURRALDE[1], G. TORRES-OVIEDO[2];
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Abstract: Mismatch between predicted and actual sensory information is thought to drive the recalibration of internal models for motor control, and perceptual adaptation has been used as a proxy to assess this recalibration process [Synofzik et al. 2008, Izawa et al. 2012]. Split-belt walking with one leg moving faster than the other has been shown to change subjects' perception of this speed asymmetry. However, it remains unclear what is the human ability to detect such asymmetry, and thus, how it changes as a result of sensorimotor adaptation. To address these questions we combined a two-alternative forced-choice and a belt-speed matching tasks [Vazquez et al. 2015]. In experiment 1 (N=9), we characterized the baseline accuracy of belt-speed difference perception in a cohort of young, healthy subjects. We found that humans can detect speed differences as small as 25mm/s (<2.5% of mean walking speed) with above chance levels (64% accuracy, p=0.018). Also, differences of 100mm/s and higher were detected with >80% accuracy. Moreover, subjects' reaction time was predictive of response accuracy even after accounting for task difficulty (p=1.2e-5), suggesting that reaction time could be used as a proxy for confidence in the participant's response. Computational modeling of the active perceptual task through a drift-diffusion model was unable to characterize this relation between accuracy, reaction time, and task difficulty. We also observed that in the belt-speed matching component of the perceptual task, subjects were able to reduce the initial speed differences by about 85%, regardless of the initial speed asymmetry. In experiment 2 (N=10), we tracked the adaptation of speed difference perception throughout a split-belt walking adaptation and deadaptation protocol. Subjects were exposed to a split-belt walking environment (905 strides at 1300 & 800 mm/s). At periodical intervals, the same task of experiment 1 was performed. Results show the evolution of perception of belt-speed differences throughout the adaptation and deadaptation periods. We observed perceptual aftereffects during post-adaptation of at least 200mm/s (population median), which decayed exponentially with a time constant of approximately 93 strides. We conclude that humans are able to perceive very accurately speed differences between their legs of much smaller magnitude than previously reported [Lauziere et al. 2014, Hoogkamer et al. 2015]. Further, our speed matching task enabled us to confirm the perceptual aftereffects following split-belt walking and revealed their temporal dynamics during adaptation and deadaptation.

Disclosures: P.A. Iturralde: None. **G. Torres-Oviedo:** None.

Poster

762. Posture and Gait II

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Program #/Poster #: 762.04/M13

Topic: E.06. Posture and Gait

Support: NSERC
FRQS
FCQ

Title: Using electrically-evoked ankle pain to study gait adaptations to fixed versus movement-dependent pain duration: A model of musculoskeletal lower limb pain

Authors: *R. JEFFREY-GAUTHIER[1], M. BERTRAND-CHARETTE[1], C. MERCIER[1], J.-S. ROY[1], L. J. BOUYER[2];
[1]Rehabil. Dept - CIRRIS, [2]Rehabil. Dept- CIRRIS, Univ. Laval Fac Med., Quebec, QC, Canada

Abstract: INTRODUCTION: Following musculoskeletal (MSK) injuries, pain avoidance strategies modify movement execution, including gait. It has been proposed that such modifications may lead to maladaptive behaviors and to pain chronicization. To study this theory, a better understanding of the physiological basis of movement adaptation to pain is needed. The first aim of this study was therefore to develop an experimental paradigm that simulate MSK pain during gait. A second aim was to assess the effect of fixed versus movement-dependent pain duration, to better understand the consequences of a mismatch between gait adaptation and pain relief. Our hypotheses were that 1) phasic pain would alter the gait pattern (temporal and EMG parameters) and 2) gait adaptation would differ for fixed versus movement-dependent pain.
METHODS: Six healthy participants took part in a single experiment. They had to walk normally on a treadmill at 4 km/h for 6 bouts of 3-min duration. EMG activity from flexor (rectus femoris, biceps femoris, tibialis anterior) and extensor (vastus lateralis, gastrocnemius medialis, soleus) muscles of both lower limbs were recorded and right and left foot load distributions were measured with insole force sensors matrices. Painful trains of electrical stimulations (intensity of 2-4/10), were delivered to the right lateral malleolus during bouts 3 and 5. Pain conditions (matched or unmatched duration to right heel loading) were presented in randomized order. Repeated-measure ANOVAs were used to examine foot pressure distribution and EMG activity changes between pain conditions and baseline.
RESULTS: Stimuli intensity ranged between 9.5 to 13.5 mA, and were described as a electrical, sharp or stabbing pain in the malleolus area. Regardless of the pain condition, pain altered gait in all participants. The foot load distribution pattern was modified: right heel load duration and right heel load peak were significantly decreased during both pain bouts compared to baseline.

Step duration was decreased and cadence, increased. Extensor muscles activation was prolonged during late stance. Flexor muscles activation was not altered.
DISCUSSION: These results suggest that electrical stimulation can be used as a model for investigating movement adaptation to musculoskeletal-like pain. Electrically-evoked phasic pain alters gait, regardless if pain duration was dependent or not on heel loading.
These findings are relevant to the understanding of movement adaptation to pain and will be used to investigate mechanisms underlying motor adaptation to MSK pain.

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Poster

762. Posture and Gait II

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Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 762.05/M14

Topic: E.06. Posture and Gait

Support: NSF IIS160811

Title: Effect of over-actuation on neuromechanical model of rat hindlimb with biarticular muscles

Authors: *K. DENG[1], A. J. HUNT[2], R. D. QUINN[1];
[1]Mechanical and Aerospace Engin., Case Western Reserve Univ., Cleveland, OH; [2]Portland State Univ., Portland, OR

Abstract: This work compares two neuromechanical models of rat hind-limb sagittal walking. One model uses antagonistic muscle pairs (extensor and flexor) actuating each joint in the sagittal plane, and the second introduces biarticular muscles into the biomechanical body. The muscle number of each limb increased from 6 to 8 in the second model, and 3 of them are biarticular muscles, BFP (biceps femoris Posterior), RF (Rectus femoris), and GA (Gastrocnemii). Each model is controlled by a synthetic nervous system composed of a two-level central pattern generator. In order to test the stability of the models, different perturbations were applied to the network. These include inhibitory tonic stimuluses to the synthetic nervous system and forces applied to the limb. Results show that the neuromechanical model with biarticular muscles exhibit more robustness than the monoarticular model when external force was applied to the body, and there is no significant difference when a stimulus is applied to the synthetic nervous system. In addition, the biarticular muscle model shows better kinematic matching when compared to animal data. It turns out over-actuating the model not only reifies the biomechanical body, but also makes it more stable for several reasons. In the monoarticular model, the joint coordination is only relying on proprioceptor feedback to mediate the phase of walking rhythm,

so the stability of the model is dependent on the robustness of the synthetic nervous system. However, in the biarticular muscle model, the biarticular muscles link related joint motions during walking. When joints are linked together through muscles, rejection of a perturbation at one joint can be distributed through the whole leg. Additionally, biarticulate muscles can serve multiple purposes through the course of a step. For example, at the start of stance, the BFP provides hip extensor force, however when switching from stance to swing, the BFP also produces flexion in the knee, assisting in lifting the leg from the ground.

Disclosures: K. Deng: None. **A.J. Hunt:** None. **R.D. Quinn:** None.

Poster

762. Posture and Gait II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 762.06/M15

Topic: E.06. Posture and Gait

Title: Balance impairment investigation of pediatric medulloblastoma patients with wearable motion capture system

Authors: *M. B. KILICOGLU[1], M. TANRIVERDI[2], F. B. CAKIR[2], H. ARGUNSAH BAYRAM[1];
[1]Acibadem Mehmet Ali Aydinlar Univ., Istanbul, Turkey; [2]Bezmialem Vakif Univ., Istanbul, Turkey

Abstract: Objective: The goal of this study was to assess balance impairment of pediatric medulloblastoma patients based on kinematic data, which has been collected with wearable motion capture (WMC) system and compare the results with current assessment tools used by physical therapists. This study hypothesized that these patients have balance impairment at concerning degrees, which cannot be detected only by commonly used subjective forms.
Methods: 25 children with brain tumor were recruited with the exclusion of the ones who had communication problems. Patients and their families were informed about the study protocol and signed the informed consent form that has been approved by the Institutional Review Board. The kinematic data was collected with Xsens MVN (Xsens Technologies BV ® (Netherlands)), which allows an unrestricted, 3D and spontaneous gait analysis. WMC sensors were placed on participant's body as described by the manufacturer. After calibrating the WMC system, data collected during standard 10-meter walk test at self-selected walking speed for 2 minutes and single leg stance assessment tests.
Results: According to the preliminary results, sternum orientation degree values showed that patients had foot drop during the late-stance phase due to improper and insufficient ankle joint dorsiflexion and knee joint flexion/extension. Additionally, stance phase knee joint flexion, which is critical for efficient energy flow in lower extremity, was not observed. Paired t-test

analysis revealed that the patient's knee joint range of motion was significantly asymmetrical throughout the data collection session when the walking pattern was compared with the control group (61.995 ± 3.497 SD vs. 54.810 ± 1.661 SD; t (0.05,29) = 10.172, $p<0.001$).
Conclusion: The ability to provide stability and balance is critical for the neurological and orthopedic diseases rehabilitation, because the goal is to achieve functional independence during ambulation. Pediatric brain tumor patients have difficulties in coordination and balance problems while performing daily life activities, and these not only affect their motivation, but also limit their motor abilities in daily life. The absence of gait symmetry, which is the ratio of kinetic and kinematic parameters between right and left extremities, results in differences in muscle contraction, balance and biomechanical parameters during mobilization. Accurate knowledge of static and dynamic proprioception is essential to maintain proper body weight and sustain normal ambulation and in order to achieve this information innovative engineering techniques should be integrated to conventional physical therapy practices.

Disclosures: M.B. Kilicoglu: None. **M. Tanriverdi:** None. **F.B. Cakir:** None. **H. Argunsah Bayram:** None.

Poster

762. Posture and Gait II

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Topic: E.06. Posture and Gait

Support: NIH NINDS R01NS102333
NIH NIA R01AG057330
NIH BRAIN Initiative U19NS104655

Title: Optogenetic activation and silencing of leg motor neurons and proprioceptors alters walking dynamics in *Drosophila melanogaster*

Authors: *E. S. DICKINSON, J. C. TUTHILL;
Univ. of Washington, Seattle, WA

Abstract: Locomotion requires rapid integration of proprioceptive sensory cues with ongoing motor rhythms. However, it has been challenging to assess the role of specific sensory and motor neurons in the coordination of locomotor behaviors like walking. In this study, we combined optogenetics and quantitative analysis of walking behavior to test the function of genetically-defined populations of leg proprioceptors and motor neurons in the fruit fly, *Drosophila melanogaster*. Walking in the fly is fast and complex, requiring the coordination of five leg segments across six legs with step cycles of just 30 ms. Each fly leg is controlled by 52 motor neurons and monitored by 135 proprioceptors. We used visual stimuli to elicit forward running

and turning in tethered flies on a frictionless spherical treadmill. We measured the walking dynamics of flies while optogenetically manipulating the activity of tibial proprioceptors and motor neurons with a 532nm laser focused on the fly's front left leg. We activated genetically-defined neurons using a red-shifted channelrhodopsin, CsChrimson, and silenced neurons using an anion channelrhodopsin, GtACR1. We found that sustained activation or inhibition of specific leg proprioceptors interrupted all locomotion, leaving the fly unable to run or turn. In contrast, activating or silencing specific motor neurons led to subtle changes in forward walking and turning. Thus, flies appear to overcome perturbations to motor output but not proprioceptive feedback. These results reveal the critical role of sensory feedback in coordinating walking behavior and suggest that there exists a high level of redundancy within the leg motor control system.

Disclosures: E.S. Dickinson: None. **J.C. Tuthill:** None.

Poster

762. Posture and Gait II

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Program #/Poster #: 762.08/M17

Topic: E.06. Posture and Gait

Support: NIH/NICHD R01HD082216

Title: Enhanced variation in lateral pelvis assistance force during walking may facilitate weight shifting in individuals post-stroke

Authors: *M. WU[1,2], C.-J. HSU[3], J.-T. LIN[3], W. DEE[3];
[1]Shirley Ryan Ability Lab- Chicago, Chicago, IL; [2]Bioengneering, Univ. of Illinois at Chicago, Chicago, IL; [3]Legs and Walking Lab., Shirley Ryan Ability Lab., Chicago, IL

Abstract: Individuals post stroke often show insufficient weight shifting toward their paretic side during walking due to the weakness of the paretic leg muscles. Insufficient weight shifting has been shown to be correlated to impairment in walking function in individuals post stroke. Previous studies indicated that increased variability of training may improve motor learning. The goal of this study was to determine whether applying varied assistance force to the pelvis was effective in facilitating weight shifting toward the paretic side in individuals post-stroke. We hypothesized that compared to abrupt pelvis assistance force, applying varied pelvis assistance force would be more effective in facilitating weight shifting toward the paretic side during walking in individuals post-stroke. Five individuals with chronic (> 6 months) stroke participated in 2 testing sessions. In session 1 (varied condition), participants walked on a treadmill at their comfortable speed without force for 1 minute (baseline), and then a controlled lateral pelvis assistance force was applied to the pelvis toward the paretic side during early stance phase of gait

for 10 minutes (adaptation). Afterward, the force was removed and participants continued to walk on the treadmill for another 1 minute (post-adaptation). The magnitude of force was set at ~8% of body weight, and varied from step to step (variation of peak force ranged from 30% - 100%). In session 2 (abrupt condition), a protocol was similar to session 1 was used except the magnitude of pelvis assistance force was the same from step to step. The order of testing condition was randomized across subjects. The displacement of the pelvis and leg was measured using custom designed position sensors. The primary outcome measure was the maximum pelvis lateral displacement during stance phase. During early adaptation period, increased pelvis displacement toward the paretic side was observed for both conditions, suggesting an improved weight shifting toward the paretic side when the pelvis assistance force was applied. During the late adaptation period, participants gradually reduced their pelvis displacement toward the paretic side for the abrupt force condition, suggesting the weight shifting toward the paretic side was reduced. For the varied condition, the increased pelvis displacement toward the paretic side was still partially retained, suggesting improved weight shifting toward the paretic side was partially retained. This preliminary study indicated that increased variability in the magnitude of lateral pelvis assistance force may enhance motor learning of weight shifting toward the paretic side in individuals post stroke.

Disclosures: **M. Wu:** None. **C. Hsu:** None. **J. Lin:** None. **W. Dee:** None.

Poster

762. Posture and Gait II

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Program #/Poster #: 762.09/M18

Topic: E.06. Posture and Gait

Title: Development of a wearable balance sensor that provides real-time tactile biofeedback and preliminary test results on pediatric brain tumor patient

Authors: *B. YALCIN[1], M. TANRIVERDI[2], F. B. CAKIR[2], M. B. BAYRAM[1], H. ARGUNSAH BAYRAM[1];
[1]Acibadem Mehmet Ali Aydinlar Univ., Istanbul, Turkey; [2]Bezmialem Vakif Univ., Istanbul, Turkey

Abstract: Objective: This study aimed to develop an innovative wearable balance sensor, capable of providing real-time stimulus for maintaining balance and postural control, and investigate the biomechanical and physiological changes of a pediatric brain tumor patient in response to tactile biofeedback.
Methods: A wearable tactile real-time balance biological feedback mechanism was developed, which is intended to be used during the neurological, orthopedic and neuromuscular disease rehabilitation practices and its accuracy and sensitivity were validated with Xsens MVN Awinda

wearable motion capture system. Real-time balance was monitored with Motion Processor Unit 9250, which was placed on patient's sternum. All motors and the MPU were controlled by Raspberry Pi. The innovative real-time balance sensor device is composed of a motion processor unit, microprocessor and four vibration motors. Vibration motors -for front-back-left-right directions, were located between the participant`s under bust and natural waist line with an adjustable strap. Accurate positioning of the motors was obtained by using ergonomic 3D printed cases attached to the participant's body. A 16 year old brain tumor (medulloblastoma) patient, who has undergone surgical intervention, participated in this study. 16 year old healthy subject participated as the control subject. 10 meter walking and single leg stance assessment tests were examined with and without vibrobalance biological feedback device.
Results: IBM SPSS Statistics v21.0 was used to perform the statistical analyses. Paired t-test analysis (two-tailed) revealed that the patient's knee joint range of motion was significantly symmetrical throughout the data collection session when real-time tactile biofeedback was provided to the patient (61.995 ± 3.497 SD vs. 54.810 ± 1.661 SD; $t_{(0.05,29)} = 10.172$, $p<0.001$). Statistically, the effect of the sensor was not found to be significant with the healthy control (71.987 ± 2.178 SD vs. 72.774 ± 0.906 SD; $t_{(0.05,29)} = -1.814$, $p=0.08$).
Conclusions: According to the results, there are significant improvements when haptic and visiual biological feedback is provided during all exercises in the data collection sessions, especially in data of the medulloblastoma patient. Biofeedback is a method of providing real-time feedback to the patient using auditory, visual, and tactile stimulus. Additionally, physician and/or physical therapist can utilize biofeedback mechanisms in order to regulate the gait pattern, correct balance/posture, and thus create personalized physical therapy programs for the patients while regulating the physiological, kinetic and kinematic variables.

Disclosures: B. Yalcin: None. **M. Tanriverdi:** None. **F.B. Cakir:** None. **M.B. Bayram:** None. **H. Argunsah Bayram:** None.

Poster

762. Posture and Gait II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 762.10/M19

Topic: E.06. Posture and Gait

Support: Virginia Horne Henry Fund
University of Wisconsin Graduate School

Title: Intermittent linearity of foot force direction vs center of pressure in quiet standing

Authors: K. NICHOLS, A. LEFRANC, J. BARTLOFF, ***K. G. GRUBEN**;
Univ. Wisconsin, Madison, WI

Abstract: Humans maintain quiet standing by modulating lower limb joint torques to maintain translational and rotational balance in the sagittal plane. Mechanically, joint torque coordination directly maps to the force of the ground on the feet (*F*). Previous research has shown that quiet standing can be characterized as a series of frequency dependent intersection points (*IP*) of *F* (Boehm et al, J Biomechanics 2019). These *IPs* arise from the linearity of band-passed time signals of force direction (approximately *Fx/Fz*) and center of pressure (*xCP*) where *F* tended to intersect above the center of mass (*zCM)* for slow frequencies (below 2Hz) and below *zCM* for fast frequencies. This frequency method was limited as it displayed the average characteristics of *F* behavior over time periods generally longer than 15 seconds. To investigate the presence of *IPs* at shorter time scales, we analyzed short time windows (~0.1 to 1 s) of force direction and *xCP*. We hypothesized that *xCP* and force direction will be modulated so as to have an *IP* and that the height of the *IP* (*zIP*) will correlate with some measure of the amount of or rate of change of *xCP*. Kinetic and kinematic data for quiet standing was analyzed from a public data set of 27 quietly standing humans (Santos & Duarte, PeerJ 2016). Time windows were selected between time points where *xCP* velocity was 0. The principal component of the force direction vs *xCP* was used to calculate the *zIP*. Interestingly, the results showed increases of *zIP* with window duration and *xCP* range. This relationship is similar to the previous results (Boehm et al, J Biomechanics 2019) where window duration correlates with the inverse of frequency (low *zIP* with short duration or high frequency). Using *zIP* as a metric to evaluate balance can be helpful because it reduces the dimensionality of torque coordination from 3+ variables (hip, knee, ankle + vertebral) to one variable, *zIP*. Coordination, expressed as an *IP*, relates to the translational and rotational requirements of balance and can be useful for powered prostheses and biomimetic robotic control, and for accessing and improving rehabilitation of neuromuscular balance problems.

Disclosures: K. Nichols: None. **A. Lefranc:** None. **J. Bartloff:** None. **K.G. Gruben:** Other; K Gruben has ownership interest in KIINCE LLC which develops rehabilitation technology..

Poster

762. Posture and Gait II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 762.11/M20

Topic: E.06. Posture and Gait

Support: Intramural Grants Program-Internal funding from Auburn University

Title: Cognition relates to motor output complexity during a challenging locomotor task in young adults

Authors: S. A. BRINKERHOFF, R. T. FAWCETT, *J. A. ROPER;
Auburn Univ., Auburn, AL

Abstract: Muscle activity during gait can be organized into motor modules, and can increase as task complexity or expertise in movement control increases. We sought to examine the influence of expertise in movement control and cognition on number of motor modules during flat walking and three gait tasks. Sedentary adults (n=11, 2 males), active adults (n=12, 6 males), and 'expert' adults participating in dance or tennis (n=7, 3 males) participated. Three cognitive tests were administered: the Mini-Mental State Exam (MMSE), the Digit Span test, and the Trails Making test. Participants completed four walking tasks: normal walking (GAIT), tandem walking (TANDEM), tandem walking on an 8-foot beam on the floor (BEAM), and walking over stepping stones of various surface area and height (TARGET). Electromyography was recorded unilaterally from the gluteus medius, tibialis anterior, soleus, gastrocnemius, vastus medialis, rectus femoris, and the medial and lateral hamstring of the dominant leg. Non-negative matrix factorization calculated the number of modules needed to account for at least 90% of the total variance in muscle activity. Higher scores on the MMSE were related to a higher number of modules used during GAIT and TARGET. We observed differences in the proportions of sedentary, active and expert adults displaying varying number of modules in TANDEM. Specifically, 46% of sedentary individuals used 4 modules, 58% of active used 3 modules, and 43% of experts used 3 modules. A 3(group) x 4(task) ANOVA resulted in no interaction between group and condition and no effect of group, but there was an effect of condition such that participants used more motor modules when walking over the stepping stones (4.2) than walking over flat ground (3.5), tandem walking (3.5), and beam walking (3.1). This confirmatory study signifies that individuals, regardless of expertise, have higher muscular coordination during step-targeting tasks and heightened muscular coordination is related to high global cognition. We surmise that an important association exists between neural structures governing both movement control and cognitive performance. The precise role and interplay of cognition and movement control remains to be elucidated, and should be explored in further research.

Disclosures: S.A. Brinkerhoff: None. **R.T. Fawcett:** None. **J.A. Roper:** None.

Poster

762. Posture and Gait II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 762.12/M21

Topic: E.06. Posture and Gait

Support: U.S. Department of Defense Grant W81XWH-16-1-0791

Title: Bidirectional control of a sensing powered transtibial prosthesis during walking in the cat

Authors: B. I. PRILUTSKY[1], H. PARK[2], K. OH[3], J. F. DALTON, IV[5], S. P. DEWEERTH[6], M. PITKIN[7,8], *A. N. KLISHKO[4];
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Univ., College Station, TX; [3]Biol. Sci., [4]Georgia Inst. of Technol., Atlanta, GA; [5]Georgia Hand, Shoulder & Elbow, Atlanta, GA; [6]Col. of Engin. and Applied Science,, Lehigh Univ., Bethlehem, PA; [7]Tufts Univ. Sch. of Med., Boston, MA; [8]Poly-Orth Intl., Sharon, MA

Abstract: Despite the availability of the modern multi-degree of freedom powered limb prostheses, their users often are dissatisfied with them due to complex, non-intuitive control and lack of sensory feedback (Ostlie et al. 2012). Recent case studies of bidirectional control of powered prostheses in individuals with upper and lower limb loss have demonstrated drastic improvements in quality of movements (Ortiz-Catalan et al. 2014). We recently developed a sensing powered transtibial prosthesis for the cat (Park et al. 2018) to investigate effects of bidirectional prosthetic control on locomotor mechanics. Here we present results obtained on one cat that had this prosthesis for 20 months. The prosthesis is attached to a percutaneous porous titanium pylon (Pitkin, et al., 2012) implanted into the distal tibia marrow canal. The pylon has a channel inside through which leads of EMG electrodes in implanted residual soleus and tibialis anterior and of a cuff electrode on the residual distal tibial nerve are passed through to connect to a linear actuator and onboard nerve stimulator. Nerve stimulation was triggered when a pressure sensor on the bottom of the prosthetic foot recorded contact with the ground. Three Modes of prosthetic operation were investigated: (1) pressure Mode, in which the linear actuator extended the prosthetic ankle during contact with the ground and flexed it during swing; (2) EMG Mode without stimulation, in which soleus EMG signal was used to control ankle extension during stance while ankle flexion was performed during swing; and (3) EMG Mode with nerve stimulation, in which in addition to Mode 2 the residual distal tibial nerve was stimulated during prosthesis contact with the ground. In total we recorded 346 cycles of overground prosthetic walking. We found that the duty factor of the prosthetic hindlimb was longer for Mode 2 than for Mode 1 or Mode 3 ($p=0.004$-0.050). The relative duration of the double hindlimb support phase with the contralateral hindlimb being the trailing limb was shorter in Modes 1 and 3 than in Mode 2 ($p=0.016$-0.041). We found no difference in peak of vertical ground reaction force of the prosthetic limb between Modes. We concluded that bidirectional control of the transtibial prosthesis modulates locomotor kinematics.

Disclosures: B.I. Prilutsky: None. **H. Park:** None. **K. Oh:** None. **J.F. Dalton:** None. **S.P. DeWeerth:** None. **M. Pitkin:** None. **A.N. Klishko:** None.

Poster

762. Posture and Gait II

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Program #/Poster #: 762.13/M22

Topic: E.06. Posture and Gait

Support: Grant from NIH (R01 NS- 100928)

RFBR grant №19-015-00409
RFBR Grant 17-04-01822

Title: Kinematics of simultaneous bidirectional hindlimbs locomotion in decerebrate cats

Authors: V. LYAKHOVETSKII[1,2], N. MERKULYEVA[1,2,3], O. GORSKII[1], ***P. MUSIENKO**[3,1,2];
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Abstract: The bidirectional (BIDI) locomotion, when one limb moves forward while other simultaneously moves backward, is a highly specific locomotor mode demanding during rotation in stepping or swimming in intact animals (Field, Stein, 1997) and healthy humans, either adults (Choi, Bastian, 2008) or children (Yang et al., 2005). Whether solely the spinal cord and brainstem circuitry may induce BIDI locomotion or the conscious control by the forebrain is necessary for this task? To solve this question, the model of cat (n=6) decerebrated at the precollicular-postmamilar level was used. The hindlimb locomotion was elicited by epidural stimulation of the dorsal surface of the spinal cord. For every animal, the same point of dorsal surface (L6-L7 segments) was used to elicit unilateral forward (FW), unilateral backward (BW), and BIDI stepping. The direction of the hindlimb movements was determined by the direction of movement of the treadmill belts. The kinematics of movements were recorded with the help of reflecting markers.All animals were able not only to unidirectional FW and BW stepping, but also to coordinated BIDI stepping, characterized by a high coefficient of stability of trajectories and low asymmetry of the period of stepping. During BIDI stepping, the hindlimb moving forward (FW-BIDI) was located more rostral than the hindlimb moving backward (BW-BIDI), that is coincided with the hind limbs position during corresponding unidirectional stepping. The angle range in the ankle and hip joints at unidirectional FW walking for both hindlimbs was significantly higher than for unidirectional BW walking. For BIDI walking, the angle ranges of two hindlimbs were differed significantly: the kinematic characteristics of the FW-BIDI hindlimb and BW-BIDI hindlimb were similar to the features of the corresponding unidirectional FW and unidirectional BW stepping. Despite these significant differences in kinematics, both hindlimbs had similar stepping periods. An ability of the decerebrate animals to the BIDI locomotion means that the neuronal circuitries of the spinal cord, brainstem, and cerebellum are enough to control such highly coordinated and extraordinary locomotor task.

Disclosures: V. Lyakhovetskii: None. **N. Merkulyeva:** None. **O. Gorskii:** None. **P. Musienko:** None.

Poster

762. Posture and Gait II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 762.14/M23

Topic: E.06. Posture and Gait

Support: Edward and Barbara Bell Endowed Chair

Title: The HoloLens augmented reality system provides valid measures of gait performance in healthy adults

Authors: *M. MILLER KOOP[1], A. B. ROSENFELDT[1], J. D. JOHNSTON[1], J. QU[1], M. C. STREICHER[1], J. L. ALBERTS[2];
[1]Biomed. Engin., [2]Dept. of Biomed. Engin. and the Ctr. for Neurolog. Restoration, Cleveland Clin., Cleveland, OH

Abstract: Biomechanical measures are the gold standard in the assessment of gait in healthy and neurological populations. Augmented reality systems represent an opportunity to evaluate human movement under more realistic and interactive conditions. A barrier to integrating augmented reality into healthcare is the unknown accuracy in quantification of human movement. This project aimed to determine the accuracy of the HoloLens relative to 3D motion capture in quantifying gait. Ten healthy adults completed nine walking trials (n=3 for slow, medium, and fast speed). Outcome measures included: cumulative walking distance, number of steps, step length and speed. Statistical equivalence testing, using an a-priori threshold of five percent, confirmed biomechanical measures derived from the HoloLens were equivalent to motion capture. Cumulative walking distance from the HoloLens was within 1.5- 2.1% of the motion capture system for all walking speeds. Difference between systems in terms of movement accuracy was less than 3.7 cm across trials. Equivalence in outcomes make the HoloLens appropriate for the quantification of frequently used gait variables to characterize walking performance. Future augmented reality applications have the potential to deliver digital therapeutics to patient populations under more real-world conditions in which movement performance can be quantified.

Disclosures: M. Miller Koop: None. **A.B. Rosenfeldt:** None. **J.D. Johnston:** None. **J. Qu:** None. **M.C. Streicher:** None. **J.L. Alberts:** None.

Poster

762. Posture and Gait II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 762.15/M24

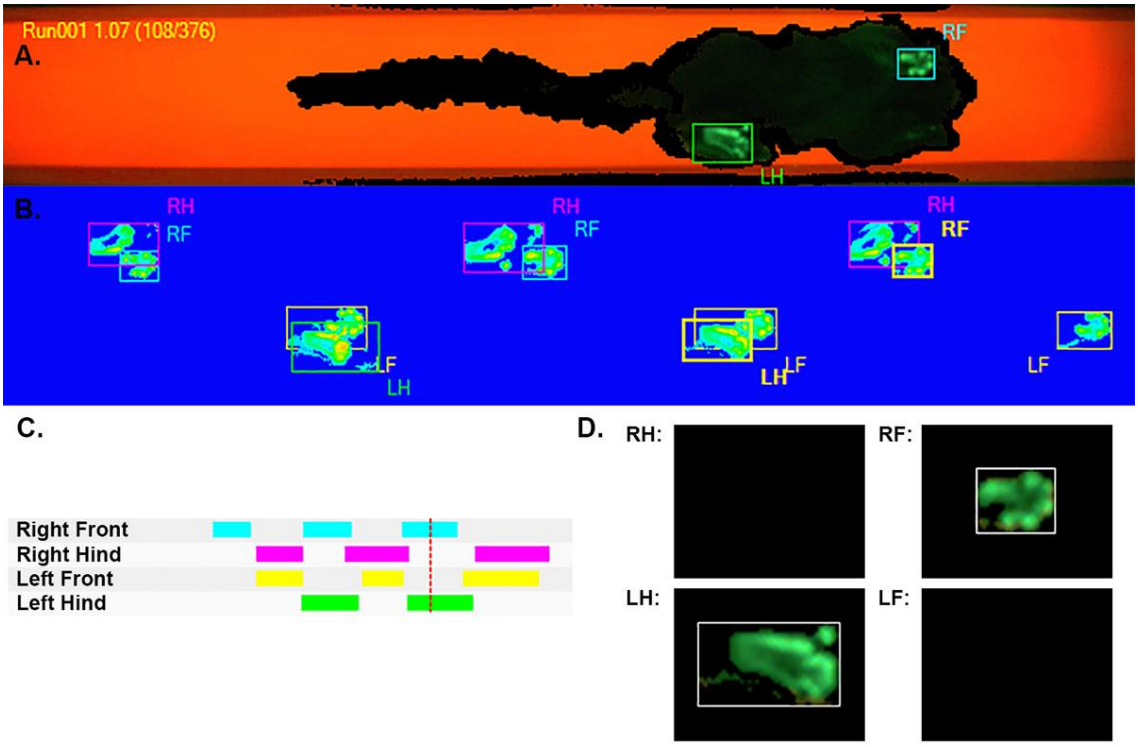
Topic: E.06. Posture and Gait

Support: NIH P51OD011106
NIH R24OD019803
NIH UL1TR002373
NIH KL2TR002374

Title: A novel approach to the spatiotemporal quantification of gait in the common marmoset

Authors: A. BRADFIELD[1], N. SCHULTZ-DARKEN[2], K. MALICKI[2], K. K. AUSDERAU[1], M. E. EMBORG[2], *K. A. PICKETT[1];
[1]Univ. of Wisconsin - Madison, Madison, WI; [2]Wisconsin Natl. Primate Res. Ctr., Univ. of Wisconsin-Madison, Madison, WI

Abstract: In humans, gait evaluation is used as a predictive disability outcome measure as well as an indicator for intervention effectiveness. Parallel methods of gait analysis in nonhuman primate models are essential for clinical translation. The goal of this study was to first assess whether gait data could be reliably collected from common marmosets in a Noldus CatWalk XT10.6 and second, establish a testing protocol to assess gait and the intraindividual variability during repeated testing. **Method:** The CatWalk system was modified and used to assess gait in eight adult common marmoset monkeys across multiple days and trials. Experiment one focused on the refinement of the methological approach and experiment two applied these techniques to a second group of subjects. Data were first analyzed to identify valid runs based on the established criteria. A further analysis examined mean base of support, average stride length, average swing time, and average stance time. **Results**: Raters had a high level of concurrence of usable data across all trials with successful trials including four consecutive hindfoot footfalls, during a continuous, uninterrupted segment of walking. A significant main effect of time ($p<0.001$) but not rater ($p=0.98$) was present with significant interactions for time by subject ($p<0.001$), but not rater per subject ($p=0.538$), time ($p=0.186$), or three-way interaction ($p=0.297$). **Discussion:** The CatWalk system allowed for reproducible, automated and translational locomotor data to be collected at multiple time points with detailed analyses. **Conclusions:** The CatWalk system, similar to those used in humans, can be effectively used to quantify spatiotemporal characteristics of gait in the common marmoset.



Disclosures: **A. Bradfield:** None. **N. Schultz-Darken:** None. **K. Malicki:** None. **M.E. Emborg:** None. **K.A. Pickett:** None. **K.K. Ausderau:** None.

Poster

762. Posture and Gait II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 762.16/M25

Topic: E.06. Posture and Gait

Support: JSPS KAKENHI Grant Number JP18K10702

Title: Influences of peripheral visual field loss on sensory reweighting system during quiet standing in virtual reality environment

Authors: ***K. TANEDA**[1], H. MANI[2], N. KATO[4], S. KOMIZUNAI[3], K. ISHIKAWA[1], T. MARUYA[1], Y. TAKAMATSU[2], T. ASAKA[2];
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Abstract: Visual, vestibular, and proprioceptive senses clearly contribute to postural control, so that individuals with peripheral visual field loss such as glaucoma have serious postural instability because of reduced visual sensory input. Some studies have proposed a hypothesis, which is called functional sensitivity hypothesis, that the peripheral or central visual field is specifically responsible for postural control in the anteroposterior (AP) or mediolateral (ML) direction, respectively. However, the hypothesis is not consistent in several other studies. In addition, no studies have investigated the relationship between postural instability due to peripheral visual field loss and reweighting of sensory input. Therefore, the purpose of this study was to investigate the influences of peripheral visual field loss on postural control. Fifteen healthy young adults participated in this study. The participants were asked to conduct quiet standing on a foam surface. Three conditions of virtual visual field loss (90 deg, 45 deg, and 15 deg) were given by a head mounted display. The ground reaction forces were recorded using by a force plate to calculate the displacements of center of pressure (COP) during quiet standing. As a result, the smaller the visual field was, the more the 95% ellipse area, root mean square (RMS), and mean velocity of COP displacements in the horizontal plane were increased. Analyzed by direction of COP displacements, the RMS in the AP direction was maintained even under the smallest visual field condition. On the other hand, the RMS in the ML direction and the mean velocity in each direction were increased according to the peripheral visual field loss. Furthermore, in the AP direction, the power spectral density of the low frequency band (0-0.3 Hz) which depends on the visual sense, was decreased. In addition, that of the middle frequency band (0.3-1 Hz) which depends on the vestibular sense, was increased. However, the power spectral density was remained in any frequency band in the ML direction. These results suggest that the functional sensitivity hypothesis is rejected in the quiet standing task, and the appropriate reweighting of sensory input contributes to maintain the postural stability in individuals with peripheral visual field loss.

Disclosures: K. Taneda: None. **H. Mani:** None. **N. Kato:** None. **S. Komizunai:** None. **K. Ishikawa:** None. **T. Maruya:** None. **Y. Takamatsu:** None. **T. Asaka:** None.

Poster

762. Posture and Gait II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 762.17/M26

Topic: E.06. Posture and Gait

Support: Japanese Grant-in-Aid for Scientific Research 18K10702

Title: Learning effects of visual and auditory feedback training on voluntarily postural control

Authors: *N. HASEGAWA[1], M. MANTINI[2], L. A. KING[2], F. B. HORAK[2], T. ASAKA[1]; [1]Dept. of Rehabil. Sci., Hokkaido Univ., Sapporo, Japan; [2]Dept. of Neurol., Oregon Hlth. and Sci. Univ., Portland, OR

Abstract: Introduction Augmented feedback (AF) training to enhance sensory information is often used to improve postural control. Our previous study showed that motor learning using continuous auditory AF was more effective compared with continuous visual AF. However, it is unknown whether similar learning effects would be present using discrete, rather than continuous, AF. Therefore, this study aimed to investigate the learning effects using discrete auditory versus visual AF training to improve postural control. Our hypothesis was that both auditory and visual AF would similarly induce the motor learning of voluntarily postural control. Methods Twenty-two healthy young adults were randomly assigned to either visual or auditory AF. Participants were asked to shift their center of pressure (COP) in line with a hidden target, which moved a sine curves, by voluntarily swaying in the sagittal plane. In the training sessions with either visual or auditory AF, participants were required to change the magnitude of a visual circle or a sound according to the distance between the COP and the target in order to reach the target, respectively. AF was given only when the target reached the inflection points of the sine curves (discrete AF). Participants performed 80 trials for two consecutive days consisting of 5 time points: before and after first training (pre-1 and post-1), before and after second training (pre-2 and post-2), and 48 hours after the second training session (retention). The average and standard deviation of the distances between the COP and the target (D_{Ave} and D_{SD}) and the coherence between the COP and the target signals were calculated to determine the learning effects on spatial (D_{Ave} and D_{SD}) and temporal domains (coherence), respectively. Two-way mixed-design ANOVA was used with factors Group and Test session for the statistical analysis. Results D_{Ave} and $D_{SD,}$ our measure of spatial domains showed a significant improvement at both post-tests ($p < 0.01$), and retention ($p < 0.01$) in each group. On the other hand, the temporal measure of coherence improved significantly at both of the post-tests and at the retention in the auditory AF group ($p < 0.01$), but not the visual AF group. Furthermore, the coherence of the auditory AF group showed a significant improvement compared with that of the visual AF group at retention ($p = 0.02$). Discussion Our findings suggest that motor learning of postural control is improved by discrete auditory AF training, and not by discrete visual AF training, particularly for temporal measures. It may be explained that auditory information is relayed faster than visual information which may improve such aspects of motor learning for postural control.

Disclosures: N. Hasegawa: None. **M. Mantini:** None. **L.A. King:** None. **F.B. Horak:** None. **T. Asaka:** None.

Poster

762. Posture and Gait II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 762.18/M27

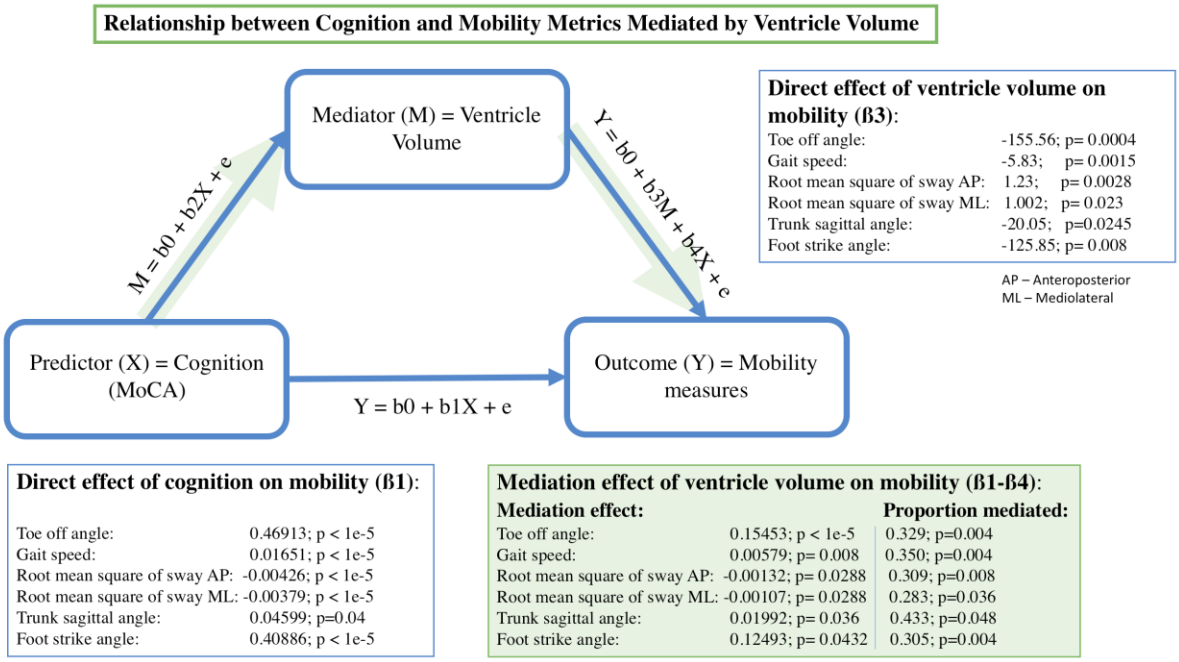
Topic: E.06. Posture and Gait

Support: NIA R01 AG006457
VA Merit Award I01 RX001075

Title: Role of ventricle volume in the association between cognitive status and mobility metrics in Parkinsonian disorders: A mediation analysis

Authors: *A. RAGOTHAMAN[1], O. MIRANDA DOMINGUEZ[2], N. HASEGAWA[4], J. G. NUTT[5], M. MANCINI[3], D. A. FAIR[6], F. B. HORAK[7];
[1]Biomed. Engin., [2]Behavioral Neurosci., [3]Oregon Hlth. and Sci. Univ., Portland, OR; [4]Rehabil. Sci., Hokkaido Univ., Sapporo-Shi, Japan; [5]Univ. Oregon Hlth. Sci. Univ., Portland, OR; [6]Oregon Hlth. Sci. Univ., Portland, OR; [7]OHSU, Portland, OR

Abstract: Besides gait and balance disturbances, cognitive problems are also common in movement disorders, such as Parkinson's disease (PD) and frontal gait disorder (FGD). While several brain areas and functional systems have been associated with such domains in isolation, the neuroanatomical reasons for the close relationships between cognition, mobility, and aging, however, is unclear. In this study, we aimed to determine if the relationship between mobility metrics and cognitive impairments is mediated by increased ventricular volume.
Ninetyseven people with idiopathic PD, 12 people with FGD parkinsonism, and 50 control subjects (age 68.7 $\pm$ 8.3 years) were recruited. Brain and ventricular size were measured using structural MRI (T1w) and Freesurfer. Total ventricular volume was computed as a percentage of intracranial volume. Wearable inertial sensors quantified the following domains of gait and balance: spatiotemporal gait, anticipatory postural adjustments (APA), automatic postural responses (APR), and standing postural sway. Cognitive status was assessed using the Montreal Cognitive Assessment score (MoCA). Mediation analysis was used to predict the balance and gait measures given MoCA using total ventricle volume as the mediator using R. Subjects were sex matched and all variables were controlled for age. Bootstrapping with 500 simulations and correction for multiple comparisons was performed.
Ventricle volume significantly mediated the association between MoCA and spatio-temporal gait measures (foot angle at toe off ($p<1e-5$), gait speed ($p=0.0080$), foot angle at heel strike ($p=0.043$), trunk sagittal range of motion while walking ($p=0.036$)); and postural sway measures (mediolateral and anteroposterior root mean square of sway with eyes open on foam surface, $p=0.028$), and as shown in figure.
Our findings suggest that increased ventricular volume mediates the association between cognitive decline and gait and standing balance dysfunctions by 28 - 43%; thus, confirming that cognition and specific mobility outcomes may share common neuroanatomical structures.



Disclosures: A. Ragothaman: None. **O. Miranda Dominguez:** None. **N. Hasegawa:** None. **J.G. Nutt:** None. **M. Mancini:** None. **D.A. Fair:** None. **F.B. Horak:** A. Employment/Salary (full or part-time):; APDM. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); APDM. F. Consulting Fees (e.g., advisory boards); Biogen, Sanofi, Takeda, Neuropore Therapies Inc.

Poster

762. Posture and Gait II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 762.19/M28

Topic: E.06. Posture and Gait

Support: NIA 5R01 AG006457 (FBH)
VA Merit Award I01 RX001075 (FBH)

Title: Effects of an agility exercise program with cognitive challenges on objective measures of gait and balance in people with Parkinson's disease

Authors: *P. CARLSON-KUHTA[1], N. HASEGAWA[2], V. SHAH[1], M. MANCINI[1], L. KING[1], K. SMULDERS[3], D. S. PETERSON[4], S. JUNG[5], F. B. HORAK[1];
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Hlth. Solutions, Arizona State Univ., Phoenix, AZ; [5]Dept. of Rehabil. Med., Seoul Natl. Univ. Boramae Med. Ctr., Seoul, Korea, Republic of

Abstract: Background: Gait and balance is impaired in Parkinson's disease (PD) and has been associated with cognitive deficits. We designed an Agility Boot Camp with Cognitive challenges (ABC-C) rehabilitation program to see if improvements could be made in gait and balance (King et al 2015). **Objective:** To investigate the effects of a 6-week cognitively challenging exercise intervention in people with Parkinson's disease (PD) on objective measures of gait and balance. We hypothesized that exercise training will improve gait and anticipatory postural adjustments (APA). **Methods:** We used a randomized, single-blinded, cross-over design, in 93 people with idiopathic PD (68±8 years, MDS-UPDRS III, Off medication 42±12; mean±SD), Forty seven subjects had freezing of gait (FoG). Subjects completed 6-weeks of ABC-C exercise program and 6-weeks of education classes (placebo), with intervention order randomized. Outcome measures (Off medication) included clinical, perceived and objective measures of balance and gait (24 metrics of gait, sway, APA, and APR; single- and dual-task (ST,DT)). We used a linear mixed-model that included fixed effects (treatment and order) and random effects (subjects). **Results:** Postural instability and gait disorder score and the PDQ ADL section improved after ABC-C program but not after education ($p=0.002$), while the MDS-UPDRS III ($p=0.25$) and total Mini-BESTest ($p=0.08$) did not change. For objective measures, the gait metrics arm range of motion (RoM), trunk coronal RoM, and foot strike angle, as well as the APA metrics first step RoM and peak medial-lateral APA were improved after exercise, while Sway and Anticipatory postural responses (APR) metrics did not improve. Dual-task cost on gait speed significantly improved after ABC-C program but not after education ($p=0.001$). For the subjects with FoG, worse baseline Motor UPDRS (>67 Off) and Mini-BESTest (<20) scores showed significant improvement ($p=.01$-$.04$). Among gait and balance measures, the spatio-temporal gait parameters significantly improved after the ABC-C program but not after education ($p<0.00001$). Postural sway with eyes open on foam showed a trend for improvement after the ABC-C program ($p=0.03$), while APR to a Push and Release test did not change. Also, for subjects who had lower baseline exercise levels, more improvements were seen following exercise intervention. **Conclusions:** A 6-week cognitively challenging exercise program improved specific characteristics of gait and balance. Spatio-temporal parameters of gait, dual-task cost of gait, and perceived functional independence, were the most sensitive to change after exercise compared to after education intervention.

Disclosures: P. Carlson-Kuhta: None. **N. Hasegawa:** None. **V. Shah:** None. **M. Mancini:** None. **L. King:** None. **F.B. Horak:** A. Employment/Salary (full or part-time):; APDM. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); APDM. F. Consulting Fees (e.g., advisory boards); Sanofi, Biogen, Takeda, Neuropore Therapies, Inc..

Poster

762. Posture and Gait II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 762.20/M29

Topic: E.06. Posture and Gait

Support: NIH 5R01 AG006457

Title: Multiple domains of postural control in Parkinson's disease; feature selection of mobility measures

Authors: *L. A. KING[1], N. HASEGAWA[2], V. SHAH[1], P. CARLSON-KUHTA[1], M. MANCINI[1], F. HORAK[1];
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Abstract: Introduction: There are distinct domains of postural control that may be impaired in people with Parkinson disease (PD) including: 1) postural control during quiet stance (Sway), 2) reactive postural reactions (APR), 3) anticipatory postural adjustments (APA), 4) dynamic balance during walking (Gait), and limits of stability (LOS). This study aimed to determine the most sensitive objective measures of postural control that may differ between people with PD and healthy control subjects (HC), and investigate the association between those metrics with clinical measures of balance confidence, quality of life, and disease severity.
Methods: We recruited 144 subjects with PD (age: 68±8 yrs.) and 79 HC (age: 68±8 yrs.). All participants wore 8 inertial sensors (Opals, APDM), while performing various mobility tasks (PD in their practical *off* state), which measured performance in all 5 postural control domains; Sway, APR, APA, Gait, and LOS. All metrics were computed from inertial sensors. We first calculated the Standardized Mean Difference (SMD) and kept metrics that had SMD value greater than 0.5. Next, we computed a correlation matrix and removed highly dependent metrics ($r > 0.70$) to avoid the problem of multi-collinearity. Spearman's rho correlation was then used to determine the correlations between the most sensitive metrics and the ABC scale, PDQ-39 (total and Mobility), and MDS-UPDRS (total, part 2 and 3).
Results: We started from a comprehensive set of 93 metrics from all mobility tasks. After applying an imputation method (for missing data) and a threshold on SMD (>0.5), we were left with 44 metrics. After reducing highly correlated metrics, we were left with 24 metrics from 4 of the 5 postural domains (all except LOS). The most sensitive objective metrics were in the dynamic balance domain including turn velocity, foot strike angle at initial contact, arm range of motion and gait speed during a walk with a cognitive task. Metrics from the Gait domain also correlated most strongly with clinical measures of balance confidence (Foot strike angle and Gait speed with ABC scale; $r = 0.49$), and quality of life (Stance time with PDQ-39 total; $r = 0.35$).

Finally, dynamic turning velocity correlated most strongly with disease severity (MDS-UPDRS part 3; r = 0.51).
Conclusions: The proposed procedure reduced the objective measures of mobility while still capturing 4 of the 5 domains of postural control. From a comprehensive set of 93, we identified 24 metrics from the Sway, APR, APA and Gait domains. Our results indicate the importance of assessing multiple postural control domains and will help guide data reduction and outcome measure selection in clinical trials for people with PD.

Disclosures: L.A. King: None. **N. Hasegawa:** None. **V. Shah:** None. **P. Carlson-Kuhta:** None. **M. Mancini:** None. **F. Horak:** A. Employment/Salary (full or part-time):; APDM. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); APDM. F. Consulting Fees (e.g., advisory boards); Sanofi, Takeda, Biogen, Neuropore Therapies, Inc.

Poster

762. Posture and Gait II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 762.21/M30

Topic: E.06. Posture and Gait

Support: NIH 5R01 AG006457
I01RX001075-01

Title: Turning features in people with Parkinson's disease, spinocerebellar ataxia, and healthy control subjects

Authors: *V. V. SHAH[1], M. MANCINI[1], N. HASEGAWA[2], P. CARLSON-KUHTA[1], J. G. NUTT[1], C. GOMEZ[3], H. L. CASEY[3], M. EL GOHARY[4], F. B. HORAK[1];
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Abstract: Objective: We investigated whether objective features of turning are different among healthy controls (HC), patients with Parkinson's disease (PD) and Spinocerebellar Ataxia (SCA). **Background:** Ability to turn during walking is a complex motor skill that can be greatly impaired in both PD and SCA. However, turning features such as smoothness of turn or velocity profile have not been well-studied. We hypothesized that turning in HC will be similar to a ballistic trajectory with a single smooth peak and a bell-shaped velocity profile unlike PD and SCA. **Methods:** One hundred and forty-three people with a mild-moderate idiopathic PD (UPDRS III score: 40.60 ± 12.60), 79 age-matched HC subjects, and 52 people with SCA (SCA-1 (n=6); SCA-2 (13); SCA-3 (12); SCA-6 (21); and SARA score: 10.8 ± 4.44) participated in this study. All subjects wore 6 inertial sensors (Opals, APDM) attached to both feet, shanks, wrists

and the lumbar region, and subjects were asked to walk 7 meters back-and-forth for 2 minutes (PD in their practical *off* state). From the lumbar sensor, we detected a start and an end of the turn, and derived a total 6 measures of turning: Turn duration, Turn angle, Turn velocity, Turn peak velocity, Medio-lateral (ML) range, and ML Jerk (smoothness measure). Non-parametric ANOVA was performed using the Kruskal-Wallis Test, and post-hoc analysis was performed using the Mann-Whitney U test. **Results:** All six turning features showed a statistically significant difference among the groups. Post-doc analysis revealed that all turning features were statistically significant between Control and PD. Turn duration for completing 180° turn was longer in PD and SCA compared to HC, but very similar between PD and SCA (p=0.373). Although, PD and SCA both showed slowness during turning (e.g. longer turn duration) compared to HC, turn smoothness was significantly different between PD and SCA. Specifically, ML jerk was the lowest in PD and the highest in SCA (p=0.001). Similarly, the ML range was the lowest in PD and the highest in SCA (p=0.000). **Conclusions:** Our preliminary findings suggest that although both PD and SCA showed slowness during turning, turn smoothness was impaired in opposite ways for PD and SCA compared to HC. PD showed the smallest ML jerk indicating the more axial rigidity, and SCA showed the largest ML jerk indicating less rigidity compared to HC. Future work on exploring the velocity profile during turning will provide more information about brain circuitry involved during turning.

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Poster

762. Posture and Gait II

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Program #/Poster #: 762.22/M31

Topic: E.06. Posture and Gait

Support: NIH/NCATS grant UL1TR001855
NIH/NICHD grant R01HD091184

Title: Altering spatiotemporal asymmetry influences the reactive control of balance during walking in people post-stroke

Authors: *C. LIU[1], S. PARK[2], N. SANCHEZ[2], J. K. TILSON[2], S. J. MULROY[3], J. M. FINLEY[2,1];
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Abstract: Step length asymmetry asymmetries after stroke are commonly associated with balance impairments and may increase the risk of falls. This increase in fall risk may result, in part, from abnormal recovery responses following unexpected perturbations. Reactive recovery responses during perturbed walking are commonly characterized by measures of whole-body angular momentum (WBAM), which reflect the net contribution of all body segments to the body's rotation about a given axis. Recent work has shown that people with spatiotemporal gait asymmetry have higher peak-to-peak ranges of WBAM during walking. However, while this may suggest that spatiotemporal asymmetries impair balance during walking, no studies have quantified how reductions in asymmetry influence the reactive control of balance post-stroke. Here, we tested the hypothesis that reducing step length asymmetry would improve reactive control of WBAM in stroke survivors. Fourteen individuals post-stroke walked on a dual-belt treadmill at their self-selected speed and followed instructions to use visual feedback to either match their natural step length asymmetry or to adopt steps of equal length. During each trial, we randomly applied ten accelerations to the treadmill belts on the paretic and non-paretic sides at foot-strike. Each perturbation was characterized by a trapezoidal speed profile in which the speed increased by 0.2 m/s at an acceleration of 1.6 m/s^2, was held for 0.6 s and then decelerated back to the self-selected speed during the swing phase of the perturbed leg. We recorded full body motion capture and used these data to compute the integrated WBAM during the perturbation steps to capture the magnitude of body rotation in response to the perturbation. We found that the integrated WBAM during the perturbation step was greater on the paretic side than the non-paretic side ($p<0.001$). Also, there was a significant interaction between step length asymmetry magnitude and the direction of baseline asymmetry on WBAM ($p=0.01$) such that for people who took shorter paretic steps, reductions in asymmetry were associated with an increase in integrated WBAM. In contrast, for people who took longer paretic steps, there was no significant relationship between the magnitude of step length asymmetry and integrated WBAM. These results suggest that reducing step length asymmetry may impair the reactive control of stability for some stroke survivors, particularly those who take shorter steps with their paretic limb.

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Poster

762. Posture and Gait II

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Topic: E.06. Posture and Gait

Support: NIH/NCATS grant UL1TR001855
NIH/NICHD grant R01HD091184

Title: Impact of modifying spatiotemporal asymmetry on frontal plane whole-body angular momentum during walking post-stroke

Authors: *U. S. P. PARK[1], C. LIU[1], S. NATALIA[1], J. K. TILSON[1], S. J. MULROY[2], J. M. FINLEY[1];
[1]USC, Los Angeles, CA; [2]Rancho Los Amigos Natl. Rehabil. Ctr., Downey, CA

Abstract: Neurological impairments such as stroke, often result in asymmetric walking patterns and increased instability in the frontal plane. Because spatiotemporal gait asymmetries are associated with balance impairments post-stroke, researchers and clinicians often aim to create interventions to reduce asymmetry in these individuals. However, the acute effects of changing asymmetry on balance during walking have yet to be examined. These effects may also depend on the direction of asymmetry as some individuals take longer steps with the paretic limb and others taking longer steps with the non-paretic limb. Here, we determined how the manipulation of step length asymmetry using explicit instruction influences measures of dynamic balance in the frontal plane during walking post-stroke. When increasing step length to reduce asymmetry, we expected that people would increase frontal plane whole-body angular momentum (WBAM) and shift their center of mass toward the contralateral stance limb to advance the swing limb. A total of 15 chronic, post-stroke individuals participated in this study. Participants walked on a treadmill using visual feedback in three conditions presented in a randomized order. These conditions included walking at their natural step length asymmetry, walking with instruction to take steps of equal length, and walking with exaggerated asymmetry. Dynamic balance was characterized by measures of WBAM in the frontal plane with respect to the body's center of mass. We measured the peak-to-peak range of WBAM over the gait cycle as a metric of dynamic balance. We used mixed-effect regression models to determine if measures of WBAM were associated with step length asymmetry magnitude and the direction of asymmetry. Participants successfully modified step length asymmetry through use of visual feedback in both the symmetry and exaggerated asymmetry conditions. There was a significant association between step length asymmetry magnitude and the peak to peak range of WBAM over a stride ($F = 10.38$, $p = 0.001$) with a significant interaction between asymmetry magnitude and direction (*rpar=0.007, rnonpar=-0.011* , both $p < 0.001$). Thus, improving symmetry acutely decreased the range of angular momentum for people who have longer paretic steps, and increased the range for those who have longer non-paretic steps. These results suggest that the direction of asymmetry influences the functional consequences of instructing people post-stroke to walk more symmetrically and this may be an important consideration during rehabilitation.

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Poster

763. High-Level Control of Posture and Gait

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 763.01/M33

Topic: E.06. Posture and Gait

Support: NIH Grant T32HD007434

Title: Differences in response to auditory cues across movement types in people with Parkinson's disease with and without freezing of gait

Authors: *A. P. HORIN[1], E. C. HARRISON[2,4], K. S. RAWSON[1], G. M. EARHART[1,2,3]; [1]Program in Physical Therapy, [2]Dept. of Neurol., [3]Dept. of Neurosci., Washington Univ. Sch. of Med., St. Louis, MO; [4]Dept. of Dance, Washington Univ. in St. Louis, St. Louis, MO

Abstract: Parkinson disease (PD) is a neurodegenerative movement disorder characterized by gait impairments that reduce mobility and increase fall risk. A common gait deficit is freezing of gait (FOG), a delay in initiation or pause in locomotion. One form of gait rehabilitation is rhythmic auditory cueing, in which a person matches their footfalls to the beat of an auditory cue. Our previous research has indicated different outcomes for externally-generated (e.g., music) and self-generated (e.g., mental singing) cues, such that both music and mental singing improved velocity and stride length, but music also negatively affected temporal stability whereas mental singing did not. Gait differences, in response to cueing, have also been shown in people with PD without FOG (PD-FOG) and with FOG (PD+FOG). We expect these differences are due to underlying neural mechanisms, however, studying gait with neuroimaging is difficult. Thus simpler movements such as finger tapping or foot tapping may be useful surrogates. Here we compared the responses of gait, finger tapping, and foot tapping to externally-generated and self-generated cues in healthy older adults (Control, n=24), PD-FOG (n=17), and PD+FOG (n=16). Temporal stability of movement was assessed via coefficient of variation (CV) for gait (inter-step interval) and finger tapping (inter-tap interval). For all cued trials, participants were cued at 100% of the tempo of their uncued, preferred pace movement (UNCUED). For externally-cued trials (MUSIC), participants matched the pace of the movement to the beat of the song. For self-generated cued trials (MENTAL), participants matched the pace of the movement to the beat of them mentally singing. Repeated measures ANOVAs were used to determine differences between group, condition, and movement on CV. There was a main effect of condition ($p<.0001$) and no main effects of group or movement. There was an interaction effect of condition and movement ($p<.0001$) with pairwise comparisons (Bonferroni corrected) indicating MUSIC trials had the highest CV compared to MENTAL across all movements and groups. These results show that self-generated cues elicit greater temporal stability across movements and groups than externally-generated cues. This provides evidence for using finger

tapping as a proxy for gait in neuroimaging studies to investigate differences in neural mechanisms underlying externally and self-generated cues in people with PD with and without FOG.

Disclosures: A.P. Horin: None. **E.C. Harrison:** None. **K.S. Rawson:** None. **G.M. Earhart:** None.

Poster

763. High-Level Control of Posture and Gait

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 763.02/M34

Topic: E.06. Posture and Gait

Support: Foundation for Physical Therapy Research: Promotion of Doctoral Studies 1
NIH R01HD078330-01A1

Title: Can stroke survivors learn and retain a new walking pattern through explicit, strategic locomotor learning?

Authors: *M. FRENCH[1], D. S. REISMAN[2];
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Abstract: Background: Locomotor learning, specifically sensorimotor adaptation, has been studied extensively using the split belt treadmill. Sensorimotor adaptation, in this context, is implicit, automatic, and requires few cognitive resources. Explicit, strategic learning, on the other hand, has been minimally studied during locomotion and requires cognitive resources. Due to the differences in these forms of learning, it is important to understand whether stroke survivors can learn through explicit, strategic locomotor learning. Thus, the purpose of this study was to evaluate the ability of stroke survivors to learn and recall a new walking pattern through an explicit, strategic learning paradigm.
Methods: Stroke survivors and age-matched healthy adults were recruited to participate in a treadmill walking study. On Day 1, subjects walked for Baseline, Learning, and Learning Test phases. On Day 2, subjects walked for a Retention phase. During Baseline, step length (SL) was calculated and the leg with the shorter SL (SSL) and longer SL (LSL) were identified. During Learning, a bar graph with a target line for each leg displayed real time information about subjects' SL. Subjects were asked to match both bars to the target line; however, the bar representing the SSL was distorted resulting in subjects learning a new walking pattern to make the bars to hit the target line. During Learning Test on Day 1 and Retention on Day 2, subjects were asked to recreate the pattern they learned without the visual feedback. Step symmetry [SS, $(SL_{SSL}-SL_{LSL})/(SL_{SSL}+SL_{LSL})$] was calculated and used to quantify learning and retention. Learning was measured by Absolute Error (AE), which was the absolute difference between SS

at the end of Learning and the target SS (i.e. the SS that would result from hitting both target lines). Retention was measured by the Magnitude of Retention (MR), which was the absolute difference between the average SS during Learning Test and during Retention. A Mann-Whitney U test was used to compare AE and MR between the two groups.
Results: AE was not different between the stroke survivors (n=12; 66.08 ±10.6) and age-matched healthy adults (n=6; 69 ±7.1) (p=0.083). There was also no difference in MR between groups (p=0.417).
Discussion: Based on our results, it appears that stroke survivors learn and retain a new walking pattern through explicit, strategic learning as well as age-matched healthy adults. These results suggest that stroke survivors maintain the capacity to learn and retain new walking patterns through an explicit, strategic locomotor learning, despite the added cognitive resources required for this form of motor learning compared to sensorimotor adaptation.

Disclosures: M. French: None. **D.S. Reisman:** None.

Poster

763. High-Level Control of Posture and Gait

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 763.03/M35

Topic: E.06. Posture and Gait

Title: The characteristic of gait in children with motor coordination problems during dual cognitive and locomotor tasks

Authors: *C. W. CHAU, N. RIPIC, A. STEKL, N. WHITE, B. MALLABER, M. DONAHUE; Nazareth Col., Rochester, NY

Abstract: Previous results from our laboratory have shown gait decrement (reduced velocity, cadence, step length, swing duration and increased stance and cycle duration) in 5 and 6 year old (yo) typically developing (TD) children while walking and performing concurrent cognitive tasks. This study investigates changes of locomotion in children with motor coordination problems (MCP) during similar concurrent cognitive tasks. Children with MCP are at risk of developing developmental Coordination Disorder (DCD) and scored ≤ 46 on the Developmental Coordination Disorder Questionnaire 2007© (DCDQ) (Wilson et al, 2009). TD group has DCDQ score >47. Fifteen kindergartners (11 male and 4 females), divided into TD (N=9) and MCP (N=6) group based on DCDQ score, performed two cognitive tasks, a verbal counting backwards (VCB) task where they count backwards from 10 to 1, and a verbal sound recognition (VSR) task where they identify different familiar sounds played. Then, subjects walked on the GAITRite® (CIR System Inc. NJ), a portable carpeted walkway (2X14ft) embedded with electronic pressure sensors that record footprints and allowing us to measure spatiotemporal gait

parameters. Each subject completed 3 trials of walking without a concurrent task (Single-Task (ST)) or with a concurrent cognitive task (Dual-Task (DT)), either DT-VCB or DT-VSR in a randomized order. Each dual-task trial lasts 1-1.5 minute. The only constraint for all walking tasks is that the child may not stop on the GAITRite®. There was no statistical significance in gait parameters during all walking tasks between TD and MCP groups except for gait variability which was increased in all walking tasks from children with MCP. The step length stride to stride variability significantly increased in children with MCP (17.4%) as compared to TD children (6.5%) during DT-VSR. Similar to TD group, children with MCP showed a significant decrease in velocity (-53.9cm/s), step length (-14cm) and cadence (-34 steps/min) during DT-VSR as compared to ST. More children with MCP than TD made errors during DT-VCB (TD:11%; MCP:50%), but not during DT-VSR (TD: 44%; MCP:33%). A significant negative correlation between cadence and DCDQ score was found during DT-VCB in TD group (r=-0.83) but not in children with MCP (r=-0.49). Our results suggest that gait decrement during DT are similar between children with MCP and TD children. Children with MCP have more difficulty with DT-VCB than TD children suggesting increased difficulty in children with MCP with an internal-cued cognitive task. It is possible that children with MCP may use alternative strategy to compensate for increased cognitive demands during gait when compared to TD children.

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Poster

763. High-Level Control of Posture and Gait

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 763.04/M36

Topic: E.06. Posture and Gait

Title: The contribution of use dependent plasticity to locomotor learning

Authors: *J. M. WOOD[1], H. E. KIM[3], D. S. REISMAN[4], S. M. MORTON[2];
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Abstract: Motor learning of locomotor patterns has been studied primarily in the form of sensorimotor adaptation (SMA). SMA refers to the trial-by-trial updating of motor commands in response to sensory prediction errors elicited during perturbed movements. Despite the extensive study of different forms of motor learning in upper extremity reaching tasks, it is unclear if these forms of motor learning also exist for locomotion. For example, use-dependent plasticity (UDP), which results in the biasing of future movements towards previously repeated movement patterns, has never been examined in locomotion. We sought to assess the contribution of UDP

to visually-guided locomotor learning. Young, healthy adults walked on a treadmill while watching real-time visual feedback of their step lengths on a computer screen. Step lengths were represented as two different colored bars which increased in size as the foot advanced during the swing phase of gait and then 'held' on the screen when heel strike occurred. Subjects were instructed to make the bars hit a target line during each step. The walking paradigm consisted of three phases: a baseline phase, where subjects were familiarized with the task, a learning phase (22 minutes), where subjects were taught a new walking asymmetry, and a washout phase (22 minutes), where subjects were instructed to walk normally and no visual feedback was provided. Subjects were randomly assigned to one of two groups. Subjects in the SMA+UDP group learned the new asymmetry by viewing erroneous visual feedback with a gain perturbation. Subjects in the UDP only group learned the new asymmetry by viewing veridical feedback with adjusted target lines, thus no sensory prediction error occurred. The primary outcome was step asymmetry index, measured as [(long leg step length - short leg step length)/stride length]. To assess the contribution of UDP to learning, we compared mean step asymmetry indices between groups at late baseline, late learning and early washout phases. We found no differences between groups during any of these phases, indicating that both groups were able to learn to walk asymmetrically to the same degree and, importantly, the associated aftereffects from visually-driven learning of an asymmetric locomotor pattern through combined SMA and UDP may be explained by UDP alone. Given the prevalence of repetition during nearly all locomotor learning studies, these findings may have broad implications for our understanding of how newly acquired locomotor patterns are shaped by prior recent experience.

Disclosures: **J.M. Wood:** None. **H.E. Kim:** None. **D.S. Reisman:** None. **S.M. Morton:** None.

Poster

763. High-Level Control of Posture and Gait

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Topic: E.06. Posture and Gait

Support: NIH Grant R01-AG049735
NIH Grants R21-AG053470

Title: Walking humans regulate lateral stepping in a redundant, multi-objective, and adaptable way

Authors: ***J. B. DINGWELL**[1], J. P. CUSUMANO[2], M. E. KAZANSKI[3], A. C. RENDER[3]; [1]Kinesiology, Pennsylvania State Univ. Univ. Park, University Park, PA; [2]Engin. Sci. & Mechanics, Penn State Univ., University Park, PA; [3]Kinesiology, Pennsylvania State Univ., University Park, PA

Abstract: When humans walk, we are inherently more unstable side-to-side (laterally). Additionally, humans most often walk on paths (sidewalks, store aisles, etc.) with finite width that may be narrow or wide, straight or curved, etc. It is important to determine how people regulate lateral stepping movements in such contexts. Due to biomechanical redundancy, there are infinite choices for where to place each foot at each step. We recently extended a computational framework (Dingwell et al., PLoS Comput. Biol., 2010) to determine how humans exploit available redundancies to regulate lateral stepping movements while they walk (Dingwell & Cusumano, PLoS Comput. Biol., 2019). In general, to walk successfully on nearly any defined path, lateral stepping can be regulated to achieve various goals equating to different combinations of lateral position (z_B), heading (Δz_B), and/or step width (w) control. We then showed that during normal straight-ahead walking, humans adopt a multi-objective strategy that weighs strong (~95%) w-control against weaker z_B-control (~5%) (Dingwell & Cusumano, 2019). Here, we present results of 2 new experiments that manipulated the task of walking to elicit changes in step-to-step regulation of lateral stepping. In experiment 1, healthy adults were subjected to continuous pseudo-random lateral perturbations of either the walking surface or the visual field (e.g., as in McAndrew et al., J. Biomech., 2010). In response to these perturbations, all participants exhibited increased variability of all stepping variables. However, relevant time series analyses of step-to-step dynamics showed that participants also (and independently) more strongly corrected deviations in both z_B and w simultaneously. In experiment 2, healthy adults were given direct step-to-step visual feedback of z_B, or Δz_B, or w. Participants were asked to minimize errors relative to the desired values of each. Here, participants successfully reduced the variability of each feedback variable presented, relative to no-feedback (normal walking). Relevant time series analyses of step-to-step dynamics again showed that participants also adapted / modified the degree to which they regulated each stepping variable, according to each feedback condition and in ways generally consistent with the predictions of our computational framework. Together, these results demonstrate that regulation of lateral stepping in walking is redundant and multi-objective, and that humans adapt their step-to-step regulation in appropriate ways given relevant changes in task demands and environmental context.

Disclosures: J.B. Dingwell: None. **J.P. Cusumano:** None. **M.E. Kazanski:** None. **A.C. Render:** None.

Poster

763. High-Level Control of Posture and Gait

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 763.06/M38

Topic: E.06. Posture and Gait

Support: NIH Grant R01-AG049735

Title: Center-of-mass predictions of foot placement may reflect passive dynamics and not control

Authors: *N. S. PATIL[1], J. B. DINGWELL[1], J. P. CUSUMANO[2];
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Abstract: Humans stay upright during walking in part by choosing appropriate stepping locations on the ground. Exactly how this is accomplished from each walking step to the next in an active manner is the topic of much current research. Recent experimental studies of humans walking on a treadmill have shown that during an individual step, the pelvis or Center-of-Mass (CoM) state is a good predictor of the next foot placement, as perturbations to the upper body are consistently mapped to and, hence, successfully corrected by "appropriately chosen" foot placements. This has been interpreted by some to imply that the nervous system uses the CoM state at or near mid-stance to actively control subsequent foot placement. However, correlations of CoM state to subsequent foot placement could also, perhaps strongly, arise from passive dynamics, especially as movements of the feet are mechanically coupled to those of the rest of the body. This important alternative hypothesis has, however, not been directly tested. Here, we used a simple passive, open-loop-stable (i.e., without any active feedback) 2D walking model to show that one cannot take this ability to predict the foot placement from a CoM state in the preceding step, by itself, as evidence of active control. We simulated our uncontrolled model by adding "motor" noise. We also incorporated measurement errors in the regression variables to qualitatively replicate human walking data. In our simulations, we too found high correlations between the CoM state and the subsequent foot placement, but here, these were entirely due to intrinsic passive dynamics as our system, by design, has no control. Our simulations thus suggest that much of the aforementioned predictability in humans can perhaps be attributed to the passive or "ballistic" nature of trajectories between consecutive heel-strikes. Furthermore, they suggest that the observed correlations may, in addition, be strongly affected by even small amounts of noise in the experimental measurements. This finding does not mean the nervous system does not use CoM state to control subsequent foot placement at all. However, it does mean that such statistics should be used to characterize within-step active control in human walking only with great caution. Any conclusions about control require supporting evidence beyond the experimental correlations alone. The extent to which correlations of CoM state to foot placement in human walking reflect the effects of active control, or likely those of passive dynamics, or of some combination of both, thus remains an important and still open question.

Disclosures: **N.S. Patil:** None. **J.B. Dingwell:** None. **J.P. Cusumano:** None.

Poster

763. High-Level Control of Posture and Gait

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 763.07/M39

Topic: E.06. Posture and Gait

Title: Effects of concurrent cognitive task difficulty on cortical activation and network in a cognitive-[editor1]postural dual task: A functional near-infrared spectroscopic study

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Abstract: Background: It is well-known that a concurrent cognitive task often leads to impaired performance of postural or gait task (dual-task cost). Recent studies have revealed prefrontal involvement in cognitive-postural dual task, but a precise neural mechanism is still unclear. Objective: We investigated the effect of cognitive task difficulty on postural stability against a dynamic perturbation task and cortical activation using functional near-infrared spectroscopy (fNIRS).
Methods: We recruited 18 healthy young subjects (26.4 ± 9.5 y.o., 11 males). The subjects completed three postural-cognitive dual-task sessions. As cognitive task, they asked to sum all the numbers appeared every 2 s on the screen with three different task difficulties included simple counting (COUNT: using 0 or 1), easy calculation (EASY: using −9 to 9), and complex calculation (COMPLEX: using −99 to 99). Calculation results were checked for every 20 numbers (three times in one session). Concurrent with the calculation task, we applied brisk forward and backward translations of a platform as the postural perturbation, and evaluated the center of pressure (COP) and EMG activation of bilateral TA and GC muscle during perturbation. To measure postural task-related cortical activation, we used Oxy-Hb based signal measured by the fNIRS (FIORE-3000, Shimadzu Corp). We also evaluated effective connectivity in motor-related cortical areas during the postural task using Granger causality analysis.
Results: Normalized COP displacement (perturbation/rest) was significantly smaller in COUNT than in EASY and COMPLEX (COUNT: 2.19 ± 1.02, EASY: 2.13 ± 1.00, and COMPLEX: 2.57 ± 0.89). The normalized EMG activation (perturbation/rest) was also smaller in COUNT than in COMPLEX. Postural task-related cortical activation was most significant in COUNT, and there was significant reduction in the supplementary motor area activation (SMA) in COMPLEX than COUNT. There was also a significant correlation between cortical activation changes and COP displacement changes (Dual-task cost) in the right prefrontal cortex (PFC), SMA, and the medial sensorimotor cortex. Granger causality analysis revealed that effective connectivity from right PFC to SMA was significantly reduced in COMPLEX than that in COUNT.

Conclusion and interpretation: Our findings revealed dynamic changes in the postural task-related cortical activation and networks, suggesting an important role of the right PFC in cortical resource allocation to the SMA, which is one of the main hubs of the postural control network in cognitive-postural dual task.

Disclosures: M. Mihara: None. **S. Inazumi:** None. **H. Otomune:** None. **I. Miyai:** None. **Y. Sunada:** None.

Poster

763. High-Level Control of Posture and Gait

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Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 763.08/M40

Topic: E.06. Posture and Gait

Support: NSF CRCNS 1822568

Title: Larger visual perturbations affect the foot placement but not the ankle roll or push-off mechanism for balance control during walking

Authors: *H. REIMANN[1], T. D. FETTROW[1], M. ARCODIA[1], E. KAYE[1], D. GRENET[1], J. J. JEKA[2];
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Abstract: Humans must continuously regulate upright posture during walking, to prevent losing balance. We have previously identified three separate mechanisms for balance control in the frontal plane, that are available at different points during the gait cycle. 1) In single stance, humans use lateral ankle musculature to roll their stance foot ankle. 2) At heel-strike, they shift the location of the foot placement. 3) During double stance, they shift weight between the two feet by pushing off more or less strongly with the trailing foot. Here we investigate how these three different mechanisms are flexibly recruited depending on the strength of a sensory perturbation. Ten healthy, young subjects (5 female) walked on a self-paced, instrumented treadmill, surrounded by a virtual reality scene projected onto a curved dome covering almost their complete field of view. To provide a visual fall stimulus, the scene was rotated around the sagittal axis at floor level with a constant acceleration for 600ms, then kept at a constant angle for 2,000ms, then reset at constant speed over 1,000ms. The initial acceleration was either 45 deg/s^2 (LOW) or 90 deg/s^2 (HIGH), or no movement (control), randomized. Stimuli were triggered on heel-strike of either foot, with a randomized inter-stimulus interval of 10-12 steps. Direction of the fall stimulus was towards the triggering foot, and we merged all data assuming body symmetry. The maximal average lateral CoM shift was significantly higher for HIGH (6.0cm) vs. LOW (3.9cm), representing the overall balance response to the visual stimulus. 1) The stance leg subtalar angle change at heelstrike was not significantly higher for HIGH (1.7deg)

vs. LOW (1.4deg). 2) The foot placement change in response to the stimulus was significantly higher for HIGH (0.57cm) vs. LOW (0.38cm). 3) The maximal trailing leg plantarflexion change was not significantly higher for HIGH (0.7deg) vs. LOW (0.7deg). We expected the relative contribution of the three mechanisms to change, but were surprised that this change came almost exclusively from the foot placement mechanism, which was about 50% higher for HIGH vs. LOW, very similar to the 54% increase in CoM shift.

Disclosures: H. Reimann: None. **J.J. Jeka:** None. **T.D. Fettrow:** None. **D. Grenet:** None. **M. Arcodia:** None. **E. Kaye:** None.

Poster

763. High-Level Control of Posture and Gait

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Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 763.09/M41

Topic: E.06. Posture and Gait

Support: NIH DC2390

Title: Individual neurons in macaque deep mesencephalic nucleus display both vestibular and locomotor modulation

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Abstract: The deep mesencephalic nucleus (DpMe) is a relatively large midbrain area implicated in a wide variety of behaviors and functions, including sensory modulation, motivation, sleep, attention, eye movements, and locomotion. Its diverse connections include spinal, cortical, and basal ganglia inputs as well as outputs to thalamic nuclei and reticulospinal nuclei and tracts, and its potential clinical significance is a subject of active investigation, as demonstrated by recent human trials for Parkinson's disease symptoms using deep brain stimulation in DpMe. Specific areas within DpMe have long been known to be related to locomotion, posture, and gait. Additionally, studies across species and modalities have suggested the region plays a role in vestibular information processing. However, to date, studies of DpMe neuronal activity have predominantly focused on either motor activity or individual sensory modalities. Here, we present the first analysis of single-unit extracellular recordings from rhesus macaque DpMe during both passive vestibular stimulation recorded using a head-mounted accelerometer, and a head-fixed treadmill walking task (i.e. in the absence of vestibular input) during which we extracted animal posture using a deep-learning computer-vision tool. In particular, we demonstrate that there exist individual cells in this region which modulate their responses during both paradigms. Focusing on cells without eye movement sensitivity, we analyzed fifteen cells in macaque DpMe responsive to vestibular input, finding sensitivities

consistent with previous reports. Furthermore, the vast majority (14 of 15) of these cells' responses were also modulated by ongoing locomotion during head-fixed treadmill walking. Specifically, we find firing changes both as a function of gait phase and as a function of specific aspects of dynamic 3D posture, and we identified an increase in the power spectra of firing activity at the same frequency as the animal's step cycle. These results provide evidence that single cells in primate DpMe may be involved simultaneously in processing information from converging multimodal information streams for the purpose of complex sensorimotor processes, shedding light on a clinically relevant and intensely interconnected deep brain area.

Disclosures: O.R. Stanley: None. **E. Gugig:** None. **K.E. Cullen:** None.

Poster

763. High-Level Control of Posture and Gait

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 763.10/M42

Topic: E.06. Posture and Gait

Title: Motor adaptation to cognitive challenges and walking perturbations

Authors: *P.-C. KAO, M. A. PIERRO;
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Abstract: Walking is not a fully automated motor task but requires sufficient cognitive capacity to control walking stability and adapt to environmental complexity. When performing a cognitive task during walking (i.e., dual-task walking), a competition for information processing resources and attention would lead to a compromised performance of either or both tasks. However, majority of the dual-task walking paradigms utilized in the previous studies were focused on posing a cognitive challenge by adding a secondary cognitive task. When encountering walking perturbations (e.g., destabilizing walking environment), it is not clear whether people would still use similar task prioritization strategies. The purpose of this ongoing study is to investigate how people adjust motor responses when both cognitive and walking challenges are presented, and if the task prioritization strategies are differed when receiving cognitive tasks that challenge different sub-components of the executive function. We recorded kinematic data as subjects walked on a treadmill 1) under two walking conditions: walking with and without continuous random-amplitude treadmill platform sways (Perturbed vs. No-perturbed walking); and 2) with and without each of the four cognitive tasks: Paced Auditory Serial Addition test (PASAT), clock test, visual color-word incongruent test (V-stroop), and auditory pitch-word incongruent test (A-stroop). We quantified walking stability by computing dynamic margins of stability (MOS), gait variability, and short-term local divergence exponent (LDE) of the trunk motion (local stability). The preliminary data of five healthy younger subjects show that cognitive performance in general is significantly lower in PASAT and clock test compared

to V-stroop and A-stroop ($p<0.05$). During the perturbed walking, subjects had significantly lower cognitive performance, more walking instability, and greater gait variability compared to no-perturbed walking. Under dual-task conditions, subjects walked with lower joint angle variability and significantly larger mean MOS compared to walking only. Subjects also showed a trend to walk with more local instability during V-stroop than during other cognitive tasks. These preliminary data suggest that healthy younger individuals tend to prioritize walking over cognitive tasks when encountering walking perturbations. However, during a cognitive task with a lower difficulty level or taxing visual attention, subjects tend to prioritize the cognitive task with a cost of compromising walking stability.

Disclosures: P. Kao: None. **M.A. Pierro:** None.

Poster

763. High-Level Control of Posture and Gait

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Program #/Poster #: 763.11/M43

Topic: E.06. Posture and Gait

Support: Faculty of Health Sciences, University of Tromsø, Grant 2016/5455
Norwegian Health Association, Grant 2016/4882 & 2014/888

Title: Link of white matter tract integrity & dual-task costs on gait parameters in mild cognitive impairment and normal aging

Authors: M. M. GORECKA[1], S. CASTRO-CHAVIRA[1], T. R. VANGBERG[2], O. VASYLENKO[1], K. WATERLOO[1], ***C. RODRIGUEZ-ARANDA**[1];
[1]Univ. of Tromsø, Tromsø, Norway; [2]Univ. Hosp. of North Norway, Tromsø, Norway

Abstract: Persons with MCI experience cognitive and motor deteriorations that affect gait. These declines are assessed via dual-tasks paradigms where a cognitive task is performed during walking. Degree of change on gait parameters can be calculated by dual-task costs, i.e., the difference between single walking and dual-task performance. Because gait changes in MCI are thought to rely in part on cognitive decline and brain degeneration, the present study aims to evaluate the link between white matter tract integrity and dual-task costs on spatio-temporal gait parameters in persons with MCI and age-matched controls.
Method: 16 right-handed MCI patients (*mean* age 70.4 y, 10 women) and 20 right-handed healthy older adults (mean age 70.4 y, 13 women) were evaluated during single-task walking and on three dual-task conditions varying in difficulty. The cognitive task employed was dichotic listening which consists of simultaneous pairs of syllables presented differently for each ear on each trial. In the 3 conditions, subjects are asked to walk while a) report freely best-perceived stimulus, b) report stimuli from right-ear and c) report stimuli from left-ear. Means and

coefficients of variation were measured for gait speed, step length, and step width with the Optogait©-system. Dual-task costs (DTC) by condition for all gait parameters were calculated and analyzed with repeated-measures ANOVAs. Anatomical and diffusion-weighed (DW) images were acquired in a 3T MR scanner. The anatomical images were processed using FreeSurfer and utilized as reference for processing the DW images with the TRACULA software. Fractional anisotropy (FA) and mean diffusivity (MD) were estimated using global probabilistic tractography for the 18 major brain tracts. Then, FA and MD for each tract were entered into hierarchical regression models to predict DTCs on each dual-task condition. Age and gender were entered in Step 1 of the analyses. Statistical analyses were run on transformed z-scores.
Behavioral Results: A main effect for condition ($p < .0001$) and group ($p < .01$) were found only for mean step length with no significant interactions. *MRI Results*: Forceps minor (MD), cingular angular bundle (FA) and corticospinal tract (MD) explained 31% of the variance on DTC for mean step length ($R = 0.61$, $R^2 = 0.37$; $R^2\Delta = 0.31$, $p = 0.01$; beta = -0.61).
Conclusions: In MCI, the mean DCT of step length was nearly twice as that as the control group. The shortening in steps length as well as deterioration of forceps minor and cingular angular bundle are typical of MCI patients. The present finding linking decline on step length to white matter tracts known to deteriorate in MCI needs to be confirmed in larger samples.

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Poster

763. High-Level Control of Posture and Gait

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 763.12/M44

Topic: E.06. Posture and Gait

Support: Techniker Krankenkasse (Project PROCARE)

Title: Dual-task costs in highly aged residents of primary care settings

Authors: J. RUDISCH[1], A. KRAMER[1], *C. VOELCKER-REHAGE[1], B. WOLLESEN[2];
[1]Inst. of Human Movement Sci. and Hlth., Chemnitz Univ. of Technol., Chemnitz, Germany;
[2]Fac. of Psychology and Human Movement, Univ. of Hamburg, Hamburg, Germany

Abstract: Introduction: In addition to the effects of normal aging, immobilization and sedentary behavior may further exacerbate the deterioration of locomotor function in residents of primary care setting facilities. Therefore, more cognitive resources are required to control gait. In motor-cognitive dual-task (DT) situations, attention may be directed to one of the tasks (either the cognitive or motor task) resulting in either so called dual-task costs (DTC). As a result, risk of

falling increases these situations. In this exploratory study, we investigated cognitive and motor performance in DT of varying complexity in highly aged primary care residents to explore the impact of secondary cognitive tasks on motor function.
Methods: Twenty-one multimorbid residents (17 females; 86.9 +/- 7.2 years old) in 2 primary care facilities in Chemnitz, Germany participated in this study. Subjects walked at a self-selected speed and performed three cognitive tasks in single- or dual-task scenarios, presented in randomized order. Cognitive tasks comprised serial number tasks (counting backwards by 1 [serial1] and 3 [serial3]) and verbal fluency (naming words beginning with a specified letter). Gait parameters were measured using an Optogait system (Microgate, Bolzona-Bozen, Italy). Mean and coefficient of variation of stride-time and step-length were calculated as primary outcomes.
Results: Motor DTC, i.e., a reduction in step-length and stride-time, were found in the serial3 and verbal fluency DT, however not in serial1. Gait variability, on the other hand, increased in all three DT scenarios as compared to single-task condition . No significant positive or negative DTC were found for cognitive performance. Data, however, showed a trend level relationship between cognitive performance and DTC. That is, individuals with more correct answers showed less DTC.
Discussion: Changing cognitive load of secondary task can affect motor DTC. Intraindividual differences, however, need consideration: Better cognitive function may reduce the amount of executive control needed to perform the motor and/or cognitive task (and therefore reduce DTC). On the other hand, individuals with lower cognitive function may disregard the cognitive task and therefore prioritize the motor task (likewise reducing DTC). Larger samples are required in future studies to include both, cognitive performance and cognitive DTC as predictors of motor DTC.

Disclosures: J. Rudisch: None. **A. Kramer:** None. **C. Voelcker-Rehage:** None. **B. Wollesen:** None.

Poster

763. High-Level Control of Posture and Gait

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 763.13/N1

Topic: E.06. Posture and Gait

Title: Age differences in a combined walking and grasping task

Authors: *A. H. MASON[1], K. A. PICKETT[1], B. TRAVERS[2], A. PADILLA[1];
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Abstract: Previous studies have examined the synchronous performance of locomotion and grasping in young adults, however, it is unclear how the coordination of these two tasks changes

with age. The purpose of this study was to investigate differences in the combined control of upper and lower limbs in young adults and adolescents. ***Method:*** Twenty-one right-handed young adults (8 males, mean age 21.2 ± 1.0 years) and 23 adolescents (14 males, mean age 11.2 ± 2.0 years) participated in the study. Three-dimensional kinematic data of the torso and right upper limb was collected via infrared motion capture (VisualEyez, PTI Phoenix, inc.). Gait characteristics were collected using a six meter GAITRite instrumented walkway. Participants were asked to walk the length of the gait mat and grasp a small or large object that was positioned on a height-adjusted table mid-way along the mat. These combined walking and grasping tasks were compared to conditions where participants walked without grasping or grasped without walking. We also compared spatio-temporal gait and grasp measures across key time points such as the approach phase (steps prior to the moment of grasp) and grasp phase. ***Results:*** For normalized step length during the approach phase there were significant main effects of Group ($F_{1,42}$=8.518, p=0.006) and Condition ($F_{2, 84}$=25.011, p<0.001). Normalized step length was longer for the children than for the young adults and was longer in the forward walking condition than both the grasp small and grasp large conditions. For normalized step length during the grasp phase, there were significant main effects of Group ($F_{1,42}$=4.444, p=0.041) and Condition ($F_{1.683,70.668}$=96.040, p<0.001). Final normalized step length was longer for the children than for the young adults and was longer in the forward walking condition than both the grasp small and grasp large conditions. When comparing grasp aperture (maximum distance between the index finger and thumb) for the walking and grasping conditions and the standing and grasping conditions, there were main effects of Condition ($F_{1,41}$=39.4, p<.001) and Object Size ($F_{1,41}$=792.5, p<.001). Peak aperture was larger when participants walked and grasped compared to when they stood still and grasped. Apertures were also larger when grasping the large object when compared to the small object. There were no group differences for peak aperture. ***Conclusion:*** Although there were main effects of group across most variables, the lack of interaction effects provides preliminary evidence that adolescents and young adults coordinate the complex task of walking and grasping similarly.

Disclosures: **A.H. Mason:** None. **K.A. Pickett:** None. **B. Travers:** None. **A. Padilla:** None.

Poster

763. High-Level Control of Posture and Gait

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Topic: E.06. Posture and Gait

Support: DOD Award #SCI140238
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NREF Research Grant

Title: Deep brain stimulation of the mesencephalic locomotor region acutely enhances locomotion in a large animal model of incomplete spinal cord injury

Authors: *S. J. CHANG[1,4], A. J. SANTAMARIA[1], F. J. SANCHEZ[1], P. M. P. SARAIVA[1], L. M. VILLAMIL[1], Y. NUNEZ-GOMEZ[1], I. OPRIS[1], J. P. SOLANO[2], J. D. GUEST[1,3], B. R. NOGA[1,3];
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Abstract: Background: The mesencephalic locomotor region (MLR) is a region of the midbrain where electrical stimulation can elicit fictive/overground locomotion in decerebrate/intact small animal models, and enhance locomotion in small animal models of incomplete spinal cord injury (SCI). Assessing the effect of MLR deep brain stimulation (DBS) in a freely moving large animal model of SCI is a major step in determining the feasibility of using MLR DBS to augment gait clinically for gait disorders (i.e. SCI, Parkinson's disease).
Hypothesis: We hypothesized that DBS of putative MLR sites in awake and freely moving Yucatan micropigs would augment locomotion parameters after SCI.
Methods: Medtronic 3389 DBS electrodes were chronically implanted into putative MLR sites of Yucatan micropigs using MRI-guided stereotactic targeting. Intraoperative stimulation was used to evoke locomotor-like activity and confirm our stereotactic targeting. The ability to initiate and augment locomotion with MLR DBS was confirmed in freely moving, intact animals before they received an incomplete T9 contusive SCI by weight drop. EMG electrodes were implanted intramuscularly to record patterns of muscle activation in agonist/antagonist muscles of all four limbs during locomotion with and without MLR DBS. Kinematics data was collected using a Vicon motion capture system.
Results: We demonstrate that in addition to initiating and augmenting locomotion in the intact micropig, MLR DBS can be used after SCI to augment hindlimb EMG amplitudes, increase hindlimb frequency, and enhance coordination of limbs during locomotion.
Conclusions: Electrode location and stimulation parameters are crucial to eliciting specific locomotor outputs in the intact Yucatan micropig. Discovering these optimal electrode position and stimulation parameters allowed us to effectively evaluate the acute locomotor effects of MLR DBS in this animal model of SCI. Our research results have direct translation potential to clinical DBS trials targeting this region, and may partly explain why previous studies in Parkinson's disease patients to alleviate gait dysfunction did not produce more significant outcomes. Further research is required to ascertain the chronic effects of MLR DBS on locomotor function in this large animal model of SCI.

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Poster

763. High-Level Control of Posture and Gait

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Support: NIH (T32EB009406)
Merit Review Award # I01RX001979 from the United States Department of Veterans Affairs, Rehabilitation Research and Development Service

Title: Adaptive locomotor trajectory planning in consistent and unpredictable environments

Authors: *M. A. BUCKLIN[1,2], J. DEOL[1,3], M. WU[1], G. BROWN[1], K. E. GORDON[1,4]; [1]Physical Therapy and Human Movement Sci., [2]Biomed. Engin., Northwestern Univ., Chicago, IL; [3]Shirley Ryan Ability Lab., Chicago, IL; [4]Edward Hines Jr. Admin. Hopsital, Hines, IL

Abstract: To aid in successful execution of goal-directed walking (discrete movement from a start location to an end target) the nervous system forms a motor plan that must be adapted in response to environmental changes. Despite motor planning being inherent to goal-directed walking, it is not understood how the nervous system adapts these plans to interact with novel environments. Our purpose is to understand how people adapt motor plans of center-of-mass (COM) trajectory during goal-directed walking amid consistent or unpredictable changes in the environment. We hypothesized that participants would modify an internal model to control movement in a consistent environment and would use a high-impedance strategy in an unpredictable environment. Healthy adults performed repetitions of a discrete walking task, moving from static standing to a target located 1.5 leg lengths ahead. During some trials, a cable-driven robot applied a laterally-directed force to the participant's COM. This force field was proportional in magnitude to forward walking velocity. Participants performed 110 total trials of the task: 20 Baseline trials (no applied forces), 70 Field trials (in the force field), and 20 Washout trials (no applied forces). Trials 45, 60, 75, and 90 were Catch trials (no applied forces) to evaluate neural control strategies. Two groups of participants (n=5 per group) performed the experiment. For group one, the force field direction was consistent, always applied to the right. For group two, the force field was unpredictable, randomly applied to the right or left. We quantified Signed Deviation - deviation of COM trajectory relative to a straight line in the sagittal direction. Changes in COM trajectory were evaluated by comparing Signed Deviation between Baseline and Catch trials with a two-tailed t-test and significance set at $p < 0.05$. We observed a significant difference between Baseline and Catch for group one ($p < 0.05$) and no significant difference for group two ($p = 0.85$). During catch trials in the consistent environment, participant's trajectories deviated in the opposite direction of the force field, suggesting the use of an internal model. During Catch trials in the unpredictable environment, trajectories were

similar to Baseline, suggesting the use of a high-impedance strategy. These results support our hypothesis that people form an internal model of their COM trajectory amid a consistent environment and utilize a high-impedance strategy amid an unpredictable environment. The ability to adapt different whole-body control strategies in response to varying environments provides the nervous system flexibility to consider competing costs of walking.

Disclosures: M.A. Bucklin: None. **J. Deol:** None. **M. Wu:** None. **G. Brown:** None. **K.E. Gordon:** None.

Poster

763. High-Level Control of Posture and Gait

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 763.16/N4

Topic: E.06. Posture and Gait

Title: Effects of environments on the dual tasking timed up and go test: A pilot study

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Abstract: The Timed Up & Go (TUG) Test is a clinical measure to assess the probability of an individual having a fall [1]. Dual-task (DT) TUG test has shown to be more sensitive in detecting those who are at high risk of fall compared to standard TUG test [2]. One limitation of the DT TUG, however, is that it is performed in a controlled laboratory setting. Little is known about the effect of DT on TUG activities in an outdoor environment. Thus, the objective of this study is to evaluate the effects of the environment (indoor vs. outdoor) on the DT TUG test. Two young adults (age 27.5 ± 0.7, 1 Female) completed five conditions that were presented in a randomized order: 1. TUG, 2. TUG while carrying a cup of water (TUG_m), 3. TUG with a mental calculation task (TUG_{MCT}), 4. TUG with a verbal fluency task (TUG_{VF}), 5. TUG while texting ($TUG_{Texting}$). These conditions were performed in two environments: 1. Indoor: which was the research/biomechanics lab at West Coast University (WCU), 2. Outdoor: which was a sidewalk within a walking distance from WCU. The dependent variables include the dual tasking cost (DTC) of the time, step count, and cadence. The DTC is a calculation that reflects the change in a motor behavior occurring under high attention-demand conditions; a lower DTC would reflect poorer motor performance [3]. Environment did not alter the DTC of time, cadence, or step count. The DTC of the walking time in $TUG_{Texting}$ was lower in the outdoor environment compared to the indoor environment; however, this did not reach a significant level ($p=0.09$). Our pilot data suggest that texting might add an additional cost to motor performance in the outdoor environment compared to the indoor environment. A clearer conclusion will be drawn from this data as we enroll more participants across ages. The results from this project may help in developing an ecologically valid measure for fall risk assessment or intervention in the elderly.

References: 1. Kenny, R. A., Richardson, D. A., & Steen N. Developed by the Panel on Prevention of Falls in older Persons, American Geriatrics Society and British Geriatrics Society. Summary of the Updated American Geriatrics Society/British Geriatrics Society Clinical Practice Guideline for Prevention of Falls i. *J Am Geriatr Soc*. 2011;59:148-157. 2. Ponti M, Bet P, Oliveira CL, Castro PC. Better than counting seconds: Identifying fallers among healthy elderly using fusion of accelerometer features and dual-task Timed Up and Go. *PLoS One*. 2017;12(4). doi:10.1371/journal.pone.0175559 3. Almajid R, Keshner E. Role of Gender in Dual-Tasking Timed Up and Go Tests: A Cross-Sectional Study. *Journal of Motor Behavior*. 2019.

Disclosures: R. Almajid: None. **A. Makaremi:** None. **A. Hensley:** None.

Poster

763. High-Level Control of Posture and Gait

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 763.17/N5

Topic: E.06. Posture and Gait

Title: Muscle synergies identified from step-to-step variations of muscle activations during treadmill locomotion in rats

Authors: *J. J. WALLNER[1], C. ALESSANDRO[2], M. C. TRESCH[3];
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Abstract: It has been proposed that muscles are controlled as parts of coordinated groups, referred to as *motor primitives* or *muscle synergies*. In this hypothesis, each muscle synergy specifies a particular balance of activation amongst a set of muscles and complex behaviors are produced from a simple combination of these synergies. Dimensionality reduction techniques have demonstrated a lower-dimension latent space of muscle activations underlying a range of behaviors in a number of species, providing evidence for this muscle synergy hypothesis. However, it is currently unclear whether the identified synergies arise centrally from neural control or simply reflect the constrained requirements of individual tasks. As a step towards evaluating these issues, it has been proposed that the trial-to-trial variations in muscle activation across repetitions of a behavior might better reflect the structure of neural control. This approach assumes that muscle activations that are consistent across repetitions of a behavior reflect the consistent influence of task constraints on muscle activation. Although this assumption is likely to be a simplification, this approach might allow investigators to evaluate whether identified muscle synergies reflect neural control strategies or task constraints. We are examining these issues in the context of hindlimb muscle activations produced by rats during locomotion. We recorded the simultaneous EMG activity in up to 15 hindlimb muscles while animals walked

across a range of treadmill speeds and inclines. For each behavioral condition, we divided the EMGs into distinct steps defined by foot contact and calculated the step-averaged activation for each muscle. We subtracted this average from the observed EMG to obtain the residual EMG reflecting the trial-to-trial variations of muscle activation. We then identified the dimensionality of the latent space and muscle synergies underlying either these residual activations or underlying the total activations. In initial results we have found that the identified latent space is very similar whether analyzing either the total or the residual activations, suggesting that the observation of muscle synergies is not strictly determined by task constraints. Additionally, although the dimensionality of the residual activations was higher than that of the total activations, the synergies identified from the residual activations predicted the total activations very well. We are currently evaluating the robustness of these findings across task conditions and across animals, in order to better understand the role of task constraints in determining muscle synergies observed during behavior.

Disclosures: J.J. Wallner: None. **C. Alessandro:** None. **M.C. Tresch:** None.

Poster

763. High-Level Control of Posture and Gait

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Program #/Poster #: 763.18/N6

Topic: E.06. Posture and Gait

Support: NIH Grant R01AG054621

Title: Older adults demonstrate sustained adaptation to frequent perturbations in recumbent stepping

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Abstract: Perturbations applied during treadmill walking often result in adapted walking patterns and balance control. Applying perturbations during locomotor tasks such as recumbent stepping could lead to adapted stepping patterns and arm and leg coordination that improve walking; this allows individuals with balance or walking difficulties, such as older adults, to benefit from perturbation-based training on a recumbent stepper. The purpose of this study was to quantify stepping adaptation of older adults in response to frequent mechanical perturbations during recumbent stepping. We hypothesized that older adults would adapt to the perturbations and minimize stepping errors to return to the unperturbed kinematic profile. Subjects (n=6, age: 60-75) stepped on a robotic recumbent stepper that created brief 0.2 s perturbations on every stride. Each subject performed four 10-minute stepping trials. The first and last two minutes of

each trial had no perturbations (i.e. unperturbed baseline and post), while the middle six minutes had perturbations that were applied at the onset or middle of leg extension (2 legs * 2 time-window = 4 trials). We instructed subjects to step smoothly and to maintain a stepping pace equal to 60 steps-per-minute following a visual cue. We excluded the first minute of the baseline and the last minute of the post from our analyses and quantified stepping error as the maximum difference of the time-normalized stepper position for each stride from the averaged baseline profile. The stepping error for baseline was always less than 5 degrees. During the 6 minutes of perturbed stepping, there was a significant increase in stepping error, but the error decreased with adaptation from the first perturbed stride to the last. This decrease was only significant for mid-extension perturbations (rAnova & LSD, post-hoc $p<0.05$). Stepping error decreased in the post period but remained significantly greater than the baseline error for all perturbations (rAnova & LSD, post-hoc $p<0.05$). We found that older adults adapted to the brief, frequent perturbations applied during recumbent stepping. However, adaptation did not return to the unperturbed kinematic profile; this suggests that subjects sustained the adapted stepping patterns, which may be beneficial for rehabilitation.

Disclosures: **T. Shaffer:** None. **S. Shirazi:** None. **H.J. Huang:** None.

Poster

763. High-Level Control of Posture and Gait

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Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 763.19/N7

Topic: E.06. Posture and Gait

Support: Liberty Mutual Insurance

Title: Task-specific modulation of the functional field of view during locomotion

Authors: *V. MIYASIKE-DASILVA[1], J. J. BANKS[2], Y. R. RAWAL[1], B. SHARAFI[3], J. V. JACOBS[4];
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Abstract: During locomotion, vision plays a crucial role in the ability to identify obstacles and environmental features to guide appropriate gait changes. Relevant visual information about the environment can be extracted via the functional field of view, which is the area in the peripheral visual field within which visual stimuli can be detected while central vision is engaged in a concurrent visual task. Although it is well established that increased cognitive load in the central task causes an overall reduction in the functional field of view, the present study investigated the effect of locomotor activity on the extent of the lower and upper functional field of views.

Healthy young adults (n=14) performed a reaction-time task requiring them to discriminate letters appearing in their central visual field. Concurrently, participants detected visual stimuli appearing randomly in their upper and lower peripheral visual fields at varying eccentricities (25, 35, and 45 degrees). Central and peripheral vision stimuli were presented on a projection screen. Participants performed the visual tasks under 3 postural conditions: sitting, standing, and walking on a treadmill. For the central vision task, there were no differences in reaction times and errors across the 3 postural conditions. However, the ability to detect peripheral visual stimuli was influenced by posture. Specifically, participants missed more peripheral stimuli during walking (11.0±0.06%) than during sitting (3.00±0.044%) or standing (3.00±0.043%). Interestingly during walking, there was a higher rate of misses for peripheral stimuli presented in the upper field of view than in the lower field of view, especially for stimuli at 45 degrees. For sitting and standing, the rate of misses was balanced between upper and lower fields of view. These findings suggest that the capacity to extract visual information from the lower visual field is preserved during locomotion. This study presents evidence for a task-specific modulation of the functional field of view which likely plays an important role in the control of locomotion during daily activities such as distracted walking.

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Poster

763. High-Level Control of Posture and Gait

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Program #/Poster #: 763.20/N8

Topic: E.06. Posture and Gait

Support: NIH/NICHD grant R01HD091184

Title: Evaluating optimization principles in bipedal locomotion using dynamical movement primitives

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Abstract: Despite the many possible ways that one could walk, humans often choose stereotypical features of their gait pattern that vary systematically as a function of performance objectives and environmental constraints. The selection of these features can often be explained as arising from the optimization of one or more objectives such as energetic cost and stability. Testing hypotheses about the objective functions underlying the selection of gait features often requires models that capture the key dynamics of locomotion. Optimization of bipedal walking

models, however, is computationally challenging due to the high-dimensionality of the state and action space. One potential biologically-inspired optimization approach during locomotion is to systematically constrain the action space to a lower-dimensional manifold. Here we present a framework for evaluating optimization principles during walking through the use of dynamical movement primitives (DMPs) in simulations of bipedal gait. DMPs are low-dimensional control policies that can be extracted from demonstration by fitting a set of basis functions to observed trajectories.

We fit DMPs onto kinematic data of human walking on treadmill. These DMPs produced time-varying trajectories for lower-extremity joint angles via a small set of free parameters. We also developed a simulation of an anthropometric biped with nine degree-of-freedom and six controllable joints walking on a treadmill in Matlab SimScape. Foot-ground interactions between the biped and treadmill were modeled via viscoelastic elements. Since the biped has fewer controlled degrees of freedom than available ones, we added a feedback controller that updated the DMP amplitudes and timing to stabilize the biped's pitch and position on the treadmill.

The extracted DMPs fit the human demonstrations successfully. The controllers efficiently stabilized the biped walking on the treadmill producing a high negative correlation between the update in step length and the error in biped position ($r = -0.92$ for left and $r = -0.79$ for right leg) such that when the biped fell behind the center of the treadmill the controller produced longer steps to move back toward the set point and vice versa. In the absence of feedback control, the biped was unable to walk a full stride. The mechanical power consumed by the biped was 2.82 $W.kg^{-1}$, which is comparable to the cost of transport of ~2.38 W.kg-1 for human walking at matched speeds. Having a control policy that mimics the behavior of human walking, we now have a framework that can be used in predictive simulations to explore plausible ways in which the neuromotor system adapts to unexpected disturbances or novel environments.

Disclosures: P. Nozari Porshokouhi: None. **J.M. Finley:** None.

Poster

763. High-Level Control of Posture and Gait

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 763.21/N9

Topic: E.06. Posture and Gait

Support: NIH Grant 1U54GM104944
Kurt O. Olsson Early Career Research Grant from College of Letters, Arts, and Social Sciences at the University of Idaho

Title: Lighten up! Postural instructions affect static and dynamic postural control in healthy older adults

Authors: *R. G. COHEN[1], C. G. BILLINGS[1], J. L. BAER[2], D. KRAL[1], R. RAVICHANDRA[1], C. P. MCGOWAN[2], T. W. CACCIATORE[3];
[1]Dept. of Psychology & Communication, [2]Dept. of Biol. Sci., Univ. of Idaho, Moscow, ID; [3]Neurol., Univ. Col. London, London, United Kingdom

Abstract: Background: Aging is associated with declines in static and dynamic postural control, which may lead to falls. Previous work showed that brief postural instructions can affect steadiness and step initiation in older adults with Parkinson's disease. Here, we compared the effects of different instructions on postural control in a group of healthy older adults. **Method:** Twenty participants practiced three sets of instructions, then attempted to implement each instructional set during (1) 30-second eyes-open quiet standing on foam; (2) a three-second foot-lift. The 'Light' instructions relied on principles of reducing excess tension while encouraging length. The 'Effortful' instructions relied on popular concepts of effortful posture correction. The 'Relax' instructions encouraged minimization of effort. We measured kinematics and muscle activity. **Results:** During quiet stance, the Effortful instructions increased mediolateral jerk and path length of the center of mass. In the foot-lift task, the Light instructions led to the longest foot-in-air duration and the smallest anteroposterior variability of the center of mass, the Relax instructions led to the farthest forward head position, and the Effortful instructions led to the most activity in torso muscles. **Conclusion:** Maintaining postural intentions based on the idea of effortlessly "lightening up" may reduce excessive co-contraction and increase postural stability. This effect may partly account for the reported benefits of embodied mindfulness practices such as Tai Chi and Alexander technique on balance in older adults.

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Poster

763. High-Level Control of Posture and Gait

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 763.22/N10

Topic: E.06. Posture and Gait

Support: NIH R01NS073649

Title: Corticomuscular coherence in alpha band differentiates active and passive stepping

Authors: *S. M. BRUNSON[1], H. J. HUANG[2];
[1]Dept. of Biomed. Sci., [2]Mechanical and Aerospace Engin. Department, Biomed. Engin. Area, Univ. of Central Florida, Orlando, FL

Abstract: Previous studies have shown that active effort tends to improve recovery of walking ability compared to passive movements. This could be due to increased corticomuscular coherence, which is the determination of whether cortical impulses are synchronous with muscle activation. The purpose of this study is to analyze brain activity using electroencephalography (EEG) and muscle activity using electromyography (EMG) from both active and passive recumbent stepping for corticomuscular coherence. We analyzed EMG data from the tibialis anterior for the right leg only. We outfitted seventeen healthy young adults with a 256-channel EEG system, and they performed stepping on a robotic recumbent stepper using either active or passive effort. For active effort, subjects used their arms and legs to drive the stepper, while for passive effort, subjects relaxed and allowed the stepper to move their limbs. We performed independent component analysis and source estimation using DIPFIT. We identified four clusters for use in coherence calculations: the right parietal, right premotor, posterior cingulate, and right motor cortices. We analyzed the coherence spectra using the FieldTrip toolbox for MATLAB. Current results show small increases in coherence for active stepping in certain regions of the brain. Subjects showed increased coherence during active stepping in the right motor cortex from 10-15 Hz and within the beta band around 22 Hz. The right premotor and posterior cingulate showed higher coherence in active stepping within the alpha band (8-13 Hz). The right parietal, however, showed higher coherence during passive stepping in the alpha band. These results suggest that the brain and muscles may be communicating slightly more during active stepping than passive stepping. Beta band coherence is especially tied to conscious control of motor movements, while the alpha band is often linked to onset of dynamic movements. This provides greater evidence that active stepping is more dynamic than passive stepping. However, the high values of passive coherence in many subjects may show that cortical control persists even in passive movement. Another consideration is the difference between the biomechanics of treadmill walking and recumbent stepping, as the tibialis anterior plays a smaller role during recumbent stepping. Overall, these results indicate that active stepping has greater corticomuscular coherence than in passive stepping, though this may vary depending on the individual and the region of interest in the brain.

Disclosures: S.M. Brunson: None. **H.J. Huang:** None.

Poster

763. High-Level Control of Posture and Gait

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 763.23/N11

Topic: E.06. Posture and Gait

Support: Research Grant from the Learning Institute for Elders (LIFE) at UCF

Title: Walking speeds can be predicted from electroencephalography after dimension reduction

Authors: A. S. RAHROOH[1], H.-H. HUANG[2], *H. J. HUANG[1];
[1]Dept. of Mechanical and Aerospace Engin., [2]Dept. of Statistics, Univ. of Central Florida, Orlando, FL

Abstract: Electroencephalography (EEG) is being used to more and more to record electrical brain activity from the scalp during walking and dynamic movements. Several studies have shown that electrocortical activity is coupled with walking dynamics and more recently, that electrocortical activity is also modulated with walking speed. The purpose of this study was to determine whether common classification methods could predict walking speeds from reduced temporal dimension EEG data. Subjects (n = 7) walked with five different walking speeds (0.5 m/s, 0.75 m/s, 1.0 m/s, 1.25 m/s, and self-paced) on an instrumented treadmill while wearing a 128-channel EEG cap to record scalp EEG data. For each speed, subjects walked for 5 minutes for a total of 25 minutes. The EEG system had a sampling rate of 512 Hz. To reduce the temporal dimension, we used spatial Independent Component Analysis prior to classification on a training data set and validation on a testing data set. On the training data set, we applied seven classification methods (Bagging, Boosting, Random Forest, Naive Bayes, Logistic Regression, and Support Vector Machines with a linear and radial basis function kernel). On the test data set, we calculated and compared overall classification rate, precision, sensitivity, and specificity for each classifier. The Logistic Regression classifier had the highest overall classification rate (mean +/- standard deviation, 76.6% +/- 13.9%), the highest precision (86.3% +/- 11.7%), and highest sensitivity (88.7% +/- 8.7%). The Support Vector Machine with a radial basis function kernel had the greatest specificity, 60.7% +/- 39.1%. The overall performance was relatively good, considering that the EEG data was minimally processed or "cleaned" as we only high-pass filtered the EEG with a 1 Hz cutoff frequency. We recently performed a similar study but applied this procedure of using spatial Independent Component Analysis to reduce dimension to an isolated EEG motion artifact data set recorded as subjects walked with different speeds (0.4 m/s, 0.8 m/s, 1.2 m/s, and 1.6 m/s). The results of our previous study were similar to this study in that the Logistic Regression performed the best out of four classifiers evaluated in the previous study (K-nn, Naïve Bayes, Logistic Regression, and Support Vector Machine with a linear kernel). Together, these results indicated that walking speeds can be predicted from EEG data after the temporal dimension of EEG was reduced using spatial Independent Component Analysis.

Disclosures: A.S. Rahrooh: None. **H. Huang:** None. **H.J. Huang:** None.

Poster

763. High-Level Control of Posture and Gait

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Program #/Poster #: 763.24/N12

Topic: E.06. Posture and Gait

Support: NIH Grant R37-NS090610

Title: Transfer of the perceptual and motor components of treadmill learning to natural walking

Authors: *C. ROSSI[1], A. J. BASTIAN[2];
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Abstract: Motor adaptation is an error driven learning process that recalibrates motor commands in response to predictable changes in the environment. This learning process also changes the perception of the adapted movement. For example, when people walk on a split belt treadmill, they learn a new gait pattern that accounts for the fact that the belts are moving at different speeds. They also develop the perception that that their legs are moving at more similar speeds than they actually are during split belt walking. People exhibit aftereffects in both the motor and perceptual domain when the treadmill belts are returned to equal speeds. However, the perceptual recalibration is incomplete compared to the motor recalibration. This has led to the idea that the perceptual changes may represent one component of the overall learning process. Split belt adaptation can partially transfer to natural over ground walking. This finding is also suggestive that more than one learning process may be at play: one component that generalizes and another that is context specific. It is not known if the perceptual recalibration transfers to over ground walking. Here we asked whether the recalibration of leg speed perception could be a marker of a) context specific learning, and therefore does not transfer to over ground walking or b) generalizable learning, and hence transfers and is fully washed out by natural walking. Participants adapted on the split belt treadmill and then were tested for both motor and perceptual aftereffects, before and after a bout of over ground walking. As expected, participants exhibited both motor and perceptual treadmill aftereffects following adaptation. Motor aftereffects partially transferred to over ground walking, washed out rapidly, and were reduced when subjects returned to the treadmill. Perceptual aftereffects also transferred to natural walking and were reduced upon subsequent return to the treadmill. Thus, both motor and perceptual effects transfer incompletely. This clearly demonstrates that the perceptual recalibration is not a marker of either context specific or generalizable components of adaptation. An interesting alternative is that both types of recalibrations are context specific, but the nervous system is slow to switch between walking patterns based on environmental cues. This could explain the transient over ground transfer and the resulting washout of the adapted motor and perceptual calibrations.

Disclosures: C. Rossi: None. **A.J. Bastian:** None.

Poster

763. High-Level Control of Posture and Gait

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 763.25/N13

Topic: E.06. Posture and Gait

Support: NIH Grant R37-NS090601

Title: A walk to remember: People learn and store new locomotor memories despite competing cognitive involvement

Authors: *K. A. LEECH[1], A. J. BASTIAN[2];
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Abstract: Savings, or faster relearning after initial learning, is a phenomenon observed across motor adaptation paradigms. Evidence suggests that cognitive processes interact with error-based learning to account for savings in arm and hand movements. For example, savings of an adapted reaching movement has been attributed to the use of aiming strategies. Specifically, upon re-exposure to the perturbation participants consciously aim their reaches toward the previously learned target location. We have previously demonstrated that savings of a recently adapted walking pattern is related to the ability to explicitly recall the perturbation. Yet, the contribution of cognitive processes to savings during walking remains unclear. Here we investigated how engagement in a cognitive task while simultaneously learning a new walking pattern may influence re-learning. We collected data from healthy young and older adult participants while they walked on a split-belt treadmill. All participants initially adapted to a split-belt perturbation, de-adapted with tied belt speeds, and adapted again to the same split-perturbation. To investigate the effects of increased cognitive demand during initial learning, participants either performed the split-belt paradigm alone or simultaneously completed cognitive tasks with varying degrees of difficulty (e.g. Simple Reaction Time Task, 3-Back Task). We found that dual-task performance did not change initial motor learning behavior in either age group. Despite simultaneously engaging in cognitive tasks, participants in the dual task groups learned the new walking pattern at the same rate as participants that performed the split-belt paradigm alone. While the motor behavior was similar across groups, dual-task interference was evident in the cognitive domain. Specifically, performance in the cognitive domain was poorer early in adaptation. Importantly, we found that increasing the cognitive load during initial learning did not interfere with the formation of a motor memory or savings of the new walking pattern. These findings suggest that adaptation-based learning may be a useful treatment approach in persons with cognitive deficits. However, more work is necessary to delineate the impact of cognitive deficits on the feasibility and efficacy of motor learning mechanisms. R37-NS090601 to AJB

Disclosures: K.A. Leech: None. **A.J. Bastian:** None.

Poster

763. High-Level Control of Posture and Gait

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Program #/Poster #: 763.26/N14

Topic: E.06. Posture and Gait

Support: R21AG059184-01A1

Title: Learning a new walking pattern: The roles of movement and model formation

Authors: P. PADMANABHAN[1], V. S. CHIB[2], *R. T. ROEMMICH[3];
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Abstract: The nervous system exhibits remarkable plasticity for learning new walking patterns to navigate through novel environments. This learning is mediated by a constantly updated internal model driven by sensory prediction error. These new patterns are then committed to memory for faster re-learning in the future – a phenomenon called "savings". Here we asked if humans learn and save the new walking pattern itself or, alternatively, an internal model of the pattern.

In this study, we perturbed walking in healthy adults but prevented them from adopting a walking pattern suited to a novel environment. We hypothesised that learning and savings would be affected if these processes rely on behavioral expression of the new pattern, but not if they rely solely on the formation of a new internal model (which could form with or without changes in movement). We used a split-belt treadmill to perturb walking by making the two legs move at different speeds simultaneously. Here, people initially demonstrate a large limp (e.g., right step longer than left) but eventually restore symmetric walking. This type of locomotor learning (termed "adaptation") is signified by an "aftereffect", or limp in the opposite direction upon removal of the perturbation.

During adaptation, one treadmill belt moved twice as fast as the other. In the clamped group, participants used visual feedback to maintain their initial limp throughout adaptation. This caused their step length asymmetry to remain unchanged and asymmetric throughout the trial. The control group adapted to the same perturbation without visual feedback. In both groups, we measured learning aftereffects with both belts moving at tied speeds. Savings was assessed by re-exposure to the same perturbation without visual feedback. The clamped group showed diminished learning compared to controls as evidenced by a markedly reduced aftereffect. Furthermore, the clamped group showed a complete lack of savings. These results suggest that inhibiting expression of the intended pattern is detrimental to learning and saving new gait patterns.

We then investigated whether learning may have been impacted by physiological factors that underlie locomotor control and could have been affected in the clamped group. Specifically, energy optimisation is thought to be fundamental to healthy walking. Indeed, energy cost was significantly higher throughout adaptation in the clamped group compared to controls. Thus, we prevented both symmetric walking and energy optimisation in the clamped group, revealing a need to dissociate the causal roles of expression of intended movement and energy optimisation in learning and savings of new walking patterns.

Disclosures: P. Padmanabhan: None. **V.S. Chib:** None. **R.T. Roemmich:** None.

Poster

763. High-Level Control of Posture and Gait

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 763.27/N15

Topic: E.06. Posture and Gait

Support: NIH 1R01MH115750-01

Title: Unsupervised classification of open field mouse behavior

Authors: *U. KLIBAITE[1], J. VERPEUT[2], M. KISLIN[3], S. S.-H. WANG[4], J. W. SHAEVITZ[1]; [2]Princeton Neurosci. Inst. and Dept. of Mol. Biol., [3]Neurosci. Inst., [4]Princeton Neurosci. Inst., [1]Princeton Univ., Princeton, NJ

Abstract: Advances in computer vision and deep learning have made it possible to explore animal behavior at fine temporal and spatial scales. In particular, new advances in automated pose detection make it possible to track fine-scale movements in mice, a model system for the study of many aspects of neural function, from locomotion and coordination to complex neurodevelopmental disorders such as autism. We combined the use of a deep-learning-based approach called LEAP (LEAP Estimates Animal Pose), which produces estimates of joint coordinates, with unsupervised classification in order to discover distinct behavioral bouts in 72 wild-type mice in an open field arena over five subsequent days. We used the resulting behavioral phenotypes to explore the evolution of behavior in individuals over minutes and across days. We also identified behavioral differences among individuals and between wild-type mice and models of neurodevelopmental disease. This method can be used to capture a broader behavioral repertoire with fewer experimental constraints than traditional low-dimensional, high-throughput behavioral assays.

Disclosures: U. Klibaite: None. **J. Verpeut:** None. **S.S. Wang:** None. **J.W. Shaevitz:** None. **M. Kislin:** None.

Poster

763. High-Level Control of Posture and Gait

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 763.28/N16

Topic: E.06. Posture and Gait

Support: New Jersey Brain Injury Research Fellowship
NIH R01 NS045193
R01 MH115750
U19 NS104648

Title: Behavioral effects of the DREADD agonist clozapine-N-oxide (CNO) revealed by computational analysis of free animal movement

Authors: *J. L. VERPEUT[1], M. KISLIN[1], U. KLIBAITE[1], J. W. SHAEVITZ[2,3,1], S. S.-H. WANG[1];
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Abstract: Chemogenetic activation of ectopically-expressed receptors is now commonly used to perturb the function of specific brain circuitry. However, receptor activators may have their own effects independent of neural circuit-specific effects. To probe the effects of the DREADD (designer receptor exclusively activated by designer drugs) activator clozapine-N-oxide (CNO) on mouse behavior, we used a neural network-based approach to classify detailed body-part positions and pose transitions (see accompanying abstract by Klibaite et al.). We monitored mice for 10-20 minutes per day, up to 5 days in a row, to capture detailed movements as well as adaptations to the arena.
We analyzed the distribution of behaviors across days in untreated mice and in mice treated, either acutely or over 5 weeks of juvenile development, with CNO (1 mg/kg, PND 21-56). In the absence of perturbation, adult mice demonstrated a high degree of fast locomotion on day 1. Mice acclimated over days, as evidenced by a shift away from locomotory and toward grooming behaviors. In mice treated in juvenile life, this multiday acclimation was not observed. In already-acclimated adult mice, acute treatment with CNO, we did not detect a change in the locomotory/grooming ratio. These results show that CNO can influence mouse behavior even in the absence of its intended receptor target.

Disclosures: J.L. Verpeut: None. **M. Kislin:** None. **U. Klibaite:** None. **J.W. Shaevitz:** None. **S.S. Wang:** None.

Poster

764. Impairments of Posture and Gait

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 764.01/N17

Topic: E.06. Posture and Gait

Support: NS082151
NS095873

Title: Effects of the first dose of levodopa on multi-muscle synergies stabilizing vertical posture in drug-naive Parkinson patients

Authors: *S. M. FREITAS[1], P. B. DE FREITAS, JR[2], A. FALAKI[3], T. CORSON[4], M. M. LEWIS[4], X. HUANG[4], M. L. LATASH[3];
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Abstract: Indices of multi-muscle synergies stabilizing center of pressure (COP) coordinates, assessed within the uncontrolled manifold (UCM) framework, are reduced in patients with Parkinson's disease (PD) compared to age-matched controls. Within the UCM approach, inter-trial variance is quantified in the space of activations of muscle groups with proportional activation scaling (M-modes) in two spaces, one affecting (V_{ORT}) and the other not affecting (V_{UCM}) the COP coordinates. A synergy index (ΔV) is computed as the normalized difference (V_{UCM} - V_{ORT}). In previous studies, we have demonstrated that PD patients on chronic antiparkinsonian medication show low ΔV in the "off" state (overnight withdrawal from medication) and an increase on ΔV due to greater V_{UCM} (good variability) without any changes in V_{ORT} (bad variability) after medication administration. Our goal was to disambiguate possible effects of long-term drug exposure and PD *per se* on the index of COP-stabilizing synergy. We tested a group of 11 drug-naïve PD patients and 11 healthy controls. PD patients had no clinical postural instability, recent falls, or positive scores on the pull-back test of the UPDRS-III. Participants performed three trials of whole-body voluntary sway followed by 25 trials of a self-initiated load-releasing task during standing on a force plate. Surface electromyographic activity in 13 muscles on the right side of the body was recorded to quantify M-modes. Data were collected both before ("off") and approximately 60 min after ("on") the first dose of carbidopa/levodopa (25/100) in eight PD patients. Drug-naïve PD patients showed negative ΔV magnitudes (lack of COP-stabilizing synergy) "off" medication, whereas controls showed posture-stabilizing multi-muscle synergy ($\Delta V > 0$). After taking the first dose of levodopa, PD patients demonstrated a significant reduction in V_{ORT} with no effect on V_{UCM}, leading to higher ΔV. The results suggest that de novo, drug-naïve PD patients already show impaired posture-stabilizing multi-muscle synergies. Moreover, levodopa modifies synergy metrics differently in de novo, drug-naïve PD patients (V_{ORT}) compared to PD patients on chronic antiparkinsonian medications (V_{UCM}). These data suggest that indices of multi-muscle synergies are promising behavioral biomarkers of early-stage PD.

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Poster

764. Impairments of Posture and Gait

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 764.02/N18

Topic: E.06. Posture and Gait

Support: University of Minnesota Neuromodulation Innovations (MnDrive)
Udall Center grant of the National Institutes of Health Award Number P50NS098573
National Center for Advancing Translational Sciences of the National Institutes of Health Award Number UL1TR000114

Title: The relationship between speed and spatiotemporal gait metrics of overground and treadmill walking in Parkinson's disease

Authors: *C. LU[1], K. H. LOUIE[2], S. E. COOPER[1];
[1]Neurol., [2]Biomed. Engin., Univ. of Minnesota, Minneapolis, MN

Abstract: Gait disorders are one of the most disabling symptoms of Parkinson's disease (PD) and one of the most refractory to treatment. While treadmill provides a convenient way to study gait, it remains equivocal whether the gait varies between overground and treadmill. Therefore, the aim of this study is to investigate how the relationship between gait metrics and walking speed vary between overground and treadmill walking in people with PD and healthy controls. We compared 29 healthy controls to 27 PD patients in the off-medication state. Participants were asked to walk continuously on an instrumented mat for at least 30 valid steps at a self-paced speed. After a resting break, participants were instructed to walk at their measured overground walking speed on an instrumented treadmill for 2 minutes. Average stride length and average cadence were computed for each participant in both overground and treadmill walking. Multiple linear regression analysis was employed for overground and treadmill walking separately for each dependent variable. The predictor variables selected for the analyses were the following: age, walking speed, group, and interaction between speed and group.
Regressions of log-transformed stride length and cadence on log-transformed gait speed showed the previously reported linear relationship for both overground and treadmill [1]. Furthermore, Parkinsonian gait was associated with shorter stride length regardless of whether stride length was normalized by leg length (leg lengths did not differ significantly between PD and control) compared to controls under both conditions. Stride length difference between PD and control was slightly greater in more severely affected PD patients with lower gait speeds. On the other hand, the cadence was faster in PD than controls under both conditions and the difference in cadence between PD and control was markedly greater in more severely affected PD patients with lower gait speed. In addition, we found both stride length and cadence were marginally

different between overground and treadmill.
The results demonstrate the relationships between specific gait metrics and gait speed are very similar between overground and treadmill walking. We conclude that our treadmill protocol is suitable for laboratory use to approximate natural overground walking scenario.
1.Kuo AD (2001) A Simple Model of Bipedal Walking Predicts the Preferred Speed-Step Length Relationship. J Biomech Eng 123:264 . doi: 10.1115/1.1372322

Disclosures: C. Lu: None. **K.H. Louie:** None. **S.E. Cooper:** None.

Poster

764. Impairments of Posture and Gait

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 764.03/N19

Topic: E.06. Posture and Gait

Support: Tufts CTSI Pilot Studies Program
Northeastern University Mentored TIER 1 Seed Grant

Title: Minimizing sensorimotor encumbrances for human facilitators in locomotor rehabilitation

Authors: M. KOH[1], S.-C. YEN[1], L. Y. LEUNG[3], S. GANS[3], Y. ADIBNIA[3], M. PAVEL[2], ***C. J. HASSON**[1];
[1]Physical Therapy, Movement and Rehabil. Sci., [2]Khoury Col. of Computer Sci., Northeastern Univ., Boston, MA; [3]Tufts Med. Ctr., Boston, MA

Abstract: The field of locomotor rehabilitation robotics developed to alleviate the heavy demands imposed by manual gait training, in which one or more therapists provide assistance by pushing and pulling on a patient's legs from a kneeling or squatting position. Although numerous robotic locomotor training algorithms have been developed and tested, such as assist-as-needed algorithms, outcomes are often below expectations. A better understanding of how human locomotor facilitators (LFs) help patients achieve locomotor goals may advance robotic algorithms. LFs are defined as individuals that apply assistive forces to improve patient gait characteristics (commonly physical therapists). However, human LF performance is usually constrained by heavy physical demands and awkward positioning, which makes it difficult to extract the "unencumbered" sensorimotor control strategy of a human LF. We, therefore, developed a new telerobotics approach that allowed LFs to provide locomotor assistance to patients with minimal sensorimotor encumbrances. Two human LFs (one experienced and one novice) used coupled robotic interfaces to provide manual assistance to a chronic stroke survivor walking on a treadmill (the LFs performed separately on different days). The LFs sat comfortably at a table while holding onto a small robotic manipulandum that provided haptic feedback about the stroke survivor's locomotor behavior, and the LFs saw a visual display of

information about the on-going sensorimotor interaction with the stroke survivor. The LFs assisted by applying light forces to the manipulandum, which were amplified and transferred to the stroke survivor's affected leg by a robotic arm. The goal was to increase step length by 25%. The training was performed once per week for five weeks, including about 20 min of assisted treadmill locomotion each session. Results indicated that both LFs were able to effectively manipulate the gait of the stroke survivor using the robotic interface. The novice LF applied forces that tended to lift the stroke survivor's leg upwards during push-off and swing, which was associated with improved retention of step length increases. Notably, poorer retention was observed for the experienced LF who applied assistive forces that more directly pushed the leg forward during swing. As expected, there was significant variation of LF assistance strategies and patient adaptation, even within the same LF. These results support the feasibility of minimizing therapist sensorimotor encumbrances using therapist-in-the-loop robotic gait training, which may inform customized robotic locomotor training algorithms for improved therapy outcomes.

Disclosures: **M. Koh:** A. Employment/Salary (full or part-time):; Northeastern University. **S. Yen:** A. Employment/Salary (full or part-time):; Northeastern University. **L.Y. Leung:** A. Employment/Salary (full or part-time):; Tufts Medical Center. 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.; Tufts CTSI Pilot Studies Program. **Y. Adibnia:** A. Employment/Salary (full or part-time):; Tufts Medical Center. **S. Gans:** A. Employment/Salary (full or part-time):; Tufts Medical Center. **M. Pavel:** A. Employment/Salary (full or part-time):; Northeastern University. **C.J. Hasson:** 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.; Northeastern Univ. Internal Grant, Tufts CTSI Pilot Studies Program.

Poster

764. Impairments of Posture and Gait

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 764.04/N20

Topic: E.06. Posture and Gait

Support: VCU Presidential Research Quest Fund

Title: Children with idiopathic toe walking showed differences in areas of tactile and vestibular processing

Authors: *V. W. CHU[1], G. L. GIROLAMI[2], R. SOANGRA[3], R. BEUTTLER[4], C. HOLLANDSWORTH[3], S. CHHEDA[3], M. GRANT-BEUTTLER[3];

[1]Virginia Commonwealth Univ., Richmond, VA; [2]Physical Therapy, Univ. of Illinois at Chicago, Chicago, IL; [3]Crean Col. of Behavioral Sci., [4]Sch. of Pharm., Chapman Univ., Irvine, CA

Abstract: Idiopathic toe walking (ITW) is characterized by the absence of heel contact during gait that cannot be attributed to a known medical cause. It has been suggested that ITW may be related to impaired sensory processing, but to date, there is limited research examining this relationship. Areas of sensory processing that potentially relate to ITW include: sensory seeking, tactile defensiveness, poor proprioception, vestibular dysfunction and difficulties with sensory modulation (Sobel et. al., 1997, Williams et. al., 2014, Wick & Zanni, 2010). There is also evidence that children with ITW has difficulty with balance (Williams, et al, 2013). To test the relationship between ITW and sensory processing, we examined balance, sensory processing, and motor function in individuals with ITW at 2 sites in the US.

At Virginia Commonwealth University, we recruited 9 children with ITW between the ages of 4 to 10 years (mean=6.6, 6M/3F) , and 1 young adult with ITW (20.8 y, F), along with age-matched subjects without gait deviations. Participants completed a set of activities: balance, ankle proprioception, sensory modulation response to tactile and vestibular stimuli, tactile sensitivity (detection threshold), gait, and gross motor skills to examine sensory processing related to walking. Children with ITW have difficulty using vestibular and vision information and ineffective use of ankle strategies for balance. They also showed increased difficulty with sensory modulation of vestibular stimuli and had tactile sensitivity on the extreme ends of the spectrum.

At Chapman University, we recruited 20 children with ITW between the ages of 4 and 14 years (mean=9.6, 12M/8F). Participants completed the Sensory Organization Test (SOT) and the Balance subtest on the Bruinicks-Oseretsky Test of Motor Proficiency (BOT-2). 17 of 20 participants demonstrated more than 1 fall on the SOT with a mean standard score of -2.6. BOT-2 balance subtest mean standard score was -1.5.

At our 2 research sites, we showed that children with ITW has challenges with balance and differences in tactile and vestibular processing. This research will advance our understanding of ITW by providing a framework to detect and analyze underlying sensory differences that can be present in some children with ITW. This framework may also allow the identification of subtypes of ITW related to sensory processing differences. Our research strives to better understand the causes of ITW, so that we can develop effective interventions to guide earlier treatment and prevent long-term consequences associated with persistent toe walking.

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Poster

764. Impairments of Posture and Gait

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 764.05/N21

Topic: E.06. Posture and Gait

Support: Paralyzed Veterans of America Research Foundation #3068
NIH/NINDS R37 NS030853
T32 Neurological and Rehabilitation Sciences Training Program

Title: Persistent deficits in hindlimb locomotion following infarct in the hindlimb motor cortex of rats

Authors: *S. B. FROST[1], J. A. BORRELL[2], S. BARBAY[1], E. HOOVER[1], B. J. LAMB[3], R. J. NUDO[1];
[1]Rehabil. Med., [2]Bioengineering Program, [3]Mol. & Integrative Med., Univ. of Kansas Med. Ctr., Kansas City, KS

Abstract: The purpose of this study was to examine deficits in hindlimb locomotion and changes in ambulatory behavior following infarct in the hindlimb representation area (HLA) of primary motor cortex. Adult, male, Sprague Dawley rats were randomly assigned to one of two groups: Infarct or Surgical Control. Intracortical microstimulation (ICMS) using standard procedures was conducted to identify the origin of corticospinal projections mediating movement of the hindlimbs in each rat. At the completion of mapping, an ischemic lesion of the HLA was made in the infarct group. To induce cortical ischemia, endothelin-1 (ET-1; Bachem Laboratories, 0.3mg/mL) was injected at a depth of 1.5mm from the cortical surface, through a micropipette attached to a Hamilton syringe using a micro syringe injector. Surgical control rats were mapped using ICMS but did not receive an infarct. Behavioral testing included Ledged Beam walking, Horizontal Ladder walking, Treadmill Gait Analysis via the DigiGait and TreadScan system, and Open Field Walking using OptiTrack (NaturalPoint, Inc.) kinematic analysis. Motor performance of each rat was evaluated on each test before surgery, and once a week for 4-10 weeks post-surgery. RESULTS: Foot fault scores for the contralateral hindlimb revealed greater deficits in animals with HLA infarct than pre-infarct or control rats on the Ledged Beam and Horizontal Ladder tests, up to 8-10 weeks after surgery. Additionally, persistent differences in some gait measurements of stride were observed in HLA infarct rats. These results demonstrate prolonged, measurable deficits following infarct in the HLA of motor cortex of rats, that suggests, contrary to current dogma, that HLA plays an important role in hindlimb locomotion in rats.

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Poster

764. Impairments of Posture and Gait

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 764.06/N22

Topic: E.06. Posture and Gait

Title: Neck muscle activation latency in older adults

Authors: *J. J. SOSNOFF, T. WOOD;
Kinesiology and Community Hlth., Univ. of Illinois at Urbana-Champaign, Urbana, IL

Abstract: Traumatic brain injuries (TBI) are a major cause in morbidity and mortality in older adults, with upwards of 80% of TBIs resulting from head impact during a fall. Recently it was observed that older adults are 3-times more likely than young adults to impact their head during an experimentally induced fall. Based in part on the observation that neck muscle latency is associated with mild TBIs in athletes, it was of interest to determine how aging impacts neck muscle activation latency in response to perturbation. It was hypothesized that old-old would have the largest muscle latencies. A total of 57 volunteers participated in the investigation and were divided into groups based on age (20 young (10 male, 22.3±3.8 yrs), 23 young-old (13 male, 67.2±3.8 yrs) and 14 old-old (4 male, 81.1±5.3 yrs). To examine muscle activation latency, participants underwent postural perturbations while muscle activation of the sternocleidomastoid (SCM), upper trapezius, and splenius capitis (Trigno wireless system, Delsys Inc, Natick MA) was recorded. Participants stood with their feet shoulder width with arms at their side staring straight ahead. The platform translated anteriorly or posteriorly 6.35 cm at a velocity of 20 cm/sec in a random fashion. Participants underwent three trials in each direction (randomized). Muscle activation latency was calculated as the onset of EMG signal subtracted from the onset of the translation. A Kruskal-Wallis nonparametric test was used to assess group differences. For anterior perturbations, a significant group effect for muscle latency of the right ($X^2(2) = 7.033$, $p = 0.030$) and left upper trapezius ($X^2(2)=12.2$, $p<0.05$) was observed. The young displayed shorter muscle activation latency (~175 ms) in comparison to young-old (~220 ms) and Old-Old groups (~230 ms). For posterior perturbations, a significant group effect for the right ($X^2(2)=9.0$, $p<0.05$), and left SCM ($X^2(2)=11.9, p<0.05$), the right upper trapezius ($X^2(2) = 7.326$, $p = 0.026$) were observed. The Young group (~150 ms) displayed quicker muscle activation latency compared to the Young-Old (~180 ms) and Old-Old groups (~215 ms). The current study revealed that there are greater neck muscle activation latencies in response to translations as a function of age. Given that neck muscle activation delays of 40 ms increase TBI risk by 20-25%, the functional importance of these observations are paramount. Future research examining the association between aging, head control and fall-related TBI is warranted.

Disclosures: **J.J. Sosnoff:** 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.; Johnson & Johnson, Inc. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); MC10, Inc.. F. Consulting Fees (e.g., advisory boards); Abbvie, Inc. **T. Wood:** None.

Poster

764. Impairments of Posture and Gait

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 764.07/N23

Topic: E.06. Posture and Gait

Support: NIH K01HD088762

Title: Dual-task cognitive motor interference exacerbates turn deficits in fragile X-associated tremor/ataxia syndrome (FXTAS)

Authors: *J. GUAN[1], J. A. O'KEEFE[2];
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Abstract: Individuals with a 55-200 CGG repeat expansion in the fragile X mental retardation 1 gene are at risk for developing FXTAS, a neurodegenerative disorder characterized by cerebellar ataxia and cognitive dysfunction. Balance and gait deficits are a major problem in FXTAS that lead to falls and progressive mobility disability. The impact of dual task (DT) cognitive motor interference or fast paced gait which are real life/challenging conditions has never been studied in FXTAS. We hypothesized that these gait "stress tests" would exacerbate gait and turn deficits and increase fall risk. Thirty individuals with FXTAS (age 66.9 ± 8.8 yrs.) and 35 controls (age 65.5 ± 8.3 yrs.) performed gait analysis using an inertial sensor based 25-meter two-minute walk test (APDMTM) under self-selected (SS) typical pace, fast as possible (FAP) pace and, DT cognitive interference condition asking subjects to perform a concurrent verbal memory task while walking at their normal speed. The dual task cost (DTC) for gait and turn parameters was calculated as (ST-DT/ST x 100). Linear regression analyses were performed to assess the association between FXTAS diagnosis on gait and turn outcomes under the three different gait conditions, controlling for age and sex. FXTAS subjects had marked reductions in stride length and velocity, increased double support and reduced swing phase times, and slower turn velocity and greater number of steps to turn compared to controls ($0.0001 > p < 0.039$) under all 3 test conditions. Under fast paced gait, FXTAS individuals displayed increased gait variability ($p = 0.025$) which is associated with instability and falls. Men participants with FXTAS had significantly elevated DTC for turning speed ($p = 0.036$), indicating cognitive interference for turning, which requires greater motor control compared to straight walking. There were no elevated DTC for spatiotemporal aspects of gait during straight walking, suggesting that men and women with FXTAS prioritized gait over cognition during the DT walking. This was supported by the finding that FXTAS individuals had greater DTC for the cognitive verbal fluency task ($p = 0.004$). The use of DT gait paradigms to cognitively challenge subjects significantly exacerbates turn function in men with FXTAS. Gait stress testing paradigms and associated gait and cognitive markers may be useful in future studies to: 1) help determine fall risk in FXTAS,

2) determine effective treatment interventions for both cognitive and motor deficits to improve cognition, gait and turning and thereby reduce fall risk and 3) provide clinically relevant outcome measures for clinical research.

Disclosures: J. Guan: None. **J.A. O'Keefe:** None.

Poster

764. Impairments of Posture and Gait

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 764.08/N24

Topic: E.06. Posture and Gait

Title: Ageing brain shows less gait-phase-related modulation of midline sensorimotor cortex

Authors: *H. YOKOYAMA[1], T. YOSHIDA[2], K. MASANI[3];
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Abstract: Introduction: The elderly tend to show instability during walking compared to the young. Recent studies suggest that the cortical activity plays an important role in the dynamic balance during walking. For example, the modulation of the cortical activity is coupled to gait cycle phases. However, this has been shown only in the young. As ageing is associated with structural and functional changes in the brain, the cortical contribution to the dynamic balance during walking may be also affected by ageing. Here, we tested the hypothesis that the elderly exhibit a different cortical activity during walking competed to the young.
Methods: Fourteen young and nine older men participated in this study. The participants walked straight on a path 40 times. We measured electroencephalographic (EEG) signals using 20 electrodes and lower limb kinematics for 80−120 strides data in each participant. The event related spectral perturbations (intra-stride changes in the spectral power) were calculated for three electrodes: Fz, Cz and Pz.
Results: We found significant spectral power modulations ($p<0.05$) relative to the gait cycle phases in a wide frequency band (10–40 Hz) at Cz in the young group. The power increased during 0−25% and 50−75% of the gait cycle and decreased during 25−50% and 75−100% of the gait cycle. On the other hand, there were no clear spectral power modulations at the other electrodes in the young group and all electrodes in the elderly group. A comparison between the spectral power modulations at Cz between the two groups showed significantly larger power modulations ($p<0.05$) in the gamma band (25–40 Hz) in the young group.
Discussion: The clear gait-related spectral power modulations at Cz (i.e., leg sensorimotor area) in the young group agree with previous studies. We found that the gait-related spectral power is attenuated in the elderly. This agrees with previous studies that showed the attenuation of motor-related cortical activity due to ageing in other motor tasks. Given that the gamma band activity

may be involved in muscle control and perception binding, the significant attenuation in the gamma band activity in the elderly may be related to their gait instability.

Disclosures: H. Yokoyama: None. **K. Masani:** None. **T. Yoshida:** None.

Poster

764. Impairments of Posture and Gait

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 764.09/N25

Topic: E.06. Posture and Gait

Title: Individuals with an ACL reconstruction adopt a more rigid coordination pattern during dynamic movement

Authors: *C. N. ARMITANO, S. MORRISON, D. M. RUSSELL;
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Abstract: The anterior cruciate ligament (ACL) is the most commonly injured ligament in the knee accounting for approximately 200,000 injuries in the United States each year. While the majority of research on individuals with and ACL reconstruction has focused on the local mechanical implications of this surgery, increased attention has been directed towards understanding the impact this injury (and subsequent surgery) could have on neuromuscular function. The aim of the current study was to examine if persons post-ACL reconstruction exhibit slower reaction times under postural conditions. Further, it was also of interest to assess whether there were difference in muscle recruitment patterns and/or movement strategies for persons with an ACL reconstruction compared to healthy controls. Sixteen adults with unilateral ACL reconstruction and 16 age-matched healthy controls participated in this study. Participants stood facing a reaction time light panel where they performed both simple and choice reaction time tasks under postural conditions. When the light source from the reaction time device turned on, participants were instructed to step forward as quickly as possible. Muscle activation of the lower extremity was assessed bilaterally using surface EMG on the gastrocnemius, soleus, vastus medialis, rectus femoris, biceps femoris, and gluteus medius. In addition, accelerometers were placed on the lower trunk, neck, and head to compare upper body acceleration patterns during a dynamic task. The reaction time device as well as the EMG and accelerometers were synced to capture the onset of the light stimulus as well as the onset of movement. The results revealed that the ACL reconstructed group were slower to initiate a step under the postural reaction time conditions. This slowing was seen irrespective of the limb used to initiate the step (i.e. unaffected or surgically repaired). In addition, persons with a reconstructed ACL also exhibited tighter coupling between the upper and lower body while taking a step compared to the controls. The muscle activation patterns of the ACL group revealed increased co-contraction of both lower limbs, possibly in an effort to increases stabilization of the body prior to taking a step. Overall,

these findings indicate that persons who have had an ACL reconstruction adopted a more rigid, coordination pattern during the dynamic stepping tasks that may account for their slower movement responses.

Disclosures: C.N. Armitano: None. **S. Morrison:** None. **D.M. Russell:** None.

Poster

764. Impairments of Posture and Gait

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 764.10/N26

Topic: E.06. Posture and Gait

Title: Sonic Hedgehog expression by pyramidal tract neurons is critical for quadrupedal gait coordination

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Abstract: Restoring the corticospinal tract (CST) after spinal injury is an unmet need. Recently, seminal studies demonstrated that forced neuronal activity greatly improves functional outcomes in rodent paradigms that are based on partial CST transection. The mechanisms by which electrical activity facilitates restorative and compensatory neuronal growth and synaptogenesis is not well understood. Layer 5 pyramidal tract (PT) neurons express multiple signaling factors throughout life in addition to glutamate including the cell signaling factor Sonic Hedgehog (Shh) (Harwell et al., 2012). In the adult CNS, Shh can be released from nerve terminals by neuronal burst firing. During spinal cord development, Shh is well known for regulating differentiation and congruent growth of neuronal and glial cell populations. In addition Shh signaling is critical for neuronal growth cone guidance of commissural neurons and synaptogenesis. Whether Shh signaling takes part in neuronal repair upon spinal cord injury in the adult is not well understood. We found that pyramidotomy increases up to 5 fold the expression of Shh in the soma of injured PT neurons (PT_{Shh}), indicating that Shh expression might be repressed by negative feedback signaling originating distal to the injury site. These results are reminiscent to the up-regulation of Shh expression in motor neurons and in dopamine neurons by motor neuron axotomy (Akazawa et al., 2003) or neurotoxin induced degeneration of striatal dopamine neuron targets (Gonzales Reyes et al., 2012), resp.. Together these observations suggest that increased Shh signaling is an acute response of projection neurons to their injury. We further find that animals with conditional ablation of Shh from PT neurons incompletely adapt to a complex running wheel: while control litter mates progressively improve running on a wheel in which random rungs were removed, mutants selectively improve placement of front limbs but not hind limbs. These observations suggest that Shh expression by PT neurons is critical for the coordination of

brachial and lumbar motor activity. One mechanism by which PT_{Shh} could influence quadrupedal coordination is by influencing structural plasticity of long distance intra spinal projection neurons. These neurons are critical for transmitting gait cycle status information from the brachial to lumbar spinal cord. We are currently identifying the neuronal subtypes in the spinal projection fields of PT neurons that express the Shh receptor Patched using gene expression tracer alleles. Further, we will test the degree of functional recovery to hemi-section of the spinal cord in animals with Shh ablation from PT neurons and controls.

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Poster

764. Impairments of Posture and Gait

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Program #/Poster #: 764.11/N27

Topic: E.06. Posture and Gait

Support: KGM4621922

Title: Influence of neural electrode implant in the median nerve of rhesus monkey on gait parameters of quadruped locomotion

Authors: *J. WON, J. PARK, J. SEO, Y.-J. AHN, H.-G. YEO, K. KIM, C.-Y. JEON, Y. LEE; Natl. Primate Res. Ctr., Korea Res. Inst. of Biosci. & Biotech., Cheongju, Korea, Republic of

Abstract: The aim of this study was to evaluate the gait parameters of rhesus monkeys after implantation of neural electrode. A total of six adult female rhesus monkeys (Macaca mulatta) were used in this study. Three of the monkeys were implanted with fork-type sieve electrode in the median nerve of right upper limb for 4 weeks while the other three were used as a normal control group. We characterized the spatio-temporal and kinetic parameters of quadrupedal gait of rhesus monkeys using a pressure-sensing walkway. In addition, we compared the longitudinal changes in gait parameters and symmetry index to baseline data that acquired prior to surgical implantation. All parameters for gait analysis following neural electrode implant showed significant difference. The laterality of symmetry index was progressively recovered over the course of 4 weeks after surgical implantation. These results indicated that peripheral nerve injury following neural electrode implant could be improved during the post-recovery period. These findings highlighted the features of neural electrode implant for monkey and process of peripheral nerve injury characteristics, providing a basis for the assessment of quadruped locomotion.

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Poster

764. Impairments of Posture and Gait

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 764.12/N28

Topic: E.06. Posture and Gait

Title: Post-concussion recovery timeline of postural stability in a division 1 baseball athlete

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Abstract: Concussions are traumatic brain injuries that alter brain functions such as balance and coordination. Sport-related concussions are critical to assess to avoid further permanent brain damage. The American Medical Society for Sport Medicine advises the use of postural control assessments to detect concussion-related abnormalities. Most of these assessments subjectively quantify balance errors, and these test scores tend to resolve within 72 hours post concussive incident; this may be problematic for athletes. We have recently shown that the use of Balance Tracking System (BTrackS) to assess balance is twice as sensitive as some of the subjective assessments immediately following a concussion. The BTrackS quantifies body sway control from total center of pressure excursion created by foot forces using a gold-standard balance measurement technology. In the current case study, we report the recovery timeline for postural sway from a 20-year-old male Division-I baseball catcher who suffered a concussion due to a direct foul ball hit to his helmet. BTrackS Balance Tests (BBT) were administered during pre-season and again 48 hours, 7, 14, and 21 days post-concussion. Testing consisted of three, 20 second trials where the athlete stood still on the BTrackS Balance Plate with eyes closed, hands on hips and feet shoulder width apart. BBT score was calculated as the average COP excursion across the testing trials. COP excursion is a proxy for total body's sway control. Larger BBT values indicate postural instability and worse balance. Recovery was quantified as the COP values returning to baseline within the Minimum Detectable Change (MDC; 5 cm) criterion for the test. Following the concussion, the athlete exhibit a significant balance decline. His immediate post-concussion sway was over 4 times larger than baseline, which is indicative of significant postural instability. There were two stages of recovery noted. An acute phase where balance improved to 4x MDC by day 7. A second recovery occurred from days 14-21 where the athlete tested within the criterion from baseline. In this report we show that it took more than 72 hours for recovery. While not all concussions cause balance deficits, those that do must be evaluated with sensitive objective tools to ensure complete recovery prior to return to play. A

premature return significantly increases the chances of a second impact in athletes and would have devastating effects on neurological function.

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Poster

764. Impairments of Posture and Gait

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 764.13/N29

Topic: E.06. Posture and Gait

Support: NIH Grant R44NS083098

Title: Wearable sensor system to monitor PD gait in activities of daily living

Authors: B. SHIWANI[1], S. H. ROY[1], M. M. SAINT-HILAIRE[2], C. A. THOMAS[2], P. CONTESSA[1], G. DE LUCA[1], *J. C. KLINE[1];
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Abstract: Current technologies to track the quality of gait for monitoring the presence and progression of neurodegenerative diseases such as Parkinson's disease (PD) are limited to instrumented lab setups or can track only a few basic gait parameters with portable settings. Consequently, monitoring clinically relevant metrics of gait in daily living activities remains a challenge. To satisfy this need, our group has developed a system of wearable sensors and automated detection algorithms that can automatically detect the gait activity and quality of gait within each cycle during activities of daily living. We tested this system during a pre/post L-dopa medication protocol among n=6 patients (age: 60.8 ± 11 y) with Parkinson's disease (Hoehn & Yahr 1-3) where gait deviations associated with medication wearing-off was tracked during 3-hours of unscripted activities of daily living in a simulated home environment. Two wearable

sensors were placed on the Extensor Digitorum (ED) and Tibialis Anterior (TA) muscles, respectively, on their most symptomatic side to record surface electromyography (sEMG) and inertial measurement (IMU) signals. Algorithms were designed to autonomously detect and monitor, in real-time, 4 key characteristics of PD gait: 1) angular range of arm movement - to assess degree of arm swing; 2) angular velocity of leg movement- to assess gait velocity; 3) EMG RMS - to analyze the muscle activation patterns during different phases of gait cycle; and 4) heel strike and toe-off dynamics - to analyze landing and propulsive phases of gait. We successfully detected instances of gait amidst other unscripted activities with 99.5% accuracy. All four gait metrics were significantly different ($p<0.05$) between the medication ON and OFF periods (based on expert video annotation). These results demonstrate that our wearable monitoring system can objectively characterize PD gait impairments in non-clinical settings.

Disclosures: **B. Shiwani:** A. Employment/Salary (full or part-time):; Delsys Inc. and ALtec Inc., USA. **S.H. Roy:** A. Employment/Salary (full or part-time):; Delsys Inc. and Altec Inc. USA. **M.M. Saint-Hilaire:** None. **C.A. Thomas:** None. **P. Contessa:** A. Employment/Salary (full or part-time):; Delsys Inc. and Altec Inc., USA. **G. De Luca:** A. Employment/Salary (full or part-time):; Delsys Inc. and Altec Inc., USA. **J.C. Kline:** A. Employment/Salary (full or part-time):; Delsys Inc. and Altec Inc. USA.

Poster

764. Impairments of Posture and Gait

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 764.14/N30

Topic: E.06. Posture and Gait

Support: National Center for Advancing Translational Sciences (NCATS), National Institutes of Health, through Grant Award Number UL1TR001111

Title: Cognitive load does not impact gaze behavior during walking in a real-world environment in older adult fallers and non-fallers

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Abstract: Everyday walking often involves simultaneous performance of a cognitive task in environments with competing auditory and visual stimuli. Previous research has not evaluated task performance in these situations, where older adults are known to fall, limiting our understanding of how older adults adjust their gait, visual scanning (gaze), and cognitive processing to avoid falls (or not). The purpose of this study was to examine the effect of dual-

task walking in a high-distraction real-world environment on cognitive performance, gait performance, and gaze behavior in older adult fallers relative to non-fallers. **METHODS:** Fourteen older adult fallers (76±9 years of age, 11 females, 17±3 years of education) and 15 older adult non-fallers (77±8 years of age, 11 females, 17±2 years of education) participated. Participants performed single-task walking, single-task cognitive (seated category naming), and dual-task walking (category naming + walking) trials for 1 minute each in a real-world environment (busy hospital lobby). Gait speed, gaze fixation duration on 6 areas of interest (AOIs), and percentage of time fixating on 6 AOIs were recorded during single- and dual-task walking trials. Number of correct responses, time to first response, and mean subsequent response time (measure of rate of decline of response retrieval throughout trial) were determined for single-task cognitive and dual-task walking trials. Two-factor mixed MANOVAs (Group x Task) compared cognitive and gait variables for fallers and non-fallers during single- and dual-task trials. A 3-factor mixed MANOVA (Group x Task x AOI) analyzed the gaze variables. **RESULTS:** Compared to single-task trials, during dual tasks, participants walked 0.2 m/s slower ($p<0.01$), had 1.5 fewer responses ($p=0.03$), and a 2823 ms shorter mean subsequent response time ($p<0.01$), indicating a faster declining rate of retrieval. Fallers walked 0.2 m/s slower than non-fallers ($p=0.01$). They also had 3.8 fewer responses than non-fallers during the single-task trial ($p=0.03$) and were 759 ms slower for the first response than non-fallers during dual tasking ($p=0.05$). Gaze behavior (fixation patterns) did not differ by group or condition. **CONCLUSIONS:** Older adult fallers and non-fallers exhibited dual-task decreases in gait and cognitive performance, but they did not change their gaze behavior, which may signify prioritization of visual scanning over gait and cognition. The apparent prioritization by fallers of cognitive performance over gait in a real-world environment, as evidenced by the slowed gait speed during single- and dual-task trials but less consistent cognitive decreases, may be contributing to fall risk.

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Poster

764. Impairments of Posture and Gait

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Topic: E.06. Posture and Gait

Support: NIH/NIA R01 AG013934-20
NIH/NIA R01 AG057013
NIH/NIA P30 AG21332

Title: Hand2 transcription factor enhances NMJ organization and function in old mice

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Abstract: Over time, declining muscle force and power leads to mobility disability and impaired quality of life. In aging rodents and humans, a denervation and reinnervation process is strongly implicated in *sarcopenia*: the progressive decline of skeletal muscle mass, composition, and function. We propose that the concomitant decline in expression of Hand2, a key transcription factor (TF) for sympathetic neuron maintenance, induces motor pre- and postsynaptic neuromuscular junction (NMJ) instability and disorganization. To counter the deleterious effect of sympathetic denervation, we developed a novel viral vector (AAV9-Hand2-eGFP, Hand2) carrying Hand2 expression exclusively to sympathetic neurons. Male and female, 16-month-old mice, were examined for signs of muscle denervation and sarcopenia 6 months after IV injection with either Hand2 or control empty virus (AAV9-eGFP, EV). We found that Hand2 increased preterminal synaptic vesicle release, neurofilament phosphorylation (Neurite length: Hand2: 3732±496 µm, EV: 2674±165 µm; P <0.01), NMJ pre/postterminal co-localization, hindlimb muscle mass (EDL: 25%, soleus: 14%, tibialis anterior: 17% and gastrocnemius: 25%; n = 6-8 muscles per treatment group; P < 0.01), myofiber cross-sectional area, and protein kinase-A RIIα/RIα ratio (EV, RIIα:1.05±0.03, RIα:0.93±0.04, ratio: 1.13; Hand2, RIIα:1.81±0.03, RIα:0.94±0.03, ratio: 1.94; P<0.001) which contributes to stability of the NMJ. We also examined Hand2 gene methylation, and RNA-sequencing, muscle metabolomics, and whole body and muscle function with aging in EV and Hand2 injected mice. Our data indicate that expression of Hand2 significantly enhances skeletal muscle adrenergic receptor signaling through the canonical pathway, and prevents in NMJ transmission, and muscle mass and function decline with aging.

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Poster

764. Impairments of Posture and Gait

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 764.16/N32

Topic: E.06. Posture and Gait

Title: Open-eyed one leg stand test predicts cognitive function, grey matter volume and white matter volume in healthy older people

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Abstract: Relationships between motor functions and brain structures have been mainly investigated in patient studies. Previous studies showed the association between balance performance and hippocampal volume loss in patients with Alzheimer's disease (AD) and mild cognitive impairment (MCI). However, they focused on specific brain regions such as medial temporal lobe using Region of Interest (ROI) analysis. In addition, they focused on either grey or white matter volumes in patients with AD and MCI. In the present study, we investigated the association between balance performance and both regional grey matter volume (rGMV) and white matter volume (rWMV) using whole brain analysis in healthy older people. Cognitively healthy 109 participants (62 females, mean age = 66.99) performed open-eyed one leg stand test to measure balance performance and 17 cognitive function tests to measure general cognitive function, processing speed, executive function and memory. Regional brain volume was measured by T-1 weighted MRI. The rGMV analysis revealed that the performance of the open-eyed one leg stand test was significantly positively correlated with rGMVs in the hippocampus, the nucleus accumbens, ($p<0.0125$, FWE, TFCE). The rWMV analysis also revealed that the performance of the open-eyed one leg stand test was significantly positively correlated with rWMVs in the superior frontal gyrus, the middle frontal gyrus, the hippocampus ($p<0.0125$, FWE, TFCE). In cognitive function results, the performance of the open-eyed one leg stand test was correlated with the performance of Trail Making Test B ($r=0.28$, $p=0.004$) and that of verbal fluency test ($r=0.21$, $p=0.028$). Consistent with the previous studies in AD and MCI, rGMV and rWMV in hippocampus was significantly correlated with the balance performance in the healthy subjects. On the other hand, we firstly found significant correlations between rWMV in the frontal region. Hippocampus and nucleus accumbens are important for spatial memory, which is associated with the vestibular system. Superior and middle frontal gyri are important for executive function and are related to balance control. Furthermore, this study revealed that open-eyed one leg stand is related to executive function. For older people, open-eyed one leg stand demands somatosensory inputs from the whole body and then they have to adjust the muscle strength or the center of gravity. Therefore one leg stand is associated with these brain regions.

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Poster

764. Impairments of Posture and Gait

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 764.17/N33

Topic: E.06. Posture and Gait

Title: Effect of dopaminergic medication on balance automaticity in Parkinson's disease

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Abstract: Background: Dual-tasking is an integral part of every-day life. Despite advances in pharmacological treatments, the problem of impaired dual-tasking persists in patients with Parkinson's disease (PD). Impaired dual-tasking can exaggerate balance dysfunction and increase the risk of falling. Loss of motor automaticity is considered a major reason for impaired dual-tasking in individuals with PD. There is a need to understand the influence of current dopaminergic medication on balance automaticity in PD. Furthermore, studies have shown non-analyses can provide another perspective about balance control, i.e., regularity in the body sway. An increased regularity in body sway indicate an improved and more efficient postural control. Along with conventional measures, non-linear parameters can facilitate to understand better the changes in postural control dynamics in patients with PD.
Research objective: To investigate the effect of dopaminergic medication on standing balance automaticity during a phoneme monitoring dual-task in PD.
Methods: Sixteen individuals with PD participated in a cross-over study involving single- and dual-task upright standing for 3 min, off and on dopaminergic medication, with eyes open and eyes closed (4 trials total). Linear and non-linear analyses were used to evaluate balance performance. The linear measures consisted of 95% confidence ellipse area, anterior-posterior (AP) sway velocity, medial-lateral (ML) sway velocity, and integrated time to boundary (iTTB). The non-linear measure involved percentage of determinism (%DET) based on recurrence quantification analysis.
Results: Compared to medication-off state body sway was more regular during medication-on state indicated by increase in %DET (p=0.007), but only during eyes open condition. Furthermore, medication caused significant increase in ellipse area (p= 0.002) and decrease in the performance on the secondary task (p= 0.004). In addition, different eyes conditions (open vs. closed) significantly increased both sway velocities (AP = $p < 0.001$, ML = $p < 0.001$) and increased iTTB ($p < 0.001$). There was also task by eyes condition interaction effect for AP velocity and iTTB (p= 0.015 and p= 0.009, respectively.
Conclusion: Conventionally, an increase in sway velocity and area is interpreted as poorer balance performance. However, the regularity in body sway increased indicated by increase in %DET. Therefore, in the context of stability, an alternate interpretation for medication-induced balance changes in PD suggest an increase in maneuverability without sacrificing the stability.

Disclosures: R. Mishra: None. **C. Workman:** None. **A. Thrasher:** None.

Poster

764. Impairments of Posture and Gait

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Program #/Poster #: 764.18/N34

Topic: E.06. Posture and Gait

Support: National Science Foundation 1748986

Title: Changes in lumbar BDNF gene methylation and locomotor behavior following spinal cord transection in developing rats

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Abstract: Although epigenetic activity in the brain is now well documented, relatively little is known about epigenetic regulation of genes in the spinal cord, and how it contributes to neural plasticity and behavioral potential in this part of the CNS. In the brain, methylation of the brain-derived neurotrophic factor (BDNF) gene is implicated in behavioral development and neural plasticity. BDNF is known to play an important role in spinal plasticity, including neural changes that occur following a spinal cord injury and improvements in stepping behavior that are induced by exercise. Therefore, here we examined if DNA methylation of the BDNF gene in the spinal cord is related to development of hindlimb weight-bearing locomotion, in both intact rats and those that received a neonatal spinal cord transection. Neonatal male rats received a low-thoracic spinal cord transection or sham operation on postnatal day 1 (P1). On P10, subjects were behaviorally tested in an open field to measure spontaneous locomotion. Spinal cords were later dissected, and global levels of methylation and exon-specific methylation were measured on the BDNF gene in the lumbar spinal cord. Compared to shams, spinal-transected rats showed significantly less partial- and full-weight bearing locomotion on P10. Global methylation (global 5-mC) levels in the lumbar cord were significantly higher in spinal-transected rats. Bisulfate sequencing PCR was used to measure group differences in BDNF methylation at exons I and IV. Spinal-transected subjects showed significantly higher levels of methylated BDNF at exon I, whereas they showed significantly lower levels of methylated BDNF at exon IX. These data provide evidence that epigenetic alterations are associated with the development of locomotor behavior and following a spinal cord injury, and suggest that environmental influences may have exon-specific effects.

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Poster

764. Impairments of Posture and Gait

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Program #/Poster #: 764.19/N35

Topic: E.06. Posture and Gait

Title: Corticospinal drive is reduced with age during split-belt treadmill walking

Authors: S. SATO, *J. T. CHOI;
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Abstract: INTRODUCTION: Older adults are known to have difficulty adapting their gait to environmental challenges (e.g. irregular terrain, obstacles) which may lead to falls or otherwise limit their mobility. Recent studies showed reduced corticomuscular and intramuscular coherence in the beta- and low-gamma frequency band (15-45 Hz), a marker for corticospinal drive, in older adults compared to young adults during walking. However, it is unclear how age-related changes in corticospinal drive impact gait adaptability. The objective of this study was to examine age-related changes in tibialis anterior (TA) intramuscular coherence and adaptation in spatiotemporal gait parameters during split-belt treadmill walking in older adults. METHODS: 5 healthy young (Age: 28.6 ± 9.0) and 5 healthy older (Age: 74.4 ± 2.1) participants walked on a split-belt treadmill. Each session consisted of a pre-adaptation, adaptation, and post-adaptation periods. During the pre-adaptation period, participants walked symmetrically at a slow speed (0.6 m/s) for familiarization, fast (1.2 m/s) speed, and slow speed again for 5 mins each. During the adaptation period, walking was challenged by altering the speed of each leg at a 1:2 speed ratio (0.6 m/s for the slow belt, 1.2 m/s for the fast belt) for 10 mins. During the post-adaptation period, participants walked with both legs at 0.6 m/s for 10 mins. Kinematics were recorded with reflective markers on the lower extremity, and EMG was collected using two pairs of surface electrodes placed at the proximal and distal ends of TA. Intramuscular coherence was calculated between the two pairs of EMG during the swing phase of gait. RESULTS: All participants adapted and de-adapted double support (DSsym) and step length symmetry (SLsym). However, DSsym was more asymmetrical in older adults compared to young adults (DSsym: $p = 0.034$, SLsym: $p = 0.200$). Beta and gamma frequency intramuscular coherence was significantly greater in young compared to old in the fast (Beta: $p = 0.014$; Gamma: $p = 0.006$) and slow leg (Beta: $p = 0.009$, Gamma: $p < 0.001$). In young adults, beta- and gamma-band coherence was modulated in the slow leg (Beta-fast: $p = 0.262$; Beta-slow: $p = 0.003$; Gamma-fast: $p = 0.080$; Gamma-slow: $p = 0.010$). In contrast, older adults did not show any modulation in TA coherence with split-belt adaptation and de-adaptation (Beta-fast: $p = 0.059$; Beta-slow: $p = 0.619$; Gamma-fast: $p = 0.364$; Gamma-slow: $p = 0.533$). DISCUSSION: Beta- and gamma-band intramuscular coherence is reduced in amount, and modulation is absent in older adults compared to young

adults. This may reflect age-related differences in corticospinal neural mechanism during split-belt adaptation.

Disclosures: S. Sato: None. **J.T. Choi:** None.

Poster

764. Impairments of Posture and Gait

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 764.20/N36

Topic: E.06. Posture and Gait

Support: A grant from the Center for Urban Responses to Environmental Stressors (CURES)

Title: Repeated exposures to environmental-like concentrations of benzene, toluene, ethylbenzene, and xylene (BTEX) in adolescent Swiss-Webster mice results in alterations to locomotor activity

Authors: *C. J. DAVIDSON, D. W. SVENSON, K. HESLIP, M. NADDAF, S. E. BOWEN; Wayne State Univ., Detroit, MI

Abstract: Volatile organic compounds (VOCs) such as benzene, toluene, ethylbenzene, and xylene are widely utilized in combination in both industry and in-home products. Collectively known as BTEX, these VOCs are present in most urban areas. Volatile compounds are present in low concentrations within the environment and readily vaporize from liquid to gas at room temperature. Although VOC levels can vary, there are relatively higher concentrations found in urban-industrial areas, roadways, and parking structures. With no published preclinical investigation of the effects of BTEX exposure, our model was constructed using peer-reviewed publications that reported environmental concentration ratios and occupational maximums set by OSHA. Adolescent male Swiss-Webster mice were exposed Monday - Friday to BTEX concentrations that were modified to mimic human exposure (1.5 hrs/exposure x 2 exposures/day x 3 weeks = 30 total exposures). Four exposure groups were utilized which included three BTEX exposure mixture “groups”. The first two groups represented a 10- (“ENV 1”) and 100-fold (“ENV 2”) increase above previously reported environmental concentrations. The third group was a positive control which was exposed to the maximum concentrations for occupational exposure (OCC). Finally, an “air only” (“AIR”) exposure condition was used as control. Locomotor activity was assessed during exposure (N=32) and behavioral assays were conducted during and following these exposures (N = 40). Preliminary analysis of locomotor behavior show differential patterns of activity with all BTEX exposure groups (ENV 1, ENV 2, and OCC) initially displaying increases in locomotor activity as compared to AIR. Mice in the OCC group showed a reduction in locomotor activation as repeated exposures continued. Our preclinical

model illustrates that acute BTEX exposure may have significant effects on behavioral measures of gait such as locomotor activity. Pending analysis of fecal bolus, rotarod, inverted-screen, and a baited Y-maze outcomes will provide greater insight into the consequences of repeated BTEX exposure.

Disclosures: C.J. Davidson: None. **D.W. Svenson:** None. **K. Heslip:** None. **M. Naddaf:** None. **S.E. Bowen:** 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.; Center for Urban Responses to Environmental Stressors (CURES).

Poster

764. Impairments of Posture and Gait

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

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Topic: E.06. Posture and Gait

Support: This research was funded by the European Commission through MOVE-AGE, an Erasmus Mundus Joint Doctorate programme

Title: Online adjustments of foot placement during walking

Authors: *J. B. SMEETS[1], Y. ZHANG[1,2], E. BRENNER[1], J. E. DUYSENS[3], S. VERSCHUEREN[2];
[1]Human Movement Sci., Vrije Univ. Amsterdam, Amsterdam, Netherlands; [2]Dept. of Rehabil. Sci., [3]Dept of Kinesiology, KU Leuven, Leuven, Belgium

Abstract: We know that hand movements are quickly (latency of about 110 ms) adjusted to small changes in target location. Such changes are of a size that corresponds to the precision with which targets can be reached. Therefore, the circuit underlying such adjustments is presumably important for controlling any movement in a dynamic environment (Smeets et al. 2016). With age, the adjustments become less effective because the latency increases and the vigor decreases (Zhang et al. 2018). The aim of the current study was to investigate whether movements of the foot during walking are adjusted in a similar way.
Participants walked at 3 km/h on a treadmill on which rectangular stepping stones (25 x 10 cm) were projected. The distance between the centers of the stepping stones was 20 cm laterally and 50 cm in the walking direction (corresponding to a leg swing duration of about 400 ms). Every 6-9 steps, a stepping stone was displaced by 2.5 cm in the mediolateral direction 120 ms after toe-off (thus, 280 ms before heel-strike).
We found clear fast adjustments of the foot trajectory, with a latency of about 150 ms for young adults. Older adults took about 20 ms longer. The latency was 10 ms shorter for shifts in the

lateral than in the medial direction. For both age-groups, the center of pressure adjusted 30 ms before the kinematics of the foot. The older adults' responses and responses to perturbations in the medial direction were also less vigorous. The increased latency and reduced vigor in the older adults resulted in less complete responses: they corrected for about 50% of the target shift, whereas younger adults corrected for about 70%. The correction was also larger for displacements in the lateral direction (66%) than for those in the medial direction (54%).
We conclude that despite the cyclic nature of walking, the movements of the foot are controlled in a similar way as those of the hand. The effects of aging on these adjustments might explain some of the mobility problems in the elderly.
Smeets JBJ, Oostwoud Wijdenes L, Brenner E (2016) Movement adjustments have short latencies because there is no need to detect anything. Motor Control 20: 137-148
Zhang YJ, Brenner E, Duysens J, Verschueren S, Smeets JBJ (2018) Effects of aging on postural responses to visual perturbations during fast pointing. Front Aging Neurosci 10

Disclosures: J.B. Smeets: None. **Y. Zhang:** None. **E. Brenner:** None. **J.E. Duysens:** None. **S. Verschueren:** None.

Poster

764. Impairments of Posture and Gait

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 764.22/N38

Topic: E.06. Posture and Gait

Title: The relation between falls risk, slowing of movement, and variability in Parkinson's disease

Authors: *J. R. MOXEY[1], R. SIMMONS[2], A. GRUNSFELD[4], K. THOMAS[5], S. MORRISON[3];
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Abstract: Parkinson's disease (PD) is a neurodegenerative disorder linked to the loss of dopaminergic neurons within the basal ganglia. The consequences of this disease process often result in a range of neuromotor problems resulting in declines in balance control and, subsequently, increased falls risk. Additionally, the movements of individuals with PD are characterized by a general slowing and changes in variability. This study was designed to investigate the relationship between falls risk, balance, and speed of movement for persons with PD compared to age-matched healthy older adults. It was also of interest to assess whether persons with PD also exhibited changes in the pattern of intra-individual variability (IIV) of these selected neuromotor tasks. Falls risk was measured using the Physiological Profile Assessment, a validated tool which includes tests of vision, sensation, balance, and leg strength.

Values from each test are combined to provide an overall risk score with higher scores denoting greater falls risk. The specific movement tasks performed included simple reaction time, finger tapping, and gait. Reaction time was assessed for the hand and foot (20 trials each). Walking ability was assessed using a Protokinetics pressure sensitive walkway. Individuals performed five walking trials at their preferred speed and five at a self-selected fast speed. For finger tapping, persons tapped at both their preferred speed and as fast as possible on two force sensors with their index fingers. As expected, the PD persons had a significantly increased falls risk compared to the healthy older controls. The heightened falls risk was linked to slower reaction times, decreased tapping speeds, and slower walking patterns (i.e. decreased cadence, slower gait velocity). The increased falls risk and slowing of motor responses for the PD group was also associated with increased within-subject variability during the reaction time, finger tapping, and gait assessments compared to healthy older adults. Together these results illustrate that the consequences of this neurological disease are not simply characterized by slowing of motor function, but increased variability of movement responses also emerges. Further, these results highlight the potential for using IIV measures for assessing the widespread implications of this disease.

Disclosures: **J.R. Moxey:** None. **R. Simmons:** None. **A. Grunsfeld:** None. **K. Thomas:** None. **S. Morrison:** None.

Poster

764. Impairments of Posture and Gait

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 764.23/N39

Topic: E.06. Posture and Gait

Support: NIH K01HD088762

Title: The negative effects of cognitive interference on mobility in Huntington's disease

Authors: *N. L. PURCELL[1], J. G. GOLDMAN[3], B. BERNARD[2], J. A. O'KEEFE[1]; [1]Cell and Mol. Med., [2]Neurolog. Sci., Rush Univ. Med. Ctr., Chicago, IL; [3]Shirley Ryan Mobility Lab., Chicago, IL

Abstract: Huntington’s disease (HD) is characterized by a triad of motor, cognitive, and psychiatric symptoms. As HD progresses, previously automatic tasks, like walking, require more cognitive resources. By stressing the locomotor system, dual-task (DT) paradigms and fast-paced gait may reveal or exacerbate deficits not seen under single-task (ST), especially during more dynamic movements, like turning. However, how these “stress test” gait paradigms impact the mobility of HD individuals needs further investigation. Therefore, the goals of this study were to assess 1) how cognitive-motor DT paradigms and fast-paced walking impact gait and turning in

HD and 2) whether gait measures from wearable inertial sensors are sensitive to motor symptom severity in HD. Seventeen HD participants (55 ± 9.7 years) and 17 age-matched controls (56.5 ± 9.3 years) underwent quantitative gait and turn analysis via a 25m, two-minute walk test utilizing an inertial sensor system (APDM^{TM}). Gait was assessed under a 1) self-selected (SS) pace, 2) fast-as-possible (FAP) pace and 3) during a cognitive-motor DT, having subjects perform a verbal fluency task during SS walking. The Unified Huntington's disease Rating Scale-total motor score (UHDRS-TMS) was administered. A cognitive test battery was also administered to examine potential associations between cognitive and gait deficits. Significant DT costs were observed exclusively while turning. HD Individuals took more time ($p = 0.013$) and steps to complete their turns ($p = 0.028$) while dual-tasking compared to controls. HD participants demonstrated significantly slower gait speed and shorter stride length, as well as greater lateral step and stride length variability compared to controls ($p<0.00001$ to 0.034) under all gait conditions. Higher UHDRS-TMS scores, reflecting greater disease severity, correlated with greater stride length variability ($p = 0.001$ to 0.046), but unexpectedly were correlated with less time in double support ($p = 0.004$ to 0.012) and more time in swing phase ($p = 0.003$ to 0.013). These results need further investigation, though may be due to characteristics of choreatic gait and a poorly defined "stutter-step". Lower information processing speed was associated with greater gait variability under SS and FAP conditions. HD Individuals exhibited greater cognitive interference while turning. Executing a turn is a less automatic motion than straight walking, requiring inter-limb coordination, anticipatory control, and greater cortical regulation. The complexity of turning, combined with the dysfunctional motor system in HD, likely makes it more susceptible to the negative effects of DT cognitive interference.

Disclosures: **N.L. Purcell:** None. **J.A. O'Keefe:** None. **B. Bernard:** None. **J.G. Goldman:** None.

Poster

764. Impairments of Posture and Gait

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 764.24/N40

Topic: E.06. Posture and Gait

Support: NIH R01 (EB024570)
NSF Grant 1622451
CLEAR Grant

Title: Proportional myoelectric control of a powered ankle prosthesis for the enhancement of postural control under expected perturbation: A pilot study

Authors: *A. FLEMING[1], H. HUANG[2];
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Biomed. Engin., North Carolina State Univ. and Univ. of North Carolina-Chapel Hill, Raleigh, NC

Abstract: Under expected perturbation, the body works to maintain balance by employing postural control mechanisms like Anticipatory and Compensatory Postural Adjustments (APAs & CPAs). Post-amputation, transtibial amputees lose active control of their ankle-joint system and are forced to incorporate the use of a passive ankle joint into these postural control mechanisms. Without the ability to change ankle joint mechanics, amputees adopt postural control strategies that rely more heavily on their intact limb. This leads to the potential for decreased medio-lateral (ML) stability and higher risk for overuse injury of the intact limb. Proportional myoelectric control of ankle prostheses has been used to restore active ankle control by using descending neural commands via electromyography (EMG) from residual muscles in transtibial amputees. This control paradigm has been tested in cyclic tasks like walking and tasks that involve a single residual muscle. However, the ability for previously antagonistic residual muscles to generate coordinated contractions for the control of non-cyclic tasks like postural control were unaddressed.
In this pilot study, we investigated the potential for residual antagonistic muscles to generate APAs, and we investigated the potential benefit of proportional myoelectric control of a powered ankle prosthesis to stability under expected perturbation. We used a predictable pendulum drop task with a single transtibial amputee. In two sessions the participant used his prescribed passive device and a powered device controlled by residual Tibialis Anterior (TA) and Lateral Gastrocnemius (GAS) muscle activations. In the powered condition the transtibial amputee generated significantly earlier activations from the residual TA ($p=0.007$), higher anticipatory center of pressure (CoP) excursions ($p=0.017$) and reduced peak center of mass excursions ($p=0.021$). Peak ML CoP excursions were also less in the direction of the intact limb ($p=0.003$). The results from this pilot study demonstrate the promise for transtibial amputees to generate APAs with residual antagonistic muscles. This study provides a basis to further investigate the potential for proportional myoelectric control of a powered ankle prosthesis to improve stability under expected perturbation.

Disclosures: **A. Fleming:** None. **H. Huang:** None.

Poster

764. Impairments of Posture and Gait

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 764.25/N41

Topic: E.06. Posture and Gait

Title: Chronic impairments of postural stability associated with history of concussion

Authors: *N. REILLY, J. PREBOR, J. MOXEY, E. SCHUSSLER;
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Abstract: Concussion is a common type of mild traumatic brain injury (mTBI) that results in cognitive, physiological and biomechanical symptoms. Individuals recovering from a concussion display deficits in postural stability during quiet stance such as increases in center of pressure (COP) displacement and a decrease in regularity (i.e. entropy) of postural sway. However, the lack of availability of specialized equipment to assess these measures in concussed individuals is a common limitation for clinicians making return-to-play decisions, increasing the risk of premature return-to-play. This study was designed to assess persisting deficits in postural stability during upright standing in individuals with history of one or multiple previous concussions long after medical clearance in comparison to individuals that have been never sustained a diagnosed concussion. Postural stability was assessed by having participants stand on a force plate under four conditions assessing balance by challenging the vestibular system (bipedal and unipedal stance) and cognitive demand (single and dual task). COP root mean square (RMS), velocity and regularity (i.e. sample entropy) were calculated in both the sagittal and frontal planes. All participants displayed greater COP displacement and velocity in both the sagittal and frontal planes in unipedal stance compared to bipedal. Individuals with a history of multiple concussions displayed significantly increased COP displacement and decreased sample entropy values (more regular) during the dual task conditions compared to those who had suffered a single concussion and those without a history of concussion. In addition, individuals with a history of multiple concussions displayed significantly slower COP velocity in both the sagittal and frontal planes during both the single and dual task conditions compared to those with a history of a single concussion as well as those that have never sustained a concussion. Overall, our findings support the notion that deficits in postural stability persist long after the return-to-play decision is made. There appears to be a cumulative effect of concussions on deficits to integration of sensory information, exemplified by the greatest deficits in stability being seen in individuals that have a history of multiple concussions. Clinically, these findings represent the need for more sensitive measures of impairment following concussion.

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Poster

764. Impairments of Posture and Gait

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 764.26/N42

Topic: E.06. Posture and Gait

Support: DBT N1481

Title: Functional impact of white matter aging among adults aged 50 years and above: A cross-sectional study

Authors: *P. NAIR[1], P. BALASUNDARAM[2], D. VIBHA[1], S. DWIVEDI[3], N. KUMAR[4], S. GAIKWAD[2], K. PRASAD[1];
[1]Dept. of Neurol., [2]Dept. of NeuroRadiology, [3]Dept. of Biostatistics, [4]Dept. of Psychiatry, All India Inst. of Med. Sci. (AIIMS), New Delhi, India

Abstract: Background- Cerebral aging is a complex and heterogeneous process. Magnetic resonance imaging (MRI) is used to identify and quantify non-disease-related aging of the cerebral white matter. Increased white matter hyperintensities (WMHs), cerebral atrophy, reduced micro-structural integrity are common findings among older adults and have been associated with cognitive and gait impairment. This study examined the impact of multimodal white matter imaging on mobility and cognitive functions among community dwelling adults aged 50 years and above. **Design:** Cross-sectional sub-study of AIIMS cohort study. **Setting:** Medical Site; AIIMS Cohort Study. **Methods:** 36 participants (50 to 75 years) without any prior history of neurological or orthopedic disorder were included. Neuroimaging measures included volumetry ; WMH; FA & MD; Mobility was evaluated using walkway system with 30 comprehensive spatio-temporal parameters of gait (pace, rhythm, variability etc); Prospective recording of fall assessment was done. Cognitive measures included color tail test A & B for executive functions and MMSE. Depression was also evaluated using the Geriatric depression scale. **Results-** The mean age was 62 (±2.34) years, 44% were male. WMHs were found in 19 out of 36 participants; Fall was recorded in 4 out of 36 participants. WMHs were found to be significantly associated with gait velocity (P value =0.009), stride length (P value =0.025), double stance time (P value =0.036) and body mass index (p = 0.042); Reduced gait velocity was associated with reduced FA and higher MD in corpus callosum. Executive function, MMSE, depression and other vascular risks factors like hypertension, diabetes, and smoking found no significant association. **Conclusions:** The data suggests that in non-clinical aging populations, mobility measures may be sensitive to sub-clinical variance in brain MRI measures. Future studies should incorporate quantitative imaging markers of cerebral perfusion and functional imaging parameters which may offer additional clinically relevant information.

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Poster

764. Impairments of Posture and Gait

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 764.27/N43

Topic: E.06. Posture and Gait

Support: NIH DC2390

Title: Determine the kinematic differences between healthy controls and patients with unilateral vestibular deafferentation during gait and gaze stability exercises

Authors: *L. WANG, O. ZOBEIRI, J. MILLAR, M. SCHUBERT, K. CULLEN;
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Abstract: The vestibular system, which senses head motion, is critical to maintaining balance and stabilizing gaze. Patients with vestibular schwannoma (VS) resection suffer from vestibular hypofunction which significantly affects their daily activities. Clinicians prescribe rehabilitation exercises of gaze and gait stability to regain functional improvement related to vestibular hypofunction. The best exercise should challenge the patients' existing function, while not allowing errors of vestibular signal to become too large. However, the prescriptions of exercise are based on limited observation in the clinic and subjective opinion. In the current study, we aim to determine the appropriate type and dosing of exercises by looking through the kinematic differences between healthy controls and patients during gait and gaze stability exercises. Age-matched healthy controls were tested once. VS patients were tested pre-operatively and during six weekly post-surgical visits. Motion signals were recorded using six-dimensional motion sensors (3-axis linear acceleration and 3-axis gyroscope) from head, back, waist, right and left ankles, and dominant hand while they perform a series of gaze stabilization, balance, and gait exercises. We found that: 1) in most of the gaze stabilization exercises, the velocity and variability of patients' head movements were smaller than controls before surgery, decreased significantly after surgery, and gradually returned to their pre-surgery baseline after 6 weeks. 2) in balance exercises, the patients' head and waist stability was comparable to controls. 3) in gait exercises, patients' gait speed was comparable to controls, whereas their head and waist movements were smaller. While these results confirm the wide-accepted idea that increasing head movements is important for VS patients, it is also suggested that patients would benefit from increasing their waist movements during rehabilitation exercises and daily activities. Therefore, clinicians could prescribe gait exercises that require more head and waist movements and instruct patients to increase the amplitude and variability of these movements with the help of real-time kinematic data. Overall, our data suggest that both patients and clinicians can benefit from an enhanced prescription that addresses multiple aspects of vestibular symptoms by monitoring a wide range of kinematic data.

Disclosures: L. Wang: None. **O. Zobeiri:** None. **J. Millar:** None. **M. Schubert:** None. **K. Cullen:** None.

Poster

764. Impairments of Posture and Gait

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 764.28/N44

Topic: E.06. Posture and Gait

Support: American Heart Association Award Number 17IRG33420045

Title: Transcutaneous spinal cord stimulation facilitates stepping performance in stroke patients

Authors: *Y. GERASIMENKO[1], D. SAYENKO[2], N. SANCHEZ[3], J. M. FINLEY[3], *V. R. EDGERTON[4];
[1]Pavlov Inst. of Physiol, St. Petersburg, Russian Federation; [2]Dept. of Neurosurgery, Ctr. for Neuroregeneration, Houston Methodist Res. Inst., Houston, TX; [3]Div. of Biokinesiology and Physical Therapy, USC, Los Angeles, CA; [4]Dept Integrative Biol. & Physiol., Univ. of California Los Angeles, Los Angeles, CA

Abstract: The loss of joint coordination and gait dysfunction is a typical case in subjects after stroke, and gait recovery is a major objective in the rehabilitation for stroke patients. The aim of this study was to develop neuromodulatory techniques using transcutaneous spinal cord stimulation (tSCS) to improve lower-limb motor function and walking abilities in stroke patients. Our previous findings demonstrated that tSCS can activate spinal locomotor-related neuronal network and facilitate the recovery of voluntary movements in SCI patients. In the present studies we examined the effects of multisite non-invasive tSCS in regulation of stepping movements in people post-stroke. The participants were placed in a special device to suspended legs beyond the edge of a table so they could perform a bilateral oscillating stepping-like motion in the presence or absence of multisite transcutaneous spinal cord stimulation. Stroke participants (n=9 were tested while lying on their side with the upper paretic leg supported in a sling directly at the shank and the lower non-paretic leg placed on a free rotating brace segment attached to a horizontal board supported by vertical ropes secured to hooks in the ceiling. By using this "Zero-G" suspension apparatus, the participant's legs were supported and allowed to move freely in the horizontal plane in a gravity-neutral manner.
Non-invasive spinal cord stimulation at a frequency of 30 Hz using a custom-built constant-current stimulator was delivered transcutaneously at three independent sites, along the midline and between the spinous processes of vertebrae C5-C6, T11–T12, and L1–L2. The intensity (range: 40–90 mA) of tSCS was adjusted sufficiently to generate involuntary rhythmic movements without causing discomfort. EMG activity of leg muscles and limb kinematics were monitored. We have found that tSCS facilitated the limb displacement in 7 of 9 participants. During tSCS bilateral stepping-like oscillations were more symmetrical between paretic and non-paretic legs. Spinal stimulation at three sites was more effective than at one site. The mean joint

displacement for the toe, ankle, knee, and hip of the paretic leg during voluntary stepping-like oscillations in the presence of tSCS was greater by 118%, 123%, 130%, and 124%, respectively, compared to voluntary stepping-like oscillations alone. We suggest that this non-invasive spinal neuromodulation can be a viable clinical approach to improve the control of stepping in stroke patients.

Disclosures: **Y. Gerasimenko:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neurorecovery Technologies. **D. Sayenko:** None. **N. Sanchez:** None. **J.M. Finley:** None. **V.R. Edgerton:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neurorecovery Technologies, SpineX.

Poster

764. Impairments of Posture and Gait

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 764.29/N45

Topic: E.06. Posture and Gait

Support: American Heart Association Award 17IRG33420045

Title: Transcutaneous spinal stimulation modulates overground walking performance in individuals post-stroke

Authors: ***J. M. FINLEY**[1], N. SANCHEZ[1], Y. GERASIMENKO[2,3], D. SAYENKO[4], V. EDGERTON[3];
[1]Div. of Biokinesiology and Physical Therapy, USC, Los Angeles, CA; [2]Pavlov Inst. of Physiol., St. Petersburg, Russian Federation; [3]Dept Integrative Biol. & Physiol., Univ. of California Los Angeles, Los Angeles, CA; [4]Houston Methodist, Houston, TX

Abstract: Walking impairments contribute to post-stroke disability and as a result, improving walking function is a common priority of neurorehabilitation. Although the immediate deficits following stroke result from damage to supraspinal circuits, there is considerable evidence that supraspinal lesions also result in long-term changes in the properties of spinal networks. Recent efforts have demonstrated that transcutaneous spinal stimulation (tSCS) in people with spinal cord injury can lead to improvements in posture and voluntary stepping capacity. However, it remains to be seen if tSCS can overcome the brain-induced disruption of spinal function and improve walking function post-stroke. Here, we explored the use of tSCS to modulate spinal locomotor networks and improve locomotor function in stroke survivors. Our general hypothesis is that noninvasive stimulation of the lumbosacral spinal cord can attenuate the asymmetric motor impairments imposed by supraspinal stroke. Nine individuals in the chronic stage of stroke recovery participated in a study where they walked at their self-selected speed overground with

and without tSCS. Participants completed two walking trials with no stimulation, followed by a set of trials where they walked while receiving tSCS at 30 Hz using a custom constant current stimulator. Stimulation was applied at three sites, between the spinous processes of T11 and T12, T12 and L1, and C7. Stimulation intensity ranged from 60 to 140mA and was individualized based on each participant's tolerance to the stimulation. Finally, participants walked without stimulation to determine if there were any lasting effects of the stimulation. We measured joint kinematics and spatiotemporal features using a 10-system motion capture system. Seven out of nine participants increased their paretic stance and swing times by 0.04 ± 0.05 s (4.33 ± 3.45%) and 0.02± 0.02 s (3.75 ± 3.45%), respectively, when walking with tSCS. After stimulation was turned off, paretic stance time remained 0.05 ± 0.04 s (6.55 ± 5.73%) longer than baseline in eight participants. There were no consistent changes in step lengths or joint ranges of motion. These preliminary results suggest that transcutaneous electrical stimulation has the potential to be applicable in the recovery of gait post-stroke. Increases in paretic stance time following stimulation suggest that upregulation of spinal circuitry may facilitate stabilization and/or propulsion with the paretic limb. Future work is necessary to determine the mechanisms by which tSCS leads to changes in lower extremity function post-stroke.

Disclosures: J.M. Finley: None. **N. Sanchez:** None. **Y. Gerasimenko:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neurorecovery Technologies. **D. Sayenko:** None. **V. Edgerton:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neurorecovery Technologies.

Poster

765. Stress Response: Sex Differences

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 765.01/N46

Topic: F.04. Stress and the Brain

Support: Brain and behavior research foundation NARSAD young investigator award 24805

Title: Elucidating sex specific effects of stress on T helper cell subpopulations

Authors: *G. N. RIVERO BALLON[1], A. P. JOHNSON[3], J. R. RAINVILLE[1], G. E. HODES[2]; [1]Sch. of Neurosci., [2]Neurosci., Virginia Tech., Blacksburg, VA; [3]Virginia Polytechnic Inst. and State Universit, Blacksburg, VA

Abstract: Globally over 300 million people live with depression, but women are almost twice as likely to be diagnosed. Men and women often have different symptoms of depression, and women tend to have more issues with weight gain or loss, feelings of sadness and melancholy,

while men tend to have more difficulty sleeping, feelings of anger and aggressive behaviors. Current treatments for depression fail to adequate relieve symptoms in up to one third of patients, and women are more like to be treatment resistant than men. The mechanism underlying these sex difference are not fully understood, and have not been adequately addressed when developing treatments. Previously, we explored the cytokine profiles of men and women with treatment resistant depression, non- treatment resistant depression and healthy controls. Our analysis of cytokine expression in blood samples from patients undergoing depressive episodes suggests the possibility that T helper cell sub populations may be differentially regulated in men and women with depression, and that treatment resistant women experience the strongest dysregulation in cytokines associated with Th1, natural killer T (NKT) cells, and Th17 associated cytokines. Here we present data using a variable stress model to induce T cell changes and explore their relationship to behavioral responses in male and female mice. Female mice are stress susceptible following 6 and 28 days of variable stress, while males are resilient at following 6 days of variable stress, but susceptible following 28 days of variable stress. Our preliminary findings have shown that T helper cells (CD4+) expressed at a higher percentage of the total white blood cell numbers in female mice, but that neither 6 nor 28 days of stress affects the total percentage of CD4+ T cells. We hypothesize that CD4+ T cell differentiation is affected by stress in females, but not males. We will present data characterizing the effects of 6 and 28 days of stress on T cell differentiation by measuring changes in percentages of different CD4+ T cell subpopulations, including Th1, Th2, Th9, Th17, and NKT cells by flow cytometry. We will discuss the relationship between individual behaviors from a test battery and numbers of T cell subpopulations, in order to determine the contribution of specific T cell subpopulations to susceptibility or resilience to variable stress.

Disclosures: G.N. Rivero Ballon: None. **A.P. Johnson:** None. **J.R. Rainville:** None. **G.E. Hodes:** None.

Poster

765. Stress Response: Sex Differences

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 765.02/O1

Topic: F.04. Stress and the Brain

Support: Brain and behavior research foundation NARSAD young investigator award 24805

Title: Sex differences in the effects of stress on microglia morphology are region specific

Authors: *M. TSYGLAKOVA[1], J. R. RAINVILLE[2], D. MCDANIEL[1], G. E. HODES[3]; [2]Sch. of Neurosci., [3]Neurosci., [1]Virginia Tech., Blacksburg, VA

Abstract: Depression and anxiety are common and debilitating mood disorders, that are more prevalent in females than males. Stress is a trigger for many mood disorders and has effects on plasticity in the brain's reward circuitry, including Nucleus accumbens (NAc) and Hippocampus (HPC). We previously demonstrated that 6 days of variable stress (SCVS) sex specifically regulates plasticity in NAc. SCVS induced a behavioral stress response in females but not males, whereas 28 days of chronic variable stress (CVS) triggered depression-associated behavior in both sexes.Microglia are implicated in regulating neuronal plasticity during development and in disease states. To characterize the effects of SCVS and CVS on microglial populations we examined microglial number and density in the NAc core and shell sub-regions, as well as CA1 region of HPC of male and female mice. Variable stress consisted of three different stressors: foot shock, restraint tube and tail suspension. Each stressor was administered for one hour, and stressors alternated each day for either 6 (SCVS) or 28 (CVS) days. We then used immunohistochemical analysis for expression of ionized calcium binding adaptor molecule 1 (Iba1) in the NAc core and shell sub-regions and CA1 hippocampal region. We found that following SCVS, when only females were behaviorally susceptible to stress, there was a sex-specific effect on the number of microglial cells and microglial density in the NAc, but not in CA1. Both microglial density and number decreased in the core sub-region in females only, along with a decrease in cell counts in shell. In males, who are stress resilient following SCVS, we did not find any changes in microglia number or density. Following CVS, when both sexes are stress susceptible we found a significant interaction between sex and stress in the microglial density in the shell sub-region, no significant changes were observed in CA1. These data suggest that stress has sex and region-specific effects on microglia morphology and number which potentially modulate sex specific effects of neuronal plasticity and the higher rate of mood disorders in females. To further investigate functional changes of morphological alterations in microglia following stress, and to determine whether mice remain stress susceptible in the absence of microglial activation, we administered minocycline, microglial activation inhibitor in the drinking water to female mice. Our results indicate that following SCVS, minocycline has a behavior specific effect in female mice.

Disclosures: **M. Tsyglakova:** None. **J.R. Rainville:** None. **D. McDaniel:** None. **G.E. Hodes:** None.

Poster

765. Stress Response: Sex Differences

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 765.03/O2

Topic: F.04. Stress and the Brain

Support: NIH Grant MH099580
NIH Grant MH114049

Title: Sex differences in the regulation of braininterleukin 1 beta in response to chronic stress

Authors: *D. F. BARNARD[1], K. M. GABELLA[1], A. C. KULP[1], A. D. PARKER[1], P. B. DUGAN[1], J. D. JOHNSON[2];
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Abstract: Elevations in brain interleukin-1 beta (IL-1β) during chronic stress exposure have been implicated in behavioral and cognitive impairments associated with depression and anxiety. Two critical regulators of brain IL-1β production during times of stress are glucocorticoids and catecholamines. These hormones work in opposition to one another to inhibit (via glucocorticoid receptors) or stimulate (via beta-adrenergic receptors: β-AR) IL-1β production. While chronic stress often heightens both corticosterone and catecholamine levels, it remains unknown as to how chronic stress may affect the "yin-yang" balance between adrenergic stimulation and glucocorticoid suppression of brain IL-1β. To investigate this further, male and female rats underwent 4 days of stress exposure or served as non-stressed controls. On day 5, animals were administered propranolol (β-AR antagonist), metyrapone (a glucocorticoid synthesis inhibitor), vehicle, or both drugs and brain IL-1β mRNA was measured by rtPCR in limbic brain areas. In males, administration of propranolol had no effect on IL-1β expression in non-stressed controls but significantly reduced IL-1β in the hippocampus and amygdala of chronically stressed animals. In females, propranolol significantly reduced IL-1β in the amygdala and hypothalamus of both control and stressed rats. In male rats, metyrapone treatment significantly increased IL-1β mRNA regardless of stress treatment in all brain areas, while in female rats metyrapone only increased IL-1β in the hypothalamus. Interestingly, propranolol treatment blocked the metyrapone-induced increase in brain IL-1β indicating the increase in brain IL-1β following metyrapone treatment was due to increase β-AR activation. Additional studies revealed that metyrapone significantly increases norepinephrine turnover in the hypothalamus and medial prefrontal cortex in male rats and that microglia appear to be the cell type contributing to the production of IL-1β. Overall, data reveal that stress exposure in male rats affects the regulation of brain IL-1β by the norepinephrine-β-AR pathway, while stress had no effect in the regulation of brain IL-1β in female rats.

Disclosures: D.F. Barnard: None. **K.M. Gabella:** None. **A.C. Kulp:** None. **A.D. Parker:** None. **P.B. Dugan:** None. **J.D. Johnson:** None.

Poster

765. Stress Response: Sex Differences

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 765.04/O3

Topic: F.04. Stress and the Brain

Support: NIH Grant R21 AG058263

Title: Sex differences in corticotropin-releasing factor (CRF) receptor trafficking in the locus coeruleus of mice conditionally overexpressing CRF: Implications for amyloid beta distribution

Authors: *J. A. ROSS[1], B. A. REYES[2], V. B. RISBROUGH[3], E. J. VAN BOCKSTAELE[4]; [1]Pharmacol. and Physiol., Drexel Univ. Col. of Med., Philadelphia, PA; [2]Pharmacol. & Physiol., Drexel Univ., Philadelphia, PA; [3]Dept. Psychiatry, Univ. of California San Diego, La Jolla, CA; [4]Dept. of Pharmacol. & Physiol., Drexel Univ. Col. Of Med., Philadelphia, PA

Abstract: The locus coeruleus (LC)-norepinephrine (NE) system is an underappreciated and understudied area of research in the context of Alzheimer's disease (AD). Clinical studies have correlated stress with increased risk for developing AD, and preclinical studies demonstrate that amplification of the stress system disrupts cellular and molecular processes at the synapse, promoting the production of the amyloid beta (Aβ) peptide. Stress-induced activation of the LC is mediated by corticotropin releasing factor (CRF), and CRF receptor 1 (CRFR1) exhibits sex-biased stress signaling. In previous studies, we examined the cellular substrates for interactions between Aβ and tyrosine hydroxylase (TH) a marker of noradrenergic somatodendritic processes in the LC in mice conditionally overexpressing CRF in the forebrain (CRF OE) under a Doxycycline (DOX) regulated tetO promoter. These studies revealed significant sex differences in Aβ distribution in the coeruleo-cortical pathway of CRFOE mice. We hypothesize that these sex differences may partly be due to the sex-dependent trafficking of CRFR1, because CRFR1 signaling significantly influences the production of Aβ and CRF OE males internalize CRFR1 in response to stress signaling, an adaptive response that is not observed in females. In the present study we sought to determine the subcellular localization of CRFR1 in the LC of CRF OE male and female mice in relation to Aβ and TH using triple labeling immunoelectron microscopy. Some tissues sections were also processed for single immunogold labeling of CRFR1. Semi-quantitative analysis of CRFR1 trafficking was calculated as a ratio of cytoplasmic-to-total silver grains, and showed that male CRF OE have 70% ±1% (96/134) cytoplasmic immunolabeled CRFR1, compared to 47% ±1% (40/85) in male controls. Female CRF OE mice showed 49% ±1.5% (214/433) cytoplasmic CRFR1, compared to female controls that exhibited 59% ±0.5% cytoplasmic CRFR1. Two-way ANOVA indicated that the effect of sex, treatment, and interaction were significant ($p<0.05$). Tukey's post-hoc analysis indicates that CRF OE males were significantly different than CRF OE females, with males showing a greater percentage of internalized CRFR1. CRF OE male mice exhibited 63%, while female CRF OE mice exhibited 64% of TH-immunoreactive (ir) and CRFR1-ir profiles that were also Aβ-ir.Male control mice exhibited 66% while female control mice exhibited 50% of TH-ir and CRFR1-ir profiles that were also Aβ-ir.These findings are consistent with previous CRFR1 trafficking studies in behavioral models of stress, and could have significant implications for Aβ production throughout the coeruleo-cortical pathway.

Disclosures: J.A. Ross: None. **B.A. Reyes:** None. **V.B. Risbrough:** None. **E.J. Van Bockstaele:** None.

Poster

765. Stress Response: Sex Differences

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 765.05/O4

Topic: F.04. Stress and the Brain

Support: NIH Grant RO1-DK105826

Title: Androgens mediate sex differences in hypothalamic corticotropin releasing hormone gene expression following adrenalectomy of mice

Authors: *A. L. HECK, R. J. HANDA;
Biomed. Sci., Colorado State Univ., Fort Collins, CO

Abstract: Although prominent sex differences exist in the hypothalamic pituitary adrenal (HPA) axis's response to stressors, few studies of its regulation in the hypothalamic paraventricular nucleus (PVN) have compared both male and female subjects. In this study, we sought to explore sex differences in the acute regulation of PVN neuropeptide expression following glucocorticoid (GC) removal and the underlying role of gonadal hormones. We first examined the effects of short-term adrenalectomy (ADX) on PVN corticotropin releasing hormone *(*CRH*)* and arginine vasopressin (AVP) gene expression in adult mice using *in situ* hybridization. ADX increased PVN CRH mRNA levels by two days after ADX in males only, whereas both sexes showed increases in CRH mRNA after four days. In contrast, PVN AVP mRNA was increased at two and four days after ADX in both sexes. To determine if gonadal hormones contributed to this sex bias, we examined adrenalectomized (ADX'd) and gonadectomized (GDX'd) mice with or without gonadal hormone replacement. Using droplet digital PCR, we found that, unlike the pattern in intact animals, two days following ADX/GDX, PVN CRH mRNA levels did not increase in either sex. When males were given dihydrotestosterone propionate (DHTP), CRH mRNA levels increased in ADX'd/GDX'd males similar to those observed following ADX alone. To determine a potential mechanism, we examined the co-expression of androgen receptor (AR) immunoreactivity and PVN CRH neurons using the *Crh-IRES-Cre;Ai4* transgenic mouse model in which CRH neurons are permanently tagged with a fluorescent protein. Abundant colocalization was found in the anteroventral bed nucleus of the stria terminalis, but it was limited in the PVN. Our findings ultimately reveal a sex difference in PVN *Crh* expression following the removal of GC negative feedback that may depend on indirect AR actions in males. Supported by NIH RO1-DK105826.

Disclosures: A.L. Heck: None. **R.J. Handa:** None.

Poster

765. Stress Response: Sex Differences

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 765.06/O5

Topic: F.04. Stress and the Brain

Support: NSF CAREER IOS-1552416

Title: Stress effects on impulsive choice depend on sex and time of exposure during development

Authors: *E. ORDOÑES SANCHEZ[1], J. FLOWERS II[2], C. M. ROGERS[2], C. S. ARDEKANI[2], S. B. FLORESCO[4], D. A. BANGASSER[3];
[1]Psychology, [3]Dept. of Psychology and Neurosci. Program, [2]Temple Univ., Philadelphia, PA; [4]Univ. British Columbia, Vancouver, BC, Canada

Abstract: Stress can alter cognition. However, few studies have examined how stressors experienced early life versus in adulthood may affect impulsivity. Adversity early in life is of particular interest because it has lasting effects on health that persist into adulthood, but when it is not overwhelming it can promote resilience. Likewise, repeated stressors experienced in adulthood can aggravate and contribute to symptoms of several disorders. Here we examined how repeated stress either early in life or in adulthood affected impulsive choice on a delayed discounting (DD) task in male and female rats. In DD, rats chose between two levers, one of which provided a small reward immediately, versus another which delivered a larger reward following a delay. Preference for the small, immediate reinforcer served as an index of impulsive choice. Early life adversity was modeled using the limited bedding and nesting (LBN) paradigm, wherein, a dam's access to nesting materials was restricted during the pups first week of life. This manipulation increases maternal care, perhaps as a compensation for the limited resources. Once LBN rats reached adulthood, we compared impulsive choice to controls raised with ample nesting material. In comparison, the effects from moderate stressors in adulthood was probed by exposing rats to a 6-day chronic variable stress (CVS) procedure, consisting of three alternating stressors: restraint (1 hr), predator odor exposure (15 min), and forced swim (15 min). After each stressor exposure (30 min), rats were tested on the DD task and this continued for several days after stressor cessation. Early LBN exposure decreased impulsive choice in adult males relative to control reared males. Interestingly, LBN exposure had no effect on choice in adult female rats. In contrast, preliminary findings suggest that adult CVS exposure increases impulsive choice in males that persisted several days after stressor exposure. However, CVS had no effect in females. Collectively, these results indicate that stress can differentially alter impulsive choice in males in a manner dependent on the developmental timing of stress exposure. Females appear resilient to these stress manipulations and future studies will examine mechanisms that promote

this resilience. These findings also suggest that stress in adulthood may increase impulsivity in males that in turn may contribute to these symptoms observed in certain psychiatric disorders.

Disclosures: E. Ordoñes Sanchez: None. **J. Flowers II:** None. **C.M. Rogers:** None. **C.S. Ardekani:** None. **S.B. Floresco:** None. **D.A. Bangasser:** None.

Poster

765. Stress Response: Sex Differences

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 765.07/O6

Topic: F.04. Stress and the Brain

Support: NSF CAREER AWARD IOS-1552416

Title: Sex specific effects of early life stress on development and steroid hormones

Authors: *C. S. ARDEKANI[1], S. ECK[2], S. LUZ[4], E. KIM[2], M. SALVATORE[5], A. HALL[2], S. FAMULARO[2], S. BHATNAGAR[4], D. A. BANGASSER[3];
[1]Psychology, [3]Dept. of Psychology and Neurosci. Program, [2]Temple Univ., Philadelphia, PA; [4]Children's Hosp. of Philadelphia, Philadelphia, PA; [5]Psychology, Temple Univerisity, Philadelphia, PA

Abstract: Early life adversity can alter maturation and development, affecting endpoints such as the timing of puberty and reproductive function. However, these effects seem to differ depending in the type and timing of stressor exposure, and the mechanisms by which this occurs are largely unknown. Here we used limited bedding and nesting (LBN) model of early life adversity in Long Evans rats to examine its effects development and sex steroid hormones. In LBN, dams and pups are exposed to a limited resource environment where the dams lack proper materials to build a nest from the pups' postnatal days 2-9. This manipulation is compared to control housing conditions in which rat dams have access to ample nesting materials and enrichment. We found that the LBN manipulation reduced weight gain in both male and female pups and this effect was observed into adulthood. Additionally, the anal genital distance (AGD) of rats exposed to LBN was smaller in both males and females after LBN, even when controlling for weight. Smaller AGDs result from lower androgen exposure, suggesting that LBN disrupts the efficacy of this class of hormones. In females, LBN had no effect in puberty on the timing of vaginal opening or estrous cycle length in adulthood, suggesting that, in our hands, this manipulation does not have lasting effects on female reproductive function. However, LBN did increase estradiol levels in both adult male and female rats, although this effect was clearly driven by the males. In contrast, testosterone levels were comparable in adult male rats in both the LBN and control nesting condition. Given that testosterone is converted to estradiol by aromatase, these results suggest an increase in aromatase activity in males exposed to LBN. Ongoing studies are exploring whether

LBN males have altered reproductive behavior compared to controls to provide deeper insight into the consequences of early life adversity on male reproductive function. Together, these results suggest that LBN alters development in both males and females, but the effect on steroid hormones is more persistent in males.

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Poster

765. Stress Response: Sex Differences

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 765.08/O7

Topic: F.04. Stress and the Brain

Support: NSERC

Title: Pubertal chronic sleep restriction induces depression-like behavior and alters stress response in a sex-specific manner

Authors: *M. S. MURACK[1], É. MALETTE-GUYON[1], R. CHANDRASEGARAM[2], É. RHÉAUME[1], Z. NANJI[1], S. SEMCHISHEN[3], E. AH-YEN[1], O. LATUS[1], C. MESSIER[1], N. ISMAIL[1];
[1]Univ. of Ottawa, Ottawa, ON, Canada; [2]Cardiff Univ., Cardiff, United Kingdom; [3]Simon Frasier Univ., Vancouver, BC, Canada

Abstract: Depression is a highly prevalent and debilitating disorder responsible for decreased quality of life and heightened risk of suicide. The rate of major depression diagnoses increases at pubertal onset, especially in females. Puberty is a critical period of development characterized by increased synaptic pruning and plasticity in the brain. Maladaptive rewiring of neurons allow for increased vulnerability to pubertal and even adult psychiatric disorders. Exposure to chronic stress such as sleep restriction downregulates corticosterone release from the adrenal glands and decreases glucocorticoid receptor (GR) activation in areas associated with depressive behaviour (i.e. hippocampus, hypothalamus and dorsolateral prefrontal cortex). Chronic sleep restriction (CSR) is a natural characteristic of early pubertal development. Yet insomnia is a common symptom of most depressive disorders. Therefore, CSR may increase depressive behaviour via stress - related correlates. To address this possibility, eighty male and female pubertal and adult mice were allowed normal rest or were sleep restricted for eight consecutive days during the first four hours of their sleep cycle. Depressive behaviour was measured with the forced swim test. GR expression and activation via c-Fos protein staining was assessed with immunohistochemistry. Sleep restricted pubertal females displayed greater depressive behaviour

compared to non-sleep restricted controls as well as their adult counterparts. Pubertal females exposed to CSR displayed less GR activation in the hippocampus compared to pubertal males. CSR likely affects the onset of pubertal female depression along established stress pathways. Through manipulation of sleep habits in puberty, we may prevent the early onset and development of depression.

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Poster

765. Stress Response: Sex Differences

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 765.09/O8

Topic: F.04. Stress and the Brain

Support: Ohio State University startup funds to KML
Ohio State University assistantship to AIS
NARSAD Young Investigator Award from Brain & Behavior Research Foundation to KML

Title: Early life stress effects on microglia function, blood brain barrier gene expression, and sex differences in mood-related behavior

Authors: *A. I. SAULSBERY[1], C. M. DODSON[2], H. D. LICHTENSTEIN[2], S. P. MURPHY[1], K. M. LENZ[2,1,3];
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Abstract: In humans, early life stress is associated with increased vulnerability to later-life psychological disorders and cognitive dysfunction. The mechanisms that underlie this increased vulnerability are not fully understood; however, it is possible that early life stress (like adult stress in rodents) induces activation of immune cells, including mast cells and microglia. This activation could alter microglia function, or mast cell degranulation could compromise blood-brain barrier (BBB) integrity, enabling peripheral immune cell infiltration into the brain. We have previously found that daily brief handling stress increases mast cell numbers in the female hippocampus on postnatal day (PD) 11 (Joshi et al., in press). Early life stress may alter the function of microglia, including phagocytosis, which contributes to neurodevelopmental processes such as neurogenesis and synaptic patterning (Nelson et al., 2019). Here, we subjected male and female Sprague-Dawley rat pups to 4hr/day of maternal separation stress (or brief control handling) during the light cycle from PD2-20. Half of the pups were sacrificed at PD21; a randomly chosen hemisphere of each brain was subsequently processed for gene expression

analysis via qPCR. Another cohort was raised to adulthood and tested for anxiety- and depression-like behaviors in the open field (OFT), elevated plus maze (EPM), and forced swim test (FST). Separation stress significantly decreased pup weights at PD 16, 18, and 20. To explore potential mechanisms for early life stress effects on adult behavior and psychiatric vulnerability, we tested the expression of genes related to microglial phagocytosis in the PD21 hippocampus. Stress significantly increased the expression of Tyrobp. Further, we observed a trending stress-induced increase in hippocampal C1q expression. We observed no effects of sex or stress in the expression of Cybb or CD68. Although our group has found sex differences in the expression of Tyrobp, Cybb, and CD68 in the PD2 hippocampus (Nelson et al., 2017), these sex differences were no longer evident at PD21. In ongoing studies, we are assessing phagocytic gene expression in the PD21 amygdala and hypothalamus. No stress or sex effects were observed in hippocampal mRNA expression for the BBB tight junction proteins occludin, claudin-5, TJP1, or TJP2 at PD21. As adults, stressed rats spent significantly less time immobile in the FST than controls, and stressed male rats showed increased anxiety-like behaviors in the OFT. No stress effects were observed in open arm time in the EPM. These results suggest a potential mechanism whereby early life stress programs adult behavior and cognitive function.

Disclosures: A.I. Saulsbery: None. **C.M. Dodson:** None. **H.D. Lichtenstein:** None. **S.P. Murphy:** None. **K.M. Lenz:** None.

Poster

765. Stress Response: Sex Differences

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Program #/Poster #: 765.10/O9

Topic: F.04. Stress and the Brain

Support: NIMH Grant 1R01MH107556-01

Title: Developmental alterations in prefrontal cortex microglial morphology following maternal separation and lipopolysaccharide injection in male and female rats

Authors: *S. PETERZELL, K. R. GILDAWIE, J. A. HONEYCUTT, V. THOMPSON, H. C. BRENHOUSE;
Psychology, Northeastern Univ., Boston, MA

Abstract: Adverse experiences during early life have been shown to increase vulnerability to a multitude of neuropsychiatric disorders. Adversity during critical developmental time periods can have detrimental effects on neural development, particularly in the prefrontal cortex (PFC). Adversity-related aberrations in the PFC have also been found to alter neuroimmune signaling, elevating cytokine levels produced by microglia, the main resident immune cells of the brain. Microglia are reported to have increased neuroimmune activity and subsequent production of

inflammatory molecules in response to homeostasis disruption. Microglia are also capable of provoking long-term changes in brain structure and function, particularly within local microcircuitry. Importantly, they have the ability to become chronically sensitized, or 'primed' to over-activation following insult. However, it is unknown whether maternal separation (MS) early in life followed by a secondary challenge later in life alters microglial reactivity and morphology across development. To investigate the impact of MS on microglial priming in the developing immune system, male and female rat pups were separated from their dams for 4 hours per day from postnatal day (P) 2-20. Rats were then exposed to the endotoxin lipopolysaccharide (LPS) in either juvenility (P20) or adolescence (P40). Four hours after LPS injection, rats were perfused and brains were collected, cryoprotected, and sliced on a freezing microtome to 40 µm slices. Tissue sections containing the prelimbic (PL) and infralimbic (IL) PFC were immunohistochemically stained to visualize Iba1+ microglia. Fluorescent microscopy was used to capture images in three consecutive sections in the PL and IL (6 images per section). Morphological microglial alterations were quantified in ImageJ via the AnalyzeSkeleton macro plugin. Our findings reveal that MS confers sensitization to a secondary LPS insult in a sex- and age-dependent manner. Investigating variances in neuroinflammatory changes at different time points between MS and LPS induced stress can help elucidate the role that early life adversity plays in altering microglia function and pathology in later life.

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Poster

765. Stress Response: Sex Differences

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Program #/Poster #: 765.11/O10

Topic: F.04. Stress and the Brain

Support: Northeastern University Advanced Undergraduate Research & Creative Endeavors Award
NIMH Grant 1R01MH107556-01

Title: Developmentally-dependent effects of maternal separation on oxidative stress accumulation in parvalbumin neurons of male and female rats

Authors: *A. R. SOARES[1,2], K. R. GILDAWIE[2], J. A. HONEYCUTT[2], H. C. BRENHOUSE[2]; [1]Interdepartmental Neurosci. Program, Yale Univ., New Haven, CT; [2]Developmental Neuropsychobiology Laboratory, Dept. of Psychology, Northeastern Univ., Boston, MA

Abstract: Early life adversity in humans is linked to the emergence of cognitive deficits and an increased risk of mental illness later in life, including anxiety, depression, bipolar disorder, and

schizophrenia. Developmental insults, such as early adverse experiences, and the subsequent mental illness susceptibility have been associated with abnormalities in the prefrontal cortex (PFC), hippocampus (HPC), and basolateral amygdala (BLA), among others. Modeling early life adversity in rodents using a maternal separation (MS) paradigm shows similar neuropsychological deficits that may partially be driven by dysfunction in inhibitory parvalbumin (PV) interneurons. Research demonstrates that PV interneurons are particularly susceptible to oxidative stress, and that accumulation of oxidative damage may contribute to observed PV dysfunction following MS. Additionally, sex differences have been reported in the timing and severity of neurological and behavioral deficits associated with MS. The goal of the present study was to quantify oxidative stress accumulation over development in PV neurons of both male and female rats exposed to MS. To do this, pups were separated from their dam for 4 hours each day from postnatal day (P)2 to 20 and then sacrificed for neural quantification and analyses in either juvenility (P21) or adolescence (P40). Serial sections from PFC, HPC, and BLA were immunohistochemically tagged with antibodies against PV, as well as 8-oxo-dG, a marker for oxidative DNA damage. Individual and colocalization expression of these targets were measured in the PFC, HPC, and BLA to determine the oxidative effect of MS and establish whether its progression varies as a function of sex. We specifically examined the prelimbic and infralimbic cortices of the PFC, and the CA1 and CA3 fields of the HPC, as well as the dentate gyrus. We present novel and compelling data demonstrating a link between MS and increased oxidative stress in PV neurons, in a sex- and age-dependent manner, as well as sex differences in overall PV cell count. These data identify a potential timepoint at which antioxidant treatment may be administered in order to prevent further neurological dysfunction in individuals subjected to early life adversity, and highlight the importance of sex differences in the treatment of adversity-related dysfunction.

Disclosures: A.R. Soares: None. **K.R. Gildawie:** None. **J.A. Honeycutt:** None. **H.C. Brenhouse:** None.

Poster

765. Stress Response: Sex Differences

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Program #/Poster #: 765.12/O11

Topic: F.04. Stress and the Brain

Support: NSF IOS-1122074

Title: Early life stress alters the transposable element, LINE 1 in a sex-specific manner

Authors: *A. CUARENTA[1], K. E. KARLS[2], I. C. HENION[1], S. L. KIGAR[3], L. CHANG[4], V. P. BAKSHI[5], A. P. AUGER[6];
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Abstract: Line1—a retrotransposon that comprises ~17% of the human genome and ~23% of the rat genome —is aberrantly expressed in psychiatric disorders such as schizophrenia, bipolar disorder, and Rett syndrome, suggesting it may play an important role in neurodevelopment. Line1 expression was previously thought to be quiescent during typical developmental conditions through epigenetic suppression; however, recent evidence suggests that Line1 levels and DNA copy number may actually be affected by environmental experiences. Specifically, once expressed, Line1 has the ability to self-replicate via reverse transcription of an RNA intermediate and can subsequently reinsert itself throughout the genome. In the current study, we sought to understand whether early life stress (ELS), a known risk factor for the development of later psychiatric disorders, would affect Line1 expression. Our study used a neonatal predator odor exposure (POE) paradigm to model ELS in rats to examine the consequences of experiencing "fear of harm" on brain development. We examined Line1 RNA levels using RT-qPCR at two different timepoints, neonatal postnatal day 3 (PND3) and juvenile (PND33), to assess whether ELS would alter Line1 expression levels in males and females. Our results suggest that Line1 expression is sensitive to ELS and that these changes are sex and region specific. Because we see changes in RNA expression, we are exploring whether this leads to an increase in DNA copy number due to Line1 self-replication. Therefore, we are seeking to understand whether ELS creates somatic mosaicism within the developing brain.

Disclosures: A. Cuarenta: None. **K.E. Karls:** None. **I.C. Henion:** None. **S.L. Kigar:** None. **L. Chang:** None. **V.P. Bakshi:** None. **A.P. Auger:** None.

Poster

765. Stress Response: Sex Differences

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 765.13/O12

Topic: F.04. Stress and the Brain

Support: Rowan University school of osteopathic medicine startup funds

Title: Stress- and gender- dependent changes in locus coeruleus physiology and anxiety-like behavior

Authors: *O. BORODOVITSYNA[1], D. J. CHANDLER[2];
[1]Cell Biol. and Neurosci., Rowan Univ. GSBS, Stratdord, NJ; [2]Cell Biol. and Neurosci., Rowan Univ. Sch. of Osteo. Med., Stratford, NJ

Abstract: The locus coeruleus (LC) is the main source of norepinephrine (NE) in central nervous system. During exposure to a stressor, corticotropin releasing factor (CRF) is released onto LC dendrites and activates CRF receptor 1, depolarizing its neurons and enhancing NE release throughout the forebrain. We have previously demonstrated that a single stressful event produces acute and long-term changes in LC physiology and anxiety-like behavior in adolescent male rats. It is known that the female LC characterized by functional and structural differences compared to male LC, including larger size, more complex dendritic arborization patterns, increased NE biosynthesis in response to estrogen, and differences in CRFR1 trafficking and internalization. In addition to animal studies, female patients are known to be more susceptible to depressive and anxiety disorders than men. Based on these discoveries we hypothesized that the same acute stressor would have different responses in female and male rats.
Female rats (42PND) were exposed to 15 minutes of combined predator odor (TMT) and restraint stress. Immediately after animals were tested in elevated plus maze (EPM) to determine anxiety-like behavior and returned to their home cage. One week later, anxiety-like behavior was assessed in the open field test and whole-cell patch clamp recordings were performed to determine the long-term effects of stressor exposure on LC physiology. To access the endocrine branch of stress response serum was collected at baseline level before stress, 35 minutes after the beginning of stressor exposure or control conditions and a final measurement a week after. Preliminary results indicate that female rats show increased mobility in the mazes compared to males. Females also showed lower endocrine responses to stressor exposure compared to males. These findings will help to determine if and how the sexually dimorphic nature of the mammalian LC contributes to sex-specific behavioral responses to stress and anxiety-like behavior.

Disclosures: O. Borodovitsyna: None. **D.J. Chandler:** None.

Poster

765. Stress Response: Sex Differences

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 765.14/O13

Topic: H.01. Animal Cognition and Behavior

Support: FDG-SUNY OW

Title: Developmental Pb-exposure causes sex-dependent neurobiological changes in cell counts determined by isotropic fractionation and are associated with later life anxiety-like behavioral outcomes: Implications for early onset of emotional dysregulation disorders

Authors: *L. S. NEUWIRTH[1], *J. S. JOSEPH[2], J. C. SKEEN[2], K. P. LYNCH[1], I. AHMED[1], E. KHAIRI[2], E. CABANAS[2], M. A. VASQUEZ[3], G. CRUZ[2], J. R. BONITTO[2], A. CHOE[4], K. GILLENWATER[4], B. HINDI[4], S. PILOUT[4], M. KENT[5], K. G. LAMBERT[4];

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Abstract: Lead (Pb) is a well-established neurotoxicant that causes developmental neuropathologies, which result in cognitive and behavioral impairments across the lifespan. The current study assessed the effect of 150ppm and 1,000ppm perinatal Pb-exposed in offspring of Long Evans rat dams on locomotor activity and anxiety-like behaviors associated with neuronal cell counts in the prefrontal cortex (PFC) and hippocampal (HP) brain regions. The perinatal Pb-exposure began 1-month prior to breeder pairing through parturition and ceased at postnatal day (PND) 22. Control rats (0ppm) were used to evaluate the degree of neuropathological changes in behavioral and neurobiological outcomes as a function of Pb dose-response and sex. When assessed in the elevated plus maze (EPM) (PND 35), rats exposed to 150ppm and 1,000ppm of Pb exhibited increased locomotor activity when compared to control rats. Pb-exposed rats at both dose-responses frequented and spent more time active within the open arms of the EPM with females showing more Pb-sensitivity. Encephalization Quotients (EQ) were calculated for all treatment groups as a ratio of brain-to-body weight within a species index. Control females EQs were larger than Control males. However, in response to developmental Pb-exposure the 150ppm males had reduced EQs, whereas the 1,000ppm males had higher EQs, when compared to control males. Contrastingly, both 150ppm and 1,000ppm female had higher EQs when compared to control females. Cell counts are currently being conducted via isotropic fractionation (IF) in the PFC and HP to determine the effect of Pb-exposure on the number of cells (i.e., neuronal and glia) in these brain regions that are Pb-sensitive. Notably, Pb-exposure can cause inverted-U neurotoxicant relationships whereby low-doses may cause increased neurogenesis and high-doses apoptosis through compensatory mechanisms, sex-based susceptibilities remain to be elucidated. Females appear to be more sensitive to the high-doses of Pb-exposure. Given the increased risk for environmental Pb-exposure in children, understanding how Pb can impair neurodevelopment may prove useful in developing psychopharmacological interventions in addressing anxiety-like behaviors across the life span.

Disclosures: L.S. Neuwirth: None. **J.S. Joseph:** None. **J.C. Skeen:** None. **K.P. Lynch:** None. **I. Ahmed:** None. **E. Khairi:** None. **E. Cabanas:** None. **M.A. Vasquez:** None. **G. Cruz:** None. **J.R. Bonitto:** None. **A. Choe:** None. **K. Gillenwater:** None. **B. Hindi:** None. **S. Pilout:** None. **M. Kent:** None. **K.G. Lambert:** None.

Poster

765. Stress Response: Sex Differences

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 765.15/O14

Topic: F.04. Stress and the Brain

Support: NSERC Grant 138199

Title: Hemispheric and sex-dependent effects of early-life stress on synaptic plasticity, neuronal excitability and NMDAR expression in the rat postweaning basolateral amygdala

Authors: *A. GUADAGNO[1,2], H. LONG[1], T. WONG[1,3], C.-D. WALKER[3,1];
[1]Douglas Mental Hlth. Univ. Inst., Montreal, QC, Canada; [2]Integrated Program in Neurosci., [3]Dept Psychiatry, McGill Univ., Montreal, QC, Canada

Abstract: Early-life stress (ELS) exposure is associated with increased vulnerability to mental disorders. The basolateral amygdala (BLA) - medial prefontal cortex (mPFC) circuit plays an important role in emotional behavior and is extremely sensitive to ELS. Using a naturalistic rodent model of ELS, the limited bedding paradigm (LB) between postnatal days (PND) 1-10, we previously showed that LB male, but not female preweaning pups display increased BLA neuron spine density paralleled with enhanced evoked synaptic responses, in addition to altered male BLA-mPFC functional connectivity. Since ELS effects are often sexually dimorphic, we aimed to examine sex differences in the developing BLA and its relation to the mPFC. We investigated changes in synaptic plasticity and neuronal excitability of BLA neurons *in vitro* in the left and right amygdala of PND25-28 offspring of normal bedding (NB) or LB mothers. Since NMDAR are developmentally regulated and critical for synaptic plasticity, we also examined expression of GluN2A, GluN2B and GluN1 in the BLA and mPFC on PND28. We report that LB conditions enhanced evoked synaptic responses in the right, but not the left, BLA of males. Furthermore, BLA input/output function in LB males was significantly greater than that from LB females. Interestingly, the stress of LB increased long-term potentiation (LTP) formation in the right BLA of males exclusively. Action potentials fired from BLA neurons in the right amygdala of LB animals were of a larger amplitude compared to those from NB animals, and more frequent in LB compared to NB males. With respect to NMDAR, GluN1 levels were elevated only in the right side of the BLA of LB males compared to females, whereas the opposite pattern emerged for GluN2B expression in the mPFC. GluN2A expression was also largely decreased in LB compared to NB pups in the mPFC. Our data suggest that LB modifies synaptic organization and laterality in the BLA-mPFC pathway in postweaning pups, with effects being mostly exacerbated on the right side in males. We propose that increased excitability of BLA neurons might alter the strength of BLA-mPFC projections, potentially affecting NMDAR expression and excitatory/inhibitory neurotransmitter balance in the mPFC. These changes in the BLA-mPFC circuit could underlie the sexually-dimorphic behavioral phenotype we have previously observed as a long-term consequence of ELS exposure.

Disclosures: A. Guadagno: None. **H. Long:** None. **T. Wong:** None. **C. Walker:** None.

Poster

765. Stress Response: Sex Differences

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 765.16/O15

Topic: F.04. Stress and the Brain

Support: NIMH 1R56MH114833
NIMH R01MH100078

Title: Variations of early life stress and sex differentially alter hippocampal development and function leading to disruptions in contextual learning

Authors: *J. D. WHITE[1], A. PUGLIESE[1], C. H. LEE[2], T. AREFIN[2], J. ZHANG[2], A. KAFFMAN[1];
[1]Psychiatry, Yale Sch. of Med., New Haven, CT; [2]New York Univ. Langone, New York City, NY

Abstract: Stress has pronounced effects on the brain, and thus behavioral outputs. This is particularly true when the stress occurs during vulnerable points in neural development. In humans, early life stress (ELS) appears to be additive, with the severity in outcomes corresponding with the number of instances or degree of trauma experienced. Due to the wide-ranging and often compounded stressors experienced by humans, the mechanisms underlying ELS-induced changes in brain development and function can be difficult to study. To address these issues, we utilized two animal models of early life stress (ELS), i.e., limited bedding and nesting (LBN) and a modified version of the LBN paradigm that also includes intermittent 1 hr maternal separation sessions and nest disruption on postnatal days (P) 14, 16, 17, 21, 22, & 25 (UPS). We have previously shown that these ELS paradigms differentially affect anxiety behaviors and fronto-limbic connectivity in adulthood, and that these effects are further moderated by sex. In the current study, we focused on how LBN and UPS interacts with sex to affect changes in the developing hippocampus and whether this leads to differential behavioral outcomes in contextual learning in adulthood. Exposure to LBN and UPS differentially stunted hippocampal development across a number of measures, and altered postnatal neurogenesis, corticosterone levels and neuronal activation in a region-specific way within the hippocampus. RNA-seq analysis from hippocampal tissue at P17 indicated striking differences between control and ELS reared animals while also demonstrating significant differences between LBN and UPS paradigms. Our results indicate that, although LBN and UPS are closely related ELS paradigms, they lead to distinct changes in the developing hippocampus, some of which are moderated by sex. The disparate outcomes between the LBN and UPS paradigms highlights the need to further investigate how different forms of postnatal stress can modify the pathophysiology and consequences of ELS across the lifespan.

Disclosures: **J.D. White:** None. **A. Pugliese:** None. **C.H. Lee:** None. **J. Zhang:** None. **A. Kaffman:** None. **T. Arefin:** None.

Poster

765. Stress Response: Sex Differences

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 765.17/O16

Topic: F.04. Stress and the Brain

Support: NIH Grant 068283

Title: Exercise effects on activation of dorsal raphe nucleus-projecting neurons during uncontrollable stress

Authors: *K. BONAR;
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Abstract: Exercise increases stress resistance, but the neurochemical mechanisms underlying the stress-protective effects of exercise remain unknown. In rats, 6 weeks of voluntary access to running wheels prevents the anxiety- and depression-like behavioral consequences of exposure to an uncontrollable stressor. Hyperactivation and sensitization of serotonin (5-HT) neurons in the dorsal raphe nucleus (DRN) is necessary and sufficient to produce the behavioral consequences of uncontrollable stress, and exercise is thought to prevent these stress-induced behaviors by constraining the activation of DRN 5-HT neurons during uncontrollable stress. The mechanism by which exercise constrains DRN 5-HT neurons during stress is unknown. Identification of this circuitry could contribute to the development of novel targets of stress resilience. Here we used viral neural-tract-tracing to identify neurons that project to the DRN. We then quantified cFos immunoreactivity following uncontrollable stress in DRN afferents in rats allowed 6 weeks of prior wheel running vs. locked wheel conditions. Quantification of cFos expression in DRN-projecting neurons in the striatum, locus coeruleus, habenula, and prefrontal cortex is currently underway. Results could reveal novel stress-resistance neural circuitry that is sensitive to exercise and able to constrain activation of the DRN during exposure to damaging uncontrollable stressors.

Disclosures: **K. Bonar:** None.

Poster

765. Stress Response: Sex Differences

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 765.18/O17

Topic: F.04. Stress and the Brain

Support: NIH Grant R15 MH114025 (BNG)
NIH Grant R01 MH050479 (MVB)
NIH Grant R21 MH106817 (MVB)
NARSAD Young Investigator Grant from the Brain and Behavior Research Foundation (MVB)

Title: Voluntary wheel running prevents the behavioral sequelae of uncontrollable stress in females

Authors: *I. P. FALLON[1], M. K. TANNER[2], A. M. TAMALUNAS[1], D. H. ROOT[1], M. V. BARATTA[1], B. N. GREENWOOD[3];
[1]Psychology and Neurosci., Univ. of Colorado Boulder, Boulder, CO; [2]Dept. of Integrative Biol., [3]Psychology, Univ. of Colorado Denver, Denver, CO

Abstract: Women are at a higher risk for developing stress-related neuropsychiatric disorders such as generalized anxiety disorder, post-traumatic stress disorder and depression. The mechanisms underlying these differences are unknown but they may arise from different responses to stress resistance/resilience-inducing factors like physical exercise. In male rodent models, 6 weeks of voluntary wheel running (VWR) prevents exaggerated freezing and social avoidance produced by exposure to an uncontrollable stressor. However, it is unknown if the stress-buffering effects of exercise are present in females as it is in males. Here, we demonstrate that females allowed 6 weeks of access to VWR are protected from the behavioral sequelae of uncontrollable stress. In males, the buffering effects of exercise are partly due to reduced serotonergic output from the dorsal raphe nucleus (DRN). Top-down inhibition of the DRN by the medial prefrontal cortex (mPFC) has been identified as a potential endophenotype across other stress resilience models (e.g. ketamine, stressor controllability). In order to determine if prior VWR leads to the engagement of the mPFC during uncontrollable stress, we examined continuous calcium-mediated activity in the mPFC using fiber photometry in both male and female rats. Understanding the neurobiological mechanisms that mediate the protective effects of exercise, and whether there are sex-based differences, could lead to novel strategies to improve the treatment of neuropsychiatric disorders in women.

Disclosures: I.P. Fallon: None. **M.K. Tanner:** None. **A.M. Tamalunas:** None. **D.H. Root:** None. **M.V. Baratta:** None. **B.N. Greenwood:** None.

Poster

765. Stress Response: Sex Differences

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 765.19/O18

Topic: F.08. Biological Rhythms and Sleep

Support: NIH Grant R15 NS101692-01
Skidmore College Summer Faculty/Student Collaborative Research Fellowship

Title: Optogenetic activation of SIFamide neurons during adulthood causes sexually dimorphic sleep induction in *drosophila melanogaster*

Authors: *H. HUANG[1], C. G. VECSEY[2];
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Abstract: SIFamide (SIFa) is a genetically conserved neuropeptide in arthropods, and previous studies have shown that it regulates diverse behaviors, which include sexual behaviors, feeding behaviors, sleep, and rest:activity rhythms. In *Drosophila*¸ SIFa is expressed in four neurons in the pars intercerebralis (PI), and either ablating SIFa neurons or knocking down SIFa expression level shortens time spent asleep, suggesting that SIFa is sleep promoting in *Drosophila.* However, it remains unclear if: 1) acute activation of SIFa neurons during adulthood will also induce sleep, 2) other factors, which include sex, duration of neural activation, and intensity of the activation, will influence the strength of the effect, 3) the activation of SIFa neurons will lead to other behaviors besides sleep. Here, we addressed these issues by utilizing an optogenetic approach to activate SIFa-expressing neurons. By building a fly line with both SIFa-Gal4 and UAS-Chrimson, we were able to activate SIFa-expressing neurons with red-light stimulation. The current study showed that the activation of SIFa neurons when flies were active could significantly decrease flies' activity, suggesting that activity in these neurons promotes sleep. SIFa neuron activation also showed a sexual dimorphism, in that a greater effect on sleep was observed in female flies than in males. An acute study that activated SIFa neurons with a short red-light stimulation (1-5 seconds) showed that a short activation of SIFa neurons was able to induce sleep, and that the duration of sleep was intensity-dependent. In short, the current study showed that an acute activation of SIFa neurons was able to promote sleep in adulthood, and the strength of the sleep-promoting effect depended on sex, the intensity, as well as the length of the activation. Future studies will identify the neurotransmitter that promotes sleep during the activation of SIFa neurons and characterize the sleep-relevant downstream effects of SIFa neuron activity.

Disclosures: H. Huang: None. **C.G. Vecsey:** None.

Poster

765. Stress Response: Sex Differences

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 765.20/O19

Topic: F.08. Biological Rhythms and Sleep

Support: CHIRP Grant

Title: Sex differences in hypothalamic-pituitary-adrenal axis response following a single and multiple nights of sleep restriction

Authors: *K. BUBAN[1], E. A. SHUPE[2], S. W. ROTHWELL[1], T.-Y. J. WU[1];
[1]Uniformed Services Univ., Bethesda, MD; [2]Sch. of Neurosci., Virginia Tech., Blacksburg, VA

Abstract: 1 in 3 adults report experiencing inadequate or disrupted sleep throughout the night (Liu et al., 2016), with the incidence being higher in women than in men. Disturbances in nightly sleep result in hormonal, neurochemical and behavioral alterations that contribute to a number of disorders. Sleep is believed to contribute to the pathogenesis of these disorders through its interaction with the hypothalamic pituitary adrenal (HPA) axis. The HPA axis releases corticotropin-releasing factor (CRF) from the paraventricular nucleus of the hypothalamus (PVN) to ultimately result in glucocorticoid (CORT) release from the adrenals. The present study sought to investigate the effect of one and three nights of restricted sleep on HPA axis reactivity. Male and female C57BL/6J mice were sleep-deprived for a 20h period for one night or three consecutive nights using the modified multiple platform method and subjected to 20 minutes of restraint stress after an 8h recovery. Males, at both one and three days of sleep restriction, showed blunted restraint-induced rises in CORT relative to their home cage control (HCC) groups ($p< 0.05$). Similarly in females, following three nights of sleep restriction, mice showed a blunted restraint-induced CORT response ($p<.05$). However, following a single night female mice showed a complete ablation of HPA reactivity (< 0.05). Analysis of pituitary and adrenal mRNA expression revealed significant alterations in peripheral HPA axis regulatory genes. Males, regardless of sleep restriction duration showed increases in proopiomelanocortin expression ($p< 0.05$), while females showed increases after only a single night ($p< 0.05$). In contrast, females showed increases in CRFR1 expression regardless of sleep restriction duration ($p< 0.05$), while males only showed an increase following three nights of sleep restriction ($p< 0.05$). Restricted sleep also significantly increased 11β-hydroxylase mRNA expression and altered 11β-hydroxysteroid dehydrogenase 1 and melanocortin receptor 2 expression in the adrenals. Altogether, these data suggest that both central and peripheral mechanisms are involved in the HPA axis dysregulation observed following the periods of restricted sleep examined in this study. Current efforts are underway to explore the role of central regulatory mechanisms in the

HPA axis response following sleep restriction. These findings suggest there is a sex difference in how the HPA axis responds to sleep loss.

Disclosures: K. Buban: None. **E.A. Shupe:** None. **S.W. Rothwell:** None. **T.J. Wu:** None.

Poster

765. Stress Response: Sex Differences

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 765.21/O20

Topic: F.04. Stress and the Brain

Support: NIA GRANT 1 RF1 AG057884

Title: Sex differences of the phosphoproteomic profiles in APP/PS1 mice after chronic unpredictable mild stress

Authors: *S. DOMINGUEZ[1], G. RODRIGUEZ[1], H. FAZELINA[2], H. DING[2], S. SEEHOLZER[2], H. DONG[1];
[1]Dept. of Psychiatry and Behavioral Sci., Northwestern Univ., Chicago, IL; [2]Proteomics Core, The Children's Hosp. of Philadelphia, Philadelphia, PA

Abstract: Of the 5.4 million Americans suffering from Alzheimer's Disease (AD), roughly two-thirds are women. While women's longer average lifespan is a plausible explanation for the prevalence gap in AD diagnosis, increasing evidence suggests that there remains an age and risk factor-matched enhanced risk for AD in women. The biological mechanisms underlying this sex divergence in the AD prevalence, however, remains unknown. Previous research has shown sex-specific biochemical differences in central stress responses that bias female mice towards pro-AD signaling on the phosphoproteomic level via Corticotropin Releasing Factor (CRF) Receptor 1 activation after CRF overexpression. In this study, we aimed to determine if these findings could similarly be reproduced under physiological CRF expression following chronic stress. We stressed APP/PS1 mice using a Chronic Unpredictable Mild Stress (CUMS) paradigm for 1 month. CUMS is commonly used in animal models to mimic the daily life stress of humans. In our model, we used a variety of mild to moderate stressors including wet bedding, cage tilt, and acute restraint at differing times of the day. Following CUMS and behavioral assessments, we collected brain tissue and identified and quantified whole protein and phosphoprotein levels in the cortex of stressed and non-stressed APP/PS1 mice using MaxQuant. While there were no significant differences at the total protein and peptide levels, we found 909 statistically significant phosphopeptides between stressed and unstressed females and 841 statistically significant phosphopeptides between stressed and unstressed males using a False Discovery Rate of 5%. Of these significant phosphopeptides, only 301 were the same in males and females. These results indicate that while both males and females undergo protein phosphorylation

changes following stress, the peptides that are phosphorylated differ between sexes. We then compared these significant phosphopeptides using Metacore analysis to determine which biological pathways were affected. We found that several pathways were changed differently between male and female mice including NMDA receptor trafficking, cytoskeleton organization, and Tau pathology. Our next step will be to confirm such changes in statistically significant pathways of interest, specifically those associated with AD-related neuropathogenesis. The differing biological pathways affected between males and females in response to chronic stress may help us understand why women are at a higher risk of AD and what may be causing the link between female-biased, stress associated neuropsychiatric disorders such as major depression disorder with AD.

Disclosures: S. Dominguez: None. **G. Rodriguez:** None. **H. Fazelina:** None. **H. Ding:** None. **S. Seeholzer:** None. **H. Dong:** None.

Poster

765. Stress Response: Sex Differences

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 765.22/O21

Topic: F.04. Stress and the Brain

Title: Irisin injection into the hippocampus suppresses acute stress-induced memory impairment and anxiety-like behavior in a sex dependent manner

Authors: *M. JODEIRI-FARSHBAF, D. CHERKOWSKY, N. MANAL, D. P. MOUSSOUKI, K. ALVIÑA;
Texas Tech. Univ., Lubbock, TX

Abstract: Acute stress can disrupt a variety of neural processes, including reducing levels of brain-derived neurotrophic factor (BDNF) in the hippocampus. Exercise, on the other hand, can increase BDNF levels and has overall beneficial effects for health and brain function. Irisin is a myokine that is released into the peripheral blood during aerobic exercise. Although the main known functions of Irisin, both in human and rodents, are browning white adipose tissue and improving glucose homeostasis, recent findings have shown that Irisin mediates the activation of an exercise-induced BDNF-mediated neuroprotective pathway in the hippocampus. Therefore, in this study we tested the hypothesis that Irisin can counteract the deleterious effects of acute stress when directly injected into the hippocampus. To test our hypothesis, we first established a 3h physical restraint stress in adult mice that resulted in sex-dependent increased anxiety-like behaviors and memory impairment in a combined open field/novel object recognition (OF/NOR) test. Moreover, acute stress also reduced skin temperature and body weight in both female and male mice. We then injected Irisin via bilateral stereotaxic injection and repeated the acute stress paradigm and combined OF/NOR test. We found that Irisin partially blocked stress-induced

anxiety-like behavior and memory impairment in male mice, while also preventing the reduction in skin temperature and body weight. Interestingly, in female mice Irisin only prevented the skin temperature and body weight reduction but showed no beneficial effects on neurobehaviors. Taken together, our results suggest a novel role for Irisin in counteracting acute stress-induced neurobehavioral and physiological abnormalities. Also, our results support the idea that exercise can be a potentially effective tool to promote the maintenance of healthy neural function.
Keywords: irisin, hippocampus, stress, memory, anxiety-like behavior

Disclosures: M. Jodeiri-Farshbaf: None. **D. Cherkowsky:** None. **N. Manal:** None. **D.P. Moussouki:** None. **K. Alviña:** None.

Poster

765. Stress Response: Sex Differences

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 765.23/O22

Topic: F.04. Stress and the Brain

Support: NIH Grant T32MH103213
NIH Grant T32HD049336
NIH Grant UL1TR001108

Title: Chronic stress results in sex-specific deficits in behavioral flexibility and changes in gene expression in rat medial prefrontal cortex following a novel stress challenge

Authors: *K. M. MOENCH, M. R. BREACH, C. L. WELLMAN;
Indiana Univ., Bloomington, IN

Abstract: Chronic stress leads to sex-specific changes in the structure and function of rat medial prefrontal cortex (mPFC). Little is known about whether these effects persist following the cessation of chronic stress, or how these initial effects may impact responses to future stressors. We have previously shown that dendritic remodeling in mPFC during the post-stress rest period is dynamic and sex-specific. Additionally, chronically stressed males and females have different patterns of neuronal activation in mPFC in response to a novel stress challenge following a post-chronic stress rest period. Thus, there are sex differences in the lasting effects of chronic stress on mPFC that may contribute to different behavioral outcomes following a novel stress challenge in males and females. Here we examined attentional set-shifting in male and female rats following chronic restraint stress (3 h/d, 10 d), a post-chronic stress rest period, and an acute novel stress challenge (elevated platform stress, 30 min). Chronic stress resulted in a reversible impairment in extradimensional set-shifting in males, but had no effect on attentional set-shifting in females. Surprisingly, chronically stressed female, but not male, rats had impaired extradimensional set-shifting following a novel stress challenge. Alterations in the balance of

excitation and inhibition of mPFC have been implicated in behavioral deficits following chronic stress. Thus, in a separate group of rats, we examined changes in the expression of genes related to glutamatergic (NR1, NR2A, NR2B, GluR1) and GABAergic (Gad67, parvalbumin, somatostatin) neurotransmission in mPFC after acute and chronic stress, rest, and their combination. Stress significantly altered the expression of NR1, GluR1, Gad67, and parvalbumin. Notably, the pattern of stress effects on NR1, Gad67, and parvalbumin expression differed between males and females. In males, these genes were upregulated following the post-chronic stress rest period, while minimal changes were found in females. In contrast, both males and females had greater GluR1 expression following a rest period. These findings suggest that chronic stress leads to sex-specific stress adaptation mechanisms that contribute to sex differences in response to subsequent stress exposure.

Disclosures: K.M. Moench: None. **M.R. Breach:** None. **C.L. Wellman:** None.

Poster

765. Stress Response: Sex Differences

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 765.24/O23

Topic: F.04. Stress and the Brain

Title: Examination of mu-opioid receptors in sexually-dimorphic responses to chronic stress

Authors: *S. N. CASSELLA, L. HORST, S. BAHLS;
Loras Col., Dubuque, IA

Abstract: Sex-differences in the stress response - both behavioral and physiological - are not completely understood, however accumulating data has pointed to the importance of the immune system. This relationship makes sense as we know women suffer from stress-related psychiatric diseases and immune-related disorders at a higher rates than men. Unfortunately, it's still unclear if baseline differences in inflammatory profiles of brain regions are responsible for these sex-specific behaviors, or if stress itself induces sex-specific changes that lead to divergent behaviors. One behavior that differs by sex is ethanol consumption following acute stress - female rodents consume more than males. This compliments the fact that women also need more morphine for anesthesia and points to the role of β-endorphins and μ-opioid receptors on microglia in stress regulation. The current work looks to examine the sex-specific role of the μ-opioid receptor on microglia in sexually-dimorphic stress responses to chronic stress. The results at this point are mystifying - males have an increased preference for ethanol following chronic stress, however, females have increased anxiety-like behavior on the elevated plus maze. Ongoing analysis is examining the expression and function of μ-opioid receptors in this paradigm, specifically those expressed on microglia in the hypothalamus. This project may also offer insights into sex-differences in the areas of pain and addiction.

Disclosures: **S.N. Cassella:** None. **L. Horst:** None. **S. Bahls:** None.

Poster

766. Gulf War Illness: Pathological Causes and Consequences

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 766.01/O24

Topic: F.05. Neuroimmunology

Support: VA Grant I21BX003514

Title: Modeling Gulf War illness through combined chemical exposures and infection-related immune activity

Authors: *K. D. BECK[1,2], J. A. BURTON[3,1], K. J. STALNAKER[4,1], H. J. CLARK[4,1], D. PATEL[1], T. P. COMINSKI[3,1], V. DELIC[1,3], B. A. CITRON[1,2];
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Abstract: Gulf War Illness (GWI) continues to be a lingering condition for some Operation Desert Shield/Storm Veterans deployed to the Persian Gulf in 1990-1991. Recent reports suggest permanent changes in the brain white matter of those still experiencing symptoms. We hypothesized that repeated exposure to a combination of personnel-issued chemical supplies along with bacterial infection caused persistent neuroinflammation, leading to any one or combination of symptoms associated with GWI. This hypothesis was tested in male and female C57Bl/6 mice. The chemicals tested were the type I pyrethroid insecticide permethrin (PERM) and the nerve-gas prophylactic pyridostigmine bromide (PB). Both have been demonstrated to cause neuroinflammation in rodents at high doses. Lipopolysaccharide (LPS) was used to model the immune response to an infection; LPS has also been demonstrated to cause acute signs of neuroinflammation. The chemicals were applied dermally (PERM) or orally (PB) over 1 month. The LPS was administered 3 times over one week to cause week-long proinflammatory cytokine activity. The LPS was administered either during the first or last week of chemical exposure. Additional chemical-exposure alone and LPS-alone groups served as positive controls to assess the additional role of proinflammatory cytokine activity and combined chemical exposures. Behaviors were assessed 3 months and 6 months later. Motor functioning, as assessed by the rotor-rod test, was significantly impaired in the mice at both time-points only when LPS had been administered during the first week of chemical exposure. There was no evidence of any object-based memory impairment using the object recognition or object placement recognition test. There was no significant difference attributable to Sex in any of the behavioral tests. These results suggest there may be a unique temporal relationship between experiencing a significant infection and being exposed to these chemicals, with the concurrent infection during the early

exposure to the chemicals being more detrimental to motor functioning. Future work will assess whether the brains from early-LPS/chemical exposure mice demonstrate selective white matter expression differences.

Disclosures: **K.D. Beck:** None. **J.A. Burton:** None. **K.J. Stalnaker:** None. **H.J. Clark:** None. **D. Patel:** None. **T.P. Cominski:** None. **V. Delic:** None. **B.A. Citron:** None.

Poster

766. Gulf War Illness: Pathological Causes and Consequences

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 766.02/O25

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: DOD CDMRP Grant W81XWH-16-1-0626
VA RR&D Grant I01RX001520
Veterans Bio-Medical Research Institute
Bay Pines Foundation

Title: Astrocyte morphology in a Gulf War model

Authors: *B. A. CITRON[1,2], W. A. RATLIFF[3], V. DELIC[1];
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Abstract: At least 20% of the service personnel deployed to the Persian Gulf during Operation Desert Storm developed a variety of disorders. Neurological problems are common and significant neurodegeneration over time can be involved. We have been testing neuroprotective transcription factor modulation to improve the outcomes while investigating underlying mechanisms responsible for the symptoms. Previously, we have reported morphological changes to dendritic arbors in the hippocampus induced by the insult and improved by treatment. Here, we tested mice receiving the combined insult of the anti-sarin prophylactic, pyridostigmine bromide, an organophosphate insecticide, chlorpyrifos, and the insect repellent, DEET (N,N-diethyl-m-toluamide) administered subcutaneously by infusion pump. These chemicals have been previously implicated as exposure hazards that could have contributed to Gulf War Illnesses. After 2 weeks of exposure, we examined astrocytes in several brain regions. Astrocytes were counted and astrocyte structures were examined with the aid of automated routines with ImageJ. We found indications of reactive astrocytosis induced by the Gulf War toxins. For example, astrocytes in the dentate gyrus of the hippocampus displayed 50% greater overall process length (P=0.003) per cell and a 45% increase in the number of process endpoints per cell (P=0.004) in the insulted mice (n=9) compared to the vehicle treated mice (n=4). The astrocytic

responses, combined with the structural changes that we have found in neurons in the hippocampal region, raise questions concerning the cell specific regulatory pathways that are dysregulated in Gulf War Illness. Through the identification of cellular interactions and signaling pathways, we hope to uncover therapeutic targets that will lead to improved outcomes for Veterans and others suffering related neurodegenerative disorders.

Disclosures: B.A. Citron: None. **W.A. Ratliff:** None. **V. Delic:** None.

Poster

766. Gulf War Illness: Pathological Causes and Consequences

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 766.03/O26

Topic: F.04. Stress and the Brain

Support: NSF IOS1627748
VA I21 BX002085
VA IO1 BX001804
AHA 15SDG22430017
NIH MH113892

Title: Autonomic disturbances elicited by stress and pyridostigmine bromide in a rat model of Gulf War illness

Authors: J. L. WOODRUFF[1], J. PECORELLA[2], J. RIVERS[2], C. M. LOMBARD[3], B. MUNIZ[2], V. A. MACHT[6], C. A. GRILLO[4], *L. P. REAGAN[2], S. K. WOOD[5]; [1]Pharmacology, Physiol. and Neurosci., [3]Pharmacology, Physiology, and Neurosci., [4]Dept Pharmacol, Physiol & Neurosci, [5]Pharmacology, Physiol. & Neurosci., [2]Univ. of South Carolina Sch. of Med., Columbia, SC; [6]Bowles Ctr. for Alcohol Studies, Univ. of North Carolina At Chapel Hill, Chapel Hill, NC

Abstract: Pyridostigmine Bromide (PB), an acetylcholinesterase inhibitor used as a prophylactic agent against nerve gas during the Gulf War, has been suggested as a possible cause of the chronic constellation of symptoms suffered by Gulf War Veterans. Under non-stressful laboratory conditions PB was demonstrated to have minimal autonomic consequences, however it is suggested that when combined with repeated stress PB may be deleterious to the autonomic system, contributing to GWI symptomatology. In the present study male rats were treated with either vehicle or PB (1.3 mg/kg) daily for 14 consecutive days. On the final 10 days of treatment, rats were exposed to either restraint stress (RS) or non-stressed control. To identify the dynamic temporal development of autonomic changes, cardiovascular telemetry was used to measure blood pressure (mean arterial pressure; MAP) and heart rate (HR) at a delayed time point (3 months post stress/treatment) to assess the progressive nature of GWI cardiovascular

complications. Since our previous studies determined that PB + stress altered neurochemical and endocrine responses to subsequent challenges, we examined the effects of an acute immune challenge (lipopolysaccharide; LPS, 100μg/kg) and an acute RS challenge on these cardiovascular parameters. Unlike observations at earlier time points, arrhythmic burden was unchanged in PB+RS rats at the delayed time point. However, the arrhythmic burden remained heightened under a novel endotoxin stressor in the late LPS trials. Additionally, LPS induced heightened LF/HF ratio in rats with a history of PB-RRS compared to all other groups, suggesting an imbalance of the autonomic nervous system biased towards reduced vagal tone. Collectively, these data acquired at the delayed timepoint are consistent with studies in GWI patients that demonstrate evidence of deficient vagal acetylcholine tone. Moreover, these studies illustrate the distinct autonomic effects of PB treatment during repeated stress exposure and provide insight into the progressive nature of the cardiovascular complications characteristic of GWI.

Disclosures: **J.L. Woodruff:** None. **J. Pecorella:** None. **J. Rivers:** None. **C.M. Lombard:** None. **B. Muniz:** None. **V.A. Macht:** None. **C.A. Grillo:** None. **L.P. Reagan:** None. **S.K. Wood:** None.

Poster

766. Gulf War Illness: Pathological Causes and Consequences

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 766.04/O27

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: DoD Grant GWI160151
DoD Grant GWI170023

Title: Microtubule-based mechanisms and therapies for Gulf War illness using hiPSC-derived neurons

Authors: ***P. YATES**[1], A. PATIL[1], K. A. SULLIVAN[2], P. W. BAAS[1], L. QIANG[1]; [1]Neurobio. and Anat., Drexel Univ. Col. of Med., Philadelphia, PA; [2]Envrn. Hlth., Boston Univ. Sch. of Publ. Hlth., Boston, MA

Abstract: Gulf War Illness (GWI) is a chronic multisystem disorder suffered by at least 25% of the nearly 700,000 U.S. veterans who fought in the 1990-1991 Gulf War. Central nervous system (CNS) symptoms include chronic fatigue, reduced information processing speeds, memory deficits, chronic headaches, and impaired mood and sleep. Evidence suggests that GWI is caused by the combination of the stress of the battlefield and exposure to organophosphate pesticides and nerve agents at concentrations below the threshold that inhibit acetylcholinesterase, thus implicating novel biological targets. We posit there is a constellation of cellular changes in the

central nervous system contributing to the long-lasting symptoms of GWI. We are interested in elucidating these aberrant cellular phenomena, screening potential therapies that can be rushed to suffering veterans, and investigating any cellular differences that might help explain why some veterans suffer from GWI while their similarly exposed mates do not. To tackle these questions, we are using human induced pluripotent stem cells (hiPSCs) derived from veterans of the first Gulf War, both from healthy veterans and from veterans with GWI. We are differentiating the hiPSCs into glutamatergic neurons and then exposing them to the GWI regimen of Cortisol plus Diisopropyl fluorophosphate (DFP), an analog of sarin. In one line of investigation, we are screening microtubule-based therapies that might correct previously documented changes in microtubule (MT) related processes, including alterations in MT stability, axonal transport, and neuronal activity. We are testing inhibitors of the tubulin-specific histone deacetylase 6 (HDAC6), which we have already shown can correct many of these MT-based alterations in primary rodent neurons, and inhibitors of kinesin-5, which we have shown can correct some of the axonal transport deficits. However, a mechanistic explanation for these MT-based alterations is still unclear. We hypothesize that pathology of the microtubule-associated protein tau might contribute to some of the MT-related deficits. Exposure to Cortisol plus DFP dramatically increases total tau and hyperphosphorylated tau, and now we are testing whether tau knockdown can correct the alterations in MT stability, axonal transport of mitochondria, and neuronal activity. This line of investigation opens the door to therapies from the tauopathy field. Lastly, we are growing forebrain cerebral organoids to model GWI in a more complex system to examine alterations in neurogenesis, cortical laminations, synapses, and glial activation.

Disclosures: P. Yates: None. **A. Patil:** None. **K.A. Sullivan:** None. **P.W. Baas:** None. **L. Qiang:** None.

Poster

766. Gulf War Illness: Pathological Causes and Consequences

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 766.05/O28

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: UCR Undergraduate Mini Grant

Title: Modeling the behavioral and metabolic phenotype of mice exposed to Gulf War toxicants

Authors: *E. V. KOZLOVA, B. D. CHINTHIRLA, J. D. TRAN, A. E. BISHAY, G. R. LAMPEL, E. MONARREZ, M. C. CURRAS-COLLAZO;
Univ. of California Riverside, Riverside, CA

Abstract: Gulf War Illness (GWI) is a chronic multi-symptom condition that still affects a third of veterans who served in the 1991 Persian Gulf War (GW). Latently-emerging and persistent

symptoms fall into 5 general domains: neurological/cognition/mood (memory, concentration, anxiety, depression), muscle/joint pain, respiratory, gastrointestinal disturbances and especially chronic fatigue. GWI remains untreated due to lack of potential therapeutics evaluated in preclinical animal studies. The poorly understood etiology of GWI is suggested to be attributed to continuous exposure to GW agents administered to protect military personnel: 1) acetylcholinesterase inhibitor pyridostigmine bromide (PB) taken orally as prophylaxis against nerve agents, 2) topical insecticide permethrin (PER), and 3) topical insect repellent diethyltoluamide (DEET). Although GW agents were administered at safe doses, their chronic and combined use, in addition to stress, a critical component of GW deployment, may produce and/or intensify the pathophysiology of GWI for reasons not fully understood. Additionally, GW veterans report symptoms associated with delayed-onset Type II diabetes mellitus, which may be associated with chronic fatigue. To further investigate the behavioral and metabolic manifestations of GWI pathophysiology, we studied the effects of acute (AE) and chronic (CE) GW toxicant exposure in adult C57Bl6/N males utilizing a repeated measures design. The AE model consisted of 1wk exposure to PB (2 mg/kg/d; ip), PER (200 mg/kg/d in 70% ETOH; top), DEET (40 mg/kg/d in ETOH; top) and 5 min restraint stress/d (n=4-7; PND 118-252). The CE model consisted of 28 days of exposure to PB (1.3 mg/kg/d; po), PER (0.13 mg/kg/d; top) in 70% ETOH, DEET (40 mg/kg/d in ETOH; top) and 5min/d stress 5d/wk (n=6-8; PND 62-122). When compared to pre-treatment, mice exposed to AE or CE paradigms showed depressive-like behavior on forced swim and tail suspension tests. AE produced sensorimotor deficits as measured by an increased number of falls/segments crossed on SUOK beam test, and CE produced increased segments crossed relative to baseline. Increased anxiety in CE was observed as decreased risk assessment on SUOK and in AE as less percent time spent in open arm of an elevated plus maze (not due to decreased mobility). GW agent exposure had no effect on three-chambered sociability test. Both CE and AE groups displayed insulin insensitivity relative to baseline. These results show that GW agents can produce insulin insensitivity along with motor disturbance, anxiety and depressive-like behavior. Our findings will help inform studies that aim to elucidate the etiology and pathophysiology of GWI.

Disclosures: E.V. Kozlova: None. **B.D. Chinthirla:** None. **J.D. Tran:** None. **A.E. Bishay:** None. **G.R. Lampel:** None. **E. Monarrez:** None. **M.C. Curras-Collazo:** None.

Poster

766. Gulf War Illness: Pathological Causes and Consequences

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 766.06/O29

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: CDMRP Grant GW150188

Title: Transcriptome analysis reveals a persistent, dormant neuroinflammatory phenotype revealed by inflammatory challenge in a mouse model of Gulf War illness

Authors: K. A. KELLY[1], L. T. MICHALOVICZ[1], D. B. MILLER[2], *J. P. O'CALLAGHAN[3]; [2]Ctr. Dis. Control & Prevention, [1]CDC-NIOSH, Morgantown, WV; [3]Centers For Dis. Control and Prevention, Morgantown, WV

Abstract: Gulf War Illness (GWI) is a multi-symptom, neuroimmune-based disorder that presents with features similar to sickness behavior. Unfortunately, current treatments for GWI tend to focus on managing symptoms as opposed to addressing the underlying cause of the illness. Using a preclinical mouse model, we have found that GWI is associated with an exacerbated neuroinflammatory response to immune challenge, like lipopolysaccharide (LPS) exposure, and the activation of microglia. In this model, mice are exposed to the stress hormone corticosterone (CORT; 200 mg/L) in the drinking water for 7 days followed by a single injection of diisopropyl fluorophosphate (DFP; 4 mg/kg, i.p.) to model the "in theater" conditions of high physiological stress and potential nerve agent exposure. This is then followed by periodic administration of CORT for 7 days every other week to a total of 5 weeks with a systemic LPS challenge (0.5 mg/kg, s.c.) on the final day. Mice were sacrificed 6 hours after LPS challenge and brain cytokine mRNA expression was evaluated by qPCR and RNAseq. RNAseq analyses revealed 2430 statistically significant genes ±1.5 fold change over saline controls. A PCA plot of these findings illustrate good separation of groups confirming a difference between the GWI (CORT+DFP+LPS) and CORT+LPS groups. Of these genes, 114 were unique to the GWI group. Analysis of the gene list with DAVID revealed inflammatory related GO terms and KEGG pathways. Ingenuity Pathway Analysis of the significant genes reveals many inflammatory canonical pathways across the groups to be depicted in a heat map. Together these findings provide further evidence for the neuroimmune basis for Gulf War Illness. Disclaimer: *The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention.*

Disclosures: K.A. Kelly: None. **L.T. Michalovicz:** None. **D.B. Miller:** None. **J.P. O'Callaghan:** None.

Poster

766. Gulf War Illness: Pathological Causes and Consequences

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 766.07/O30

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: NIH-SNRP grant 5U54NS083924-03
NIH-RISE-R25GM110513

DoED-P031S160068

Title: An alpha7 nicotinic acetylcholine receptor modulator ameliorates behavioral performance in Gulf War illness model

Authors: J. REYES-GONZALEZ[1], D. PEREZ[2], P. A. FERCHMIN[2], *N. SABEVA[1];
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Abstract: Gulf War Illness (GWI) is a chronic multiorgan condition, which 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. PB, DEET, and Sarin are acetylcholinesterase inhibitors (AChE-I) possibly contributing to the adverse cholinergic activity in GWI veterans. DEET is a weak AChE-I but has other neurotoxic properties. Here, we report the development of a 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 was conducted every 30 days for 4 months. We assessed the learning abilities using the Barnes maze where control and GWI mice show the same ability to learn to locate the escape box during the 4 days training period. Exploratory nose-poke pattern and time in escape quadrant (EQ) was evaluated after removal of the rewarding escape box. GWI mice showed steady nose-poke exploration and time spent at the escape quadrant (EQ) during testing. Initially, control mice showed intense exploration followed by a 50 % decline at Day 75 and 105 showing that, contrary to GWI mice, controls retain the capability to extinguish obsolete spatial information. To test whether 4R restores extinction in GWI mice 4R was applied 3 times a week for 6 weeks (6mg/kg i.p.) 150 days after exposure to GW agents. The four groups (Control: -vehicle and -4R, and GWI-vehicle and -4R) demonstrated a similar ability to learn the new location of the escape box. However, 24 hrs later when the rewarding escape box was removed the GWI-4R animals had a similar spatial preference as vehicle and 4R controls assessed by time spent in EQ. Inversely, GWI-vehicle group spent 40% less time near the rewarding hole suggesting that 4R can reverse the effect of GWI and restore the memory function. The present work will contribute to the understanding of GWI and will test a promising candidate drug for the treatment for GWI veterans and future victims of similar civilian or military adverse events.

Disclosures: J. Reyes-Gonzalez: None. **D. Perez:** None. **P.A. Ferchmin:** None. **N. Sabeva:** None.

Poster

766. Gulf War Illness: Pathological Causes and Consequences

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 766.08/O31

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: GWIRP award GW170103 - W81XWH-18-1-0454

Title: Brain-derived neurotrophic factor (BDNF) in Gulf War illness: A comparison with chronic fatigue syndrome and post traumatic stress disorder

Authors: *M. V. BRAHMAJOTHI[1], M. B. ABOU-DONIA[2], S. GRAMBOW[3], D. T. PROVENZALE[5], B. SCOTT[4], N. KLIMAS[6], K. A. SIULLIVAN[7];
[1]Pharmacol. & Cancer Biol., Duke Univ., Durham, NC; [2]Pharmacol. & Cancer Biol., [3]Biostatistics, [4]Duke Univ. Movement Disorders Clin., Duke Univ. Med. Ctr., Durham, NC; [5]Gastroenterology & Epidemiology, Duke Univ. Med. Ctr. & VA, Durham, NC; [6]Dept. of Clin. Immunol. & Inst. for Neuro-Immune Med., Nova Southeastern Univ., Ft. Lauderdale, FL; [7]Sch. of Publ. Hlth., Boston Univ., Boston, MA

Abstract: Medically unexplained illness found in nearly 1/3 of the Gulf War Veterans (GWV) out of approximately 700,000 US troops deployed to the Persian Gulf theater for Operation Desert Storm still presents a major unmet progressive clinical problem, 27 years after the war. The initial concern was exposure to the plumes from the burning oil well, subsequently, the area of concern became the increased rates of multisymptom illnesses. The VA, DoD, EPA, DHHS, along with the task force of the Defense Science Board, reported the possible cause and effect of the differential levels of exposures to chemicals, environmental stressors and pollutants, vaccines, antidotes and endemic biologics. Repetitive exposures to various chemicals, especially organophosphate-related compounds, may inhibit AChE irreversibly, even at non-lethal doses. Prophylactic treatments with reversible AChE inhibitors such as anti-nerve gas pills, and various vaccines can prime the immune system. Paradoxically, it can trigger the CNS-glymphatic system to mount a neuroinflammatory response in some individuals, resulting in subclinical symptoms. There are complex networks of trophic factors that are secreted to maintain the neurons both in the central and peripheral nervous system. Many studies have reported decreased levels in various neuromuscular disorders and our objective in this study is to focus on the plasma levels of Brain-Derived Neurotrophic factor (BDNF). Two monomers of BDNF selectively bind to Trk B, a tyrosine kinase receptor. In coordination with LNGFR/P75NTR, it dimerizes and mediates its action by adding phosphate molecules to regulate cell signaling, providing various supports such as neuronal cell differentiation, growth, migration, survival, dendritic arborization, synaptogenesis, and synaptic plasticity both in developing and mature neurons. Signaling through receptor-specific tyrosine kinases are essential for performing specific functions, as they

regulate axonal growth and regeneration of injured neurons and are directly associated with the formation and modulation of short and long-term memories. We assessed the plasma levels of BDNF in 25 symptomatic GWV who were diagnosed and assessed by the Kansas Scale and CDC case definition. Plasma levels of BDNF in 25 veterans with GWI were compared to the plasma levels of BDNF in 25 non-symptomatic GWV and 25 healthy civilian controls. As our reference-disease control, we compared 25 veterans with Chronic Fatigue Syndrome (CFS) and 25 veterans with PTSD. The overall levels of plasma BDNF were significantly lower in symptomatic GWV, than in non-symptomatic GWV and healthy controls ($p<0.001$), as well as CFS and PTSD ($p<0.02$).

Disclosures: M.V. Brahmajothi: None. **M.B. Abou-Donia:** None. **S. Grambow:** None. **D.T. Provenzale:** None. **B. Scott:** None. **N. Klimas:** None. **K.A. Siullivan:** None.

Poster

766. Gulf War Illness: Pathological Causes and Consequences

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 766.09/O32

Topic: F.04. Stress and the Brain

Title: Military related exposures and the microbiome the United States-Veteran Microbiome Project (US-VMP)

Authors: *C. E. STAMPER[1,2], K. A. STEARNS-YODER[1,2,5,3], A. J. HOISINGTON[6,1,5], J. D. HEINZE[7,1], T. T. POSTOLACHE[8,1,5], D. A. HADIDI[1], C. A. HOFFMIRE[1], M. A. STANISLAWSKI[4,1], C. A. LOWRY[7,1,5,2,9], L. A. BRENNER[1,5,2,3];
[1]Rocky Mountain Mental Illness Res. Educ. and Clin. Ctr. (MIRECC), Rocky Mountain Regional VA Med. Ctr., Aurora, CO; [2]Dept. of Physical Med. and Rehabil., Univ. of Colorado Denver, Denver, CO; [3]Marcus Brain Inst. for Brain Hlth., Univ. of Colorado Denver, Aurora, CO; [4]Dept. of Epidemiology, Univ. of Colorado Denver, Denver, CO; [5]Rocky Mountain Regional VA Med. Ctr., Military and Veteran Microbiome Consortium for Res. and Educ. (MVM-CoRE), Aurora, CO; [6]Dept. of Systems Engin., Air Force Inst. of Technol., Wright-Patterson Air Force Base, OH; [7]Dept. of Integrative Physiol. and Ctr. for Neurosci., Univ. of Colorado Boulder, Boulder, CO; [8]Dept Psychiatry, Univ. of Maryland Sch. of Med., Baltimore, MD; [9]Ctr. for Microbial Exploration, Boulder, CO

Abstract: The human microbiota is a term that is used to describe the microorganisms (archaea, bacteria, eukaryotes, and viruses) associated with the human body. The past decade has been characterized by a number of landmark surveys of the human microbiome such as the Human Microbiome Project and the American Gut Project. The main objectives of those surveys were to generate a point of reference and to establish large databases of mainly healthy individuals. Nevertheless, in-depth analyses of the human microbiome in association with validated measures

of human general, physical, and mental health are lacking, especially the latter. The main goal of the US Veteran Microbiome project is to serially assess the skin, oral, and fecal microbiomes in association with validated measures of general health, physical health, insomnia, and mental health in a cohort of U.S. Veterans at 6 month intervals. We studied a group of individuals with unique environmental exposures and health outcomes to determine if there were identifiable microbial signatures associated with specific health measures. To date we have recruited over 400 US Veterans who have provided microbiome samples from three anatomical sites (skin, oral, and fecal). We have characterized the microbiome of all three sample types (skin, oral, and fecal) as they relate to metadata collected in three main categories: general and physical health, insomnia, and mental health. Based on preliminary analysis, measures of general and physical health displayed increased alpha diversity of the fecal microbiome in association with "healthy" states. We found that severe insomnia symptoms and multiple measures of mental health were associated with microbial features from the various sampling sites. Further analyses are underway to understand the biological basis of the associations between the skin, oral, and fecal microbiomes and measures of physical health, insomnia, and mental health, and if microbiome-based interventions can be developed in order to improve these health outcomes.

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Poster

766. Gulf War Illness: Pathological Causes and Consequences

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 766.10/O33

Topic: C.10. Brain Injury and Trauma

Support: CDMRP GW170093
USAMRMC W81XWH1510679
NIH NS085131
CDMRP GW170055

Title: Post-exertional brain activity associated with verbal working memory differentiates Gulf War illness from chronic fatigue syndrome

Authors: *S. D. WASHINGTON[1], R. U. RAYHAN[2], R. GARNER[1], D. PROVENZANO[1], K. ZAJUR[1], J. W. VANMETER[1], J. N. BARANIUK[1];
[1]Georgetown Univ. Med. Ctr., Washington, DC; [2]Howard Univ., Washington, DC

Abstract: Gulf War Illness (GWI) affects a third of veterans of the 1990-1991 Persian Gulf War. Post-exertional malaise with cognitive dysfunction, pain, and fatigue following physical and/or

mental effort typify GWI. These symptoms coincide with those of Chronic Fatigue Syndrome (CFS), fueling debate over whether GWI is a subtype of CFS. However, CFS mostly affects 40 to 50-year-old women, but military demographics dictate that GWI affects mostly men. Here, we modeled post-exertional malaise by assessing changes in functional magnetic resonance imaging at 3T during an N-Back working memory task performed prior to a submaximal bicycle stress test and 24 hr later following a second identical stress test. The subjects in our groups were categorized as healthy controls (HC, N=23), Gulf War Illness (GWI, N=80), and Chronic Fatigue Syndrome (CFS, N=38). After performing a 2-Back>0-Back per subject contrast, we performed a two-sample t-test in SPM12 with age and sex regressed out. Prior to exercise, GWI had significantly greater activation in the right angular gyrus relative to HC and CFS. After exercise, GWI had significantly (cluster-level: $p<0.05$, family-wise error correction) less activation in the cerebellar vermis and right intraparietal sulcus than did HC and CFS. Further, CFS had significantly greater activation in the left Rolandic operculum than HC or GWI, and CFS also had significantly greater activation than GWI in both the periaqueductal gray and right insula. HC had no significant changes in activation before or after exercise. In short, peri-insular neural activity differentiates CFS from GWI and controls whereas medial cerebellar activity differentiates GWI from CFS and controls. These findings suggest qualitatively different neural substrates of post-exertional malaise associated with cognition in GWI and CFS.

Disclosures: S.D. Washington: None. **R.U. Rayhan:** None. **R. Garner:** None. **D. Provenzano:** None. **K. Zajur:** None. **J.W. VanMeter:** None. **J.N. Baraniuk:** None.

Poster

766. Gulf War Illness: Pathological Causes and Consequences

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 766.11/O34

Topic: C.10. Brain Injury and Trauma

Support: GW170093 W81XWH-18-1-0660
GW170055
GW160118 W81XWH-17-1-0457
R01CA197964
W81XWH-15-1-0679
RO1 NS085131

Title: Exercise differentially alters ascending arousal network activity associated with verbal working memory in Gulf War illness and chronic fatigue syndrome

Authors: *H. S. PEPERMINTWALA[1], S. D. WASHINGTON[2], F. A. MARTINEZ ADDIEGO[1], R. U. RAYHAN[3], J. N. BARANIUK[2];

[1]Georgetown Univ., Washington, DC; [2]Georgetown Univ. Med. Ctr., Washington, DC; [3]Dept. of Physiol., Howard Univ. Col. of Med., Washington, DC

Abstract: Nearly 30% of the veterans who served in Operation Desert Storm (1990-1991) suffer from Gulf War Illness (GWI), a symptom cluster that includes cognitive impairment, autonomic dysfunction, chronic pain, and debilitating fatigue. Several studies detailing the neurological symptoms of GWI implicate the brainstem, where nuclei associated with arousal and autonomic function largely reside. Few of these studies provide functional neuroimaging or other physiological evidence for brainstem dysfunction in the GWI population. Here, we compared the blood oxygenation level dependent (BOLD) contrast elicited by a 2-Back working memory task (2-Back>0-Back) in veterans with GWI (n = 79) relative to that of sedentary, healthy controls (HC, n=31) and people with chronic fatigue syndrome (CFS, n=36). As GWI and CFS are both characterized by post-exertional malaise, all three groups completed fMRI scans before and after two exercise stress tests. Analyses were restricted to predetermined brainstem ROIs from the Harvard Ascending Arousal Atlas, including the dorsal raphe (DR), locus coeruleus (LC), median raphe (MR), medullary reticular formation (MRF), parabrachial complex (PBC), pedunculopontine nucleus (PPN), periaqueductal gray (PAG), pontine oralis (PO), ventral tegmental area (VTA). Medial structures (DR, MR, PAG, VTA) were maintained as single ROIs whereas lateral structures were divided into left and right hemispheric structures. One-way Analyses of Covariance (ANCOVAs) and paired t-tests were used to compare the activation in the a priori regions between HC, CFS, and GWI. Bonferroni corrections were used to adjust for multiple comparisons and significant regions were reported for regions where $p < 0.05$. Pre-exercise CFS had significantly decreased BOLD activity bilaterally in the PPN compared to HC, while all other brainstem regions were not significantly different. Post-exercise, GWI had significantly lower BOLD activity compared to CFS in most regions (DR, MR, PAG, VTA, R_LC, L_MRF, R_MRF, R_PBC, R_PPN), while HC was non-significant. Delta values were calculated, and it was found that due to the effect of exercise, CFS BOLD activity increased while GWI BOLD activity decreased in the majority of regions evaluated (DR, MR, PAG, VTA, R_LC, R_PBC, L_PO, R_PO, L_PPN, and R_PPN). These results are the first to demonstrate functional brainstem anomalies that corroborate the structural brainstem abnormalities commonly reported in GWI.

Disclosures: H.S. Pepermintwala: None. **S.D. Washington:** None. **F.A. Martinez Addiego:** None. **R.U. Rayhan:** None. **J.N. Baraniuk:** None.

Poster

766. Gulf War Illness: Pathological Causes and Consequences

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 766.12/O35

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

Support: Army Medical Res Acquisition Activity (GW150181)

Title: A small-molecule that can enhance tripartite synapses is capable of improving mood and cognitive deficits in a mouse model of Gulf War illness

Authors: *X. WANG[1], Z. XU[1], F. ZHAO[1], K. LIN[1], T. XIAO[1], N. KUNG[1], J. FOSTER[1], C. C. ASKWITH[1], K. HODGETTS[2], C.-L. G. LIN[1];
[1]Neurosci., Ohio State Univ., Columbus, OH; [2]Lab. of Drug Discovery in Neurodegeneration, Brigham and Women's Hospital/Harvard Med. Sch., Boston, MA

Abstract: Mood and memory deficits are ubiquitous among the various symptoms of Gulf War illness (GWI). It is widely believed that these clinical symptoms are linked to a combination of exposures encountered by the service personnel. Literature has indicated that chronic exposure to GWI-related chemicals and stress results in glutamate dyshomeostasis in the hippocampus, which may contribute to memory and mood deficits. The purpose of this study was to investigate if enhanced structural and functional plasticity of the tripartite synapse by a small molecule LDN/OSU-215111 can improve mood and cognitive deficits in a mouse model of GWI. Three to four months old C57BL/6J mice were exposed to GWI agents, including pyridostigmine bromide, permethrin, and DEET, and unpredictable stress daily for six weeks. At three months post-exposure, mice developed anxiety- and depression-like behaviors and cognitive difficulties. In a study designed to mimic a preventive therapy, mice received compound treatment daily during six-week of GWI conditions and the treatment continued until mice were euthanized. We found that compound treatment almost completely prevented mood abnormalities and cognitive decline. Upon completion of behavioral assessment, a subset of mice was euthanized for electrophysiological studies to assess the integrity of the hippocampal synaptic circuit by measuring long-term potentiation (LTP). Results showed that GWI mice exhibited a substantial reduction of LTP and compound treatment completely restored LTP. In addition, we measured hippocampal extracellular glutamate levels by microdialysis. We found that GWI mice exhibited a significant increase of glutamate levels and compound treatment completely normalized extracellular glutamate levels. Furthermore, in a study designed to mimic treatment after symptoms arise, GWI mice were treated with the compound at five months post-exposure when the deficits have developed. After one month of treatment, behavioral tests were conducted. We found that the compound was still able to improve anxiety- and depression-like behaviors and also cognitive functions. These results indicate that LDN/OSU-215111 has therapeutic potential for GWI. We are currently investigating the underlying molecular mechanisms of compound effects. The results will be presented.

Disclosures: X. Wang: None. **Z. Xu:** None. **F. Zhao:** None. **K. Lin:** None. **T. Xiao:** None. **N. Kung:** None. **J. Foster:** None. **C.C. Askwith:** None. **K. Hodgetts:** None. **C.G. Lin:** None.

Poster

766. Gulf War Illness: Pathological Causes and Consequences

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 766.13/O36

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: CDMRP Award W81XWH-16-1-0480 to AKS

Title: Curcumin nanoparticle therapy modulates neuroinflammation, neurogenesis and mitochondrial activity and improves brain function in a model of Gulf War illness

Authors: *S. ATTALURI[1], M. ARORA[2], B. SHUAI[1], M. KODALI[1], L. MELISSARI[1], L. N. MADHU[1], A. BATES[1], X. RAO[1], E. MITRA[1], R. MAJETI[2], A. K. SHETTY[1];
[1]Inst. For Regen Med. Texas A&M Univ. Coll Med., College Station, TX; [2]Col. of Pharmacy, Texas A&M Hlth. Sci. Ctr., College Station, TX

Abstract: Gulf War Illness (GWI) is a multi-symptom illness, which affects approximately 30% of veterans who served in the first Gulf War. Epidemiological studies have suggested that exposure to a combination of chemicals that inhibit acetylcholinesterase activity, and stress, during the war caused GWI. Indeed, concurrent exposure to low doses of chemicals widely used in GW and mild stress for 28 days in rats leads to symptoms seen in veterans with GWI. The central nervous system related symptoms in GWI include cognitive and mood dysfunction in association with chronic neuroinflammation and decreased neurogenesis in the hippocampus. We investigated the efficacy of curcumin encapsulated biodegradable nanosystems (nCUR, a compound having robust antioxidant and anti-inflammatory properties) for improving brain function and modulating neuropathological changes in animals exposed to GWI-related chemicals and stress (GWI rats). We first exposed young rats to low doses of GWI-related chemicals such as the nerve gas prophylactic drug pyridostigmine bromide (PB), mosquito repellant DEET, insecticide permethrin (PM) for 28 days. Two months later, GWI rats received nCUR at 10, 20 or 40 mg/Kg (3 days/week) or empty nanoparticles (vehicle) for eight weeks. A group of age-matched naïve control rats was included as controls. A battery of behavioral tests performed in the last four weeks of treatment revealed cognitive and memory dysfunction, pattern separation deficit, and anhedonia in GWI rats that received empty nanoparticles. Moreover, the hippocampus of these animals displayed activated microglia, hypertrophied astrocytes, decreased neurogenesis and increased expression of genes that encode proteins relevant to mitochondrial electron transport with elevated levels of mitochondrial complex proteins I, II and IV. In contrast, GWI rats that received different doses of nCUR showed better cognitive, memory and pattern separation function and no anhedonia. Besides, the hippocampus of these animals displayed reduced density of activated microglia and hypertrophied astrocytes, increased neurogenesis, and normalized expression of mitochondrial genes and complex proteins

II and IV. Interestingly, a maximal increase in neurogenesis was observed in GWI rats that received the lowest dose of nCUR (10mg/Kg). Thus, eight weeks of low-dose nCUR treatment is sufficient for improving brain function in a model of GWI. Reduced neuroinflammation, enhanced neurogenesis, and normalized mitochondrial activity likely underlie the improved brain function mediated by nCUR treatment.

Disclosures: S. Attaluri: None. **M. Arora:** None. **B. Shuai:** None. **M. Kodali:** None. **L. Melissari:** None. **L.N. Madhu:** None. **A. Bates:** None. **X. Rao:** None. **E. Mitra:** None. **R. Majeti:** None. **A.K. Shetty:** None.

Poster

766. Gulf War Illness: Pathological Causes and Consequences

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 766.14/O37

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: Department of Defense (W81XWH-17-1-0447 to A.K.S.)

Title: Efficacy of melatonin for improving cognitive and mood function in a model of Gulf War illness

Authors: *L. N. MADHU, S. ATTALURI, B. SHUAI, M. KODALI, L. MELISSARI, X. RAO, A. K. SHETTY;
Inst. For Regen Med, Texas A&M Univ. Coll Med., College Station, TX

Abstract: Gulf War Illness (GWI) affects 30-40% of 700,000 military personnel who served in the first Gulf War (GW). GWI is typified by a lingering cognitive, memory and mood impairments. Animal model studies employing exposures to GWI-related chemicals (GWIR-Cs) and moderate stress have linked these symptoms to persistent neuroinflammation, increased oxidative stress, mitochondrial dysfunction, and decreased hippocampal neurogenesis. These observations have prompted testing of various antioxidant and antiinflammatory compounds for their effectiveness to improve brain function. We investigated the efficacy of different doses of melatonin for improving cognitive and mood function in a rat model of chronic GWI. We also examined whether brain impairments and the associated pathological changes, continue into the middle age in GWI rats. Male SD rats were exposed daily to GW-related chemicals, pyridostigmine bromide, (PB, 2 mg/kg), DEET (60 mg/kg), and permethrin (PM, 0.2 mg/kg), and 15-minutes of restraint stress for 28 days. Six months later, the animals were treated with different doses (5, 10, 20, 40 and 80mg/Kg) of melatonin for eight weeks (5 days/week). Following the treatment regimen, animals were tested for cognitive and mood function through a battery of behavioral tests. The tasks comprised an object location test (OLT), a novel object recognition test (NORT), a pattern separation test (PST), an object in place test (OIPT), and a

sucrose preference test (SPT). GWI rats receiving vehicle displayed impairments in all tests, implying that cognitive and mood impairments seen at earlier time-points persist for prolonged periods. While most doses of melatonin were effective for improving memory function in NORT and OIPT, improvements in more complex behavioral tests in GWI rats required a higher dose of melatonin. Indeed, GWI animals receiving 80mg/Kg melatonin displayed improved cognitive ability for discerning minor changes in the environment as well as better pattern separation function. Doses of melatonin at 20-80 mg/Kg were also effective for reversing anhedonia. Immunostaining analyses of brain tissues revealed the persistence of activated microglia, reactive astrocytes and reduced hippocampal neurogenesis in middle-aged GWI rats. Higher doses of melatonin treatment reduced the percentage of activated microglia in GWI rats. Measurements of the effects of melatonin for modulating the population of reactive astrocytes, and increasing hippocampal neurogenesis, are currently in progress. Thus, melatonin therapy has promise for improving cognitive and mood function in GWI at relatively higher doses.

Disclosures: L.N. Madhu: None. **S. Attaluri:** None. **B. Shuai:** None. **M. Kodali:** None. **L. Melissari:** None. **X. Rao:** None. **A.K. Shetty:** None.

Poster

766. Gulf War Illness: Pathological Causes and Consequences

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 766.15/O38

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: American Legion Brain Sciences Chair

Title: Anthrax in Gulf War illness (GWI): Evidence from neuroblastoma cultures for the presence of anthrax vaccine antigen in the serum of veterans suffering from GWI

Authors: *P.-E. C. TSILIBARY[1], E. P. SOUTO[1], L. M. JAMES[1,2], B. E. ENGDAHL[1,2], M. G. KRATZKE[1], A. P. GEORGOPOULOS[1,2];
[1]Neurosci., Univ. of Minnesota, Minneapolis, MN; [2]Brain Sci., Minneapolis VA Hlth. Care Syst., Minneapolis, MN

Abstract: After the Persian Gulf War of 1990-91, about one third (more than 200,000) of veterans complained of a variety of chronic physical and neurocognitive symptoms, presently identified as Gulf War Illness (GWI) and traditionally attributed to possible exposures to toxic warfare chemicals (e.g. sarin). In 2016, we identified genetic vulnerability factors in GWI, when we discovered that veterans with GWI lacked one or more of 6 Human Leukocyte Antigen (HLA) class 2 alleles [1] the presence of which was associated with reduced GWI symptom severity in a dose-response fashion. Since these alleles are essential for mounting antibodies to foreign antigens, we hypothesized that veterans lacking those alleles could not make antibodies

to eliminate harmful antigens which would persist and cause GWI. Such antigens could come from exposure to biological and chemical substances. A unique exposure of GW veterans was to anthrax antigen(s) contained in the vaccine [2] they received. Here we tested the hypothesis that persistent, harmful anthrax antigens are involved in GWI. Using specific, recombinant polyclonal antibodies against the PA63 and PA83 anthrax antigens contained in the anthrax vaccine, we obtained evidence for the presence of these antigens in the serum of 15 veterans suffering from GWI (and lacking all 6 HLA protective alleles), causing detrimental effects on brain cultures [3] which were eliminated when anti-anthrax antibodies were added to the serum. These findings demonstrate a direct link between anthrax vaccine and GWI.

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Disclosures: P.C. Tsilibary: None. **E.P. Souto:** None. **L.M. James:** None. **B.E. Engdahl:** None. **M.G. Kratzke:** None. **A.P. Georgopoulos:** None.

Poster

766. Gulf War Illness: Pathological Causes and Consequences

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 766.16/O39

Topic: H.01. Animal Cognition and Behavior

Support: DOD Grant W81XWH-16-1-0586

Title: An immunomodulatory glycan conjugate, lacto-N-fucopentaose III (LNFPIII), restores deficits in spatial working memory and hippocampal long-term potentiation in a mouse model of Gulf War illness

Authors: *K. A. BROWN[1,2], J. M. CARPENTER[1,3], D. LUDWIG[1,2], C. J. PRESTON[1,2], R. L. DOCKMAN[1], D. A. HARN[4], N. M. FILIPOV[1,2], J. J. WAGNER[1,2];
[1]Dept. of Physiol. and Pharmacol., [2]Interdisciplinary Toxicology Program, [3]Neurosci. PhD Program, Biomed. and Hlth. Sci. Inst., [4]Dept. of Infectious Dis., Univ. of Georgia, Athens, GA

Abstract: Gulf War Illness (GWI) is a chronic multisymptom illness that affects veterans of the Persian Gulf War and presents with chronic musculoskeletal pain, fatigue, and cognitive dysfunction. While the exact etiology of GWI is unknown, the onset of GWI is associated with exposure to neurotoxic insecticides, organophosphate (OP) nerve agents, and OP prophylactics. There are currently no pharmacotherapies available for treatment of GWI. The present study

investigated the efficacy of a novel immunomodulatory agent, lacto-N-fucopentaose III (LNFPIII), in treating the persisting neurophysiological and cognitive deficits observed in a GWI mouse model. Male C57BL/6J mice were treated with 2 mg/kg pyridostigmine bromide (s.c.) and 30 mg/kg N,N-diethyl-meta-toluamide (s.c.) once per day for 14 days. On days 8 - 14 mice also received corticosterone in their drinking water (200 mg/L in 1.2% EtOH) to emulate combat-related chronic stress. On day 15, animals received a single injection of a common sarin surrogate, diisopropylfluorophosphate (3.75 mg/kg, i.p.). Control mice received saline vehicle instead of GWI chemicals. Subsets of GWI and saline-treated animals received twice-weekly LNFPIII (GWI-LNFPIII, saline-LNFPIII) or vehicle (GWI-vehicle, saline-vehicle) treatment beginning 7 months after exposure to GWI chemicals. Nine months after GWI chemical exposure, an 8-arm radial arm maze (RAM) foraging task revealed impaired performance in GWI-vehicle animals, an effect that was partially reversed in GWI-LNFPIII animals. Dorsal hippocampus (dH) and ventral hippocampus (vH) slices obtained from GWI-vehicle animals exhibited reduced LTP magnitude 10 months after GWI treatment. GWI-LNFPIII animals displayed dH and vH LTP magnitude that was similar to saline-treated mice. Moreover, a main effect of GWI treatment on LTP was observed in the dH but not the vH, suggesting sector-specific effects of GWI chemical exposure. Basal synaptic transmission was decreased in the dH and the vH of GWI-vehicle animals compared to GWI-LNFPIII, saline-LNFPIII, and saline-vehicle treated mice. Impaired performance in the RAM foraging task suggests deficits in short-term spatial working memory due to GWI chemical exposure. Reduced sector-specific LTP, as well as decreased dH and vH basal synaptic transmission, provides mechanistic insight into such working memory impairments. Importantly, LNFPIII treatment beginning 7 months after GWI chemical exposure partially restored working memory performance and fully restored dH and vH LTP magnitude, suggesting that LNFPIII may be an efficacious treatment for cognitive dysfunction observed in GWI patients.

Disclosures: **K.A. Brown:** None. **J.M. Carpenter:** None. **D. Ludwig:** None. **C.J. Preston:** None. **R.L. Dockman:** None. **D.A. Harn:** None. **N.M. Filipov:** None. **J.J. Wagner:** None.

Poster

766. Gulf War Illness: Pathological Causes and Consequences

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 766.17/O40

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: Department of Defense W81XWH-15-1-0520
American Legion Brain Sciences Chair
U.S. Department of Veterans Affairs

Title: Gulf War illness and inflammation: Association of symptom severity with c-reactive protein

Authors: *R. JOHNSON[1], L. JAMES[2], B. E. ENGDAHL[2], A. P. GEORGOPOULOS[3]; [1]Cognitive Sci., Univ. of Minnesota, Minneapolis, MN; [2]Brain Sci. Ctr., Univ. of Minnesota/Minneapolis VAHCS, Minneapolis, MN; [3]Neurosci, Univ. Minnesota, Minneapolis, MN

Abstract: Gulf War Illness (GWI) is a chronic multi-system condition that has affected one-third of U.S. veterans who served in the Persian Gulf. Although GWI etiology remains unclear, mounting evidence points to immune system involvement and inflammation, in particular, as underlying the host of symptoms associated with the condition. Here we investigated the association between GWI symptoms and C-reactive protein (CRP), a marker of inflammation, in 76 veterans with GWI. Results indicated a highly significant positive association between CRP and mean GWI symptom severity. At the symptom domain level, CRP was significantly and positively associated with Pain, Neurocognitive/Mood, Fatigue, and Respiratory symptom severity but not with Skin or Gastrointestinal symptom severity. These results support the premise that GWI symptoms, particularly those implicating brain involvement, are a result of neuroinflammation. The cause for inflammation is not known. We have hypothesized that at the root of GWI are harmful persistent antigens stemming from environmental exposures associated with service during the Gulf War that could not be successfully eliminated due to lack of specific immunity. Work is underway in our laboratory to identify and eliminate persistent antigens in veterans with GWI which we anticipate will result in reduced inflammation and reduced GWI symptoms.

Disclosures: R. Johnson: None. **L. James:** None. **B.E. Engdahl:** None. **A.P. Georgopoulos:** None.

Poster

766. Gulf War Illness: Pathological Causes and Consequences

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 766.18/O41

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: DoD W81XWH-17-1-0677

Title: Gulf war illness (GWI)-protective HLA DRB1*13:02 allele protects against harmful anthrax vaccine antigen

Authors: *S. CHARONIS[1,2], A. P. GEORGOPOULOS[1,2];
[1]Neurosci., Univ. of Minnesota, Minneapolis, MN; [2]Brain Sci. Ctr., Dept. of Veterans Affairs Hlth. Care Syst., Minneapolis, MN

Abstract: GWI has afflicted many veterans of the 1990-91 Gulf War, affecting the brain, among other organs. Brain network abnormalities [1] resemble those of immune disorders [2], hence GWI's designation as a "neuroimmune" disorder [2]. A deficit in specific, adaptive immunity in GWI was discovered in 2016 [3], namely that GWI veterans lack one or more of 6 HLA class II protective alleles [3]. Since these alleles are necessary for producing antibodies against foreign pathogens/antigens, we hypothesized that such harmful "persistent antigens" are at the root of GWI, namely antigens to which GW veterans were exposed but which could not be eliminated due to lack of HLA protection in those veterans [4]. A unique exposure of GW veterans was to anthrax Protective Antigen (aPA) contained in the vaccine they received (Bio Thrax). We show in a different presentation at this meeting [5] that aPA is indeed harmful to neural cultures, which suggests its possible involvement in causing GWI.
Here we show that aPA is also an excellent target of the HLA class II DRB1*13:02 allele which is one of the 6 GWI protective alleles [3] and which protects against GWI-related brain atrophy [6]. We used the Immune Epitope Database (www.iedb.org) to identify predicted epitopes of class II HLA proteins for aPA and ranked the matched epitopes according to the number of experimental assays they were in. We thus obtained the ranked binding affinities of aPA (UniProtKB ID P13423) of the 6 GWI-protective HLA class II alleles (DRB1*01:01, DRB1*08:11, DRB1*13:02, DQB1*02:02, DPB1*01:01 and DPB1*06:01). Small percentile ranks indicate higher binding affinity and vice versa.
We found that DRB1*13:02 had the highest binding affinity to aPA (minimum percentile rank, MPR = 0.34), closely followed by DRB1*01:01 (MPR = 0.36). The binding affinities of the remaining 4 alleles were 17-54 times lower than that of DRB1*13:02. These results support the hypothesis that the protective role of DRB1*13:02 [3,4] in GWI could be partially mediated through elimination of harmful aPA and are in keeping with the idea that anthrax vaccine containing aPA is involved in developing GWI. (Supported by the Department of Defense Award Number W81XWH-17-1-0677).

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6. James et al. (2017) EBioMEdicine 26:126-13.

Disclosures: S. Charonis: None. **A.P. Georgopoulos:** None.

Poster

766. Gulf War Illness: Pathological Causes and Consequences

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 766.19/O42

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: Department of Defense Award Number W81XWH-15-1-0520

Title: Gulf War illness brain and inflammation: Association of brain atrophy and axonal integrity with C-reactive protein

Authors: *P. S. CHRISTOVA, B. E. ENGDAHL, L. M. JAMES, R. A. JOHNSON, A. F. CARPENTER, S. M. LEWIS, A. P. GEORGOPOULOS;
VAHCS, Brain Sci. Ctr., Minneapolis, MN

Abstract: Gulf War Illness (GWI) is a chronic multi-system condition that has affected one-third of U.S. veterans who served in the Persian Gulf. We reported recently the presence of brain atrophy in GWI [1] and a positive association of GWI symptom severity with the level of C-reactive protein (CRP), an inflammatory marker [2]. Here we investigated the effect of CRP on brain atrophy and fractional anisotropy in 65 GWI veterans. Structural MR and diffusion weighted images were acquired using a 3T Philips magnet and data were analyzed using the Human connectome project pipeline, FreeSurfer and ExploreDTI packages. CRP values were log-transformed to normalize their distribution [2]. We found that higher CRP levels were associated with (a) lower volumes (i.e. higher atrophy) of the brainstem and hippocampi (bilaterally), and (b) lower values of fractional anisotropy in the fornix, the output of the hippocampus to hypothalamus, indicating a disruption in this white matter tract. Altogether, these findings point to an inflammatory basis for brain atrophy and white matter pathology in GWI. The localization of these effects in the brainstem and hippocampi, regions near the most permeable blood brain barrier (BBB), are consistent with our hypothesis [1] that harmful substances (persistent antigens [3]) circulating in the blood of GWI patients [4, 5] gain access to the brain through most vulnerable BBB regions to inflict damage on nearby areas.
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War Illness (GWI) serum in neural cultures: Paving the way to immunotherapy for GWI. J Neurol Neuromed 3(5): 23-28.

Disclosures: P.S. Christova: None. **B.E. Engdahl:** None. **L.M. James:** None. **R.A. Johnson:** None. **A.F. Carpenter:** None. **S.M. Lewis:** None. **A.P. Georgopoulos:** None.

Poster

766. Gulf War Illness: Pathological Causes and Consequences

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 766.20/O43

Topic: H.01. Animal Cognition and Behavior

Support: Department of Defense grant W81XWH-16-1-0586

Title: Delayed treatment with the immunotherapeutic LNFPIII ameliorates Gulf War illness-related behavioral deficits in a rodent model of the disease

Authors: *J. M. CARPENTER[1], R. L. DOCKMAN[1], H. D. LUDWIG[1], J. J. WAGNER[1], D. A. HARN[2], N. M. FILIPOV[1];
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Abstract: Nearly 30% of veterans from the 1990-1991 Gulf War (GW) suffer from Gulf War Illness (GWI), a complex illness with many neurological symptoms that might have immunological underpinnings. War-related stress combined with overexposures to GW related chemicals, including a nerve agent prophylactic (pyridostigmine bromide; PB), pesticides (N,N-Diethyl-methylbenzamide; DEET) and, in some cases, exposure to nerve agents (sarin/cyclosarin) have been implicated in GWI. Currently, long-term, efficacious treatment options are unavailable. Here, an established GWI mouse model was utilized to explore the (1) long-term behavioral effects of deployment related GW chemicals exposure and (2) ability of a novel immunotherapeutic, Lacto-N-fucopentaose III (LNFPIII), to modulate GWI behavioral effects when given months post the initial GW exposures. Male C57BL6/J mice (8-9 weeks) were exposed to PB and DEET for 14 days, with the second 7 days also including corticosterone to emulate war-time stress. On day 15, a single injection of the sarin surrogate diisopropylfluorophosphate was given. Seven months post GW exposures, LNFPIII treatment began and continued until study completion. A battery of rodent behavioral tests, assessing memory, mood and motor function were performed beginning 8 months post GW exposures. From the data analyzed to date, in tests of motor function, GWI mice exhibited hyperactivity as evident by more distance traveled in an open field (OF), increased cadence, stride length and interstep distance in a gait test and decreased time to descend the pole in a pole test. Sensorimotor function was impaired by GWI as mice had longer latencies to contact the sticker in a sticker removal test. Grip strength was also decreased in GWI mice. These motor related

deficits, except OF distance, were attenuated by LNFPIII. GWI disrupted short-term memory, as mice approached and spent less time at a novel object in the novel object recognition test and this was not affected by LNFPIII. LNFPIII decreased anxiety-like behavior in GWI mice on the marble burying test (less marbles buried) and elevated zero maze (more open arm time and higher latency to enter the closed arm). In the OF, GWI mice exhibited more anxiety-like behavior (more time and entries into the corners) that was not prevented by LNFPIII. Together, it appears that months after exposure to GW-related chemicals, deficits in motor function, memory and mood are present. Many of these deficits were ameliorated by LNFPIII treatment initiated months following GW exposures, highlighting its therapeutic potential for veterans with GWI.
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Poster

767. Cellular Response to Stress

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 767.01/O44

Topic: F.04. Stress and the Brain

Support: P50 MH096889
MH73136

Title: Using single-cell transcriptomics to study the effects of early-life adversity on the crh-expressing neurons of the paraventricular nucleus (PVN)

Authors: *C. WILCOX[1], A. K. SHORT[3], M. BIRNIE[2], J. L. BOLTON[4], Y. CHEN[1], A. MORTAZAVI[1], T. Z. BARAM[3];
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Abstract: Mental and cognitive health as well as vulnerability to neuropsychiatric disorders involve the interplay of genes with the environment during sensitive developmental periods. Genetic and environmental factors contribute to the development and maturation of neurons, synapses and the resulting brain circuits. Within the hypothalamus, early-life adversity causes an increase in the number of excitatory synapses onto corticotropin-releasing hormone (CRH)-expressing neurons in the paraventricular nucleus (PVN). Further, such synaptic changes suffice to induce enduring epigenomic changes within these cells, influencing programs of gene expression. However, the epigenetic mechanisms by which early-life adversity orchestrates epigenetic programs within individual CRH-expressing neurons, with enduring functional consequences, remain unknown.

We utilize animal models of an impoverished environment and unpredictable maternal care (in a limited bedding and nesting [LBN] paradigm), which provokes major alterations in cognitive and emotional outcomes. We are focused on the change in gene expression profile of stress-sensitive CRH-neurons in the PVN following LBN. Initial studies focus on the immediate consequences of adversity, studied in 10-14 day old mice of both sexes. Because of the known heterogeneity of CRH-expressing neuronal populations, we are using single cell RNA sequencing (RNA-seq) to determine differential gene expression associated with early-life adversity and establish the upstream mechanisms and downstream consequences. Specifically, we employ CRH-ires-CRE mice, where a reporter (TdTomato) is expressed in CRH+ cells, enabling FACS selection of CRH expressing neurons. We employ the SmartSeq2 protocol to build single cell RNA-seq libraries and, once sequenced, STAR and RSEM are used to map and quantify the reads, respectively.
Initial analyses confirm the striking heterogeneity of CRH+ cell populations within the hypothalamus. Ongoing studies are delineating the large-scale change in gene expression provoked by early-life adversity.
Funding: P50 MH096889 and MH73136

Disclosures: C. Wilcox: None. **A.K. Short:** None. **M. Birnie:** None. **J.L. Bolton:** None. **Y. Chen:** None. **A. Mortazavi:** None. **T.Z. Baram:** None.

Poster

767. Cellular Response to Stress

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Program #/Poster #: 767.02/P1

Topic: F.04. Stress and the Brain

Support: NRF 2016R1A6A3A04006478
MRC 2014R1A5A2009392

Title: FKBP5, a depression-associated gene, has a role in autophagy

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Abstract: Mood disorders are common psychiatric disorders caused by various genetic and environmental factors. There are many antidepressants exist, but these do not work for more than half of the patients. Therefore, genetic factors may contribute to individual variation in antidepressant response. FK506 binding protein 51 (FKBP51, also known as FKBP5) belongs to a family of immunophilins that binds to the immunosuppressants FK506 and rapamycin. The

scaffolding activity of FKBP5 enables it to play a modulatory role in the immune response, tumorigenesis, cell death, and the stress hormone axis. Moreover, single nucleotide polymorphisms in FKBP5, which increase FKBP5 protein levels, are significantly associated with increased recurrence of depressive episode. However, the molecular mechanism for how FKBP5 regulates depression remains unclear. It has been recently reported that FKBP5 not only modulates antidepressant response but also interacts with Beclin1, Akt, and PHLPP, which are critical for autophagy, an intracellular degradation system necessary for the maintenance of cellular homeostasis. To investigate the relationship between FKBP5 and autophagy, we generated FKBP5 knock-out cell lines using a CRISPR/Cas9 system and analyzed them. We found that autophagic flux was impaired by a loss of FKBP5 in both basal and induced autophagy conditions. The detailed mechanisms will be shown in the presentation. We hope these findings will help to understand the molecular mechanism of how autophagy is associated with depression.

Disclosures: H. Park: None. **S. Jung:** None. **J. Chang:** None. **S. Lee:** None.

Poster

767. Cellular Response to Stress

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 767.03/P2

Topic: F.04. Stress and the Brain

Support: NICHD R01HD087509

Title: Normalizing aberrant DNA methylation associated with maltreatment

Authors: *N. COLLINS, C. ZIMMERMAN, T. S. DOHERTY, N. L. H. PHILLIPS, T. L. ROTH;
Univ. of Delaware, Newark, DE

Abstract: Childhood adversity has negative implications for development, including increased risk for various psychological disorders. One way this may occur is through changes to the epigenome. Using a rodent model, our lab has demonstrated alterations in both adult behavior and the epigenome that are associated with exposure to maltreatment. The present study sought to investigate whether valproic acid (VPA), a histone deacetylase inhibitor (HDACi), can normalize aberrant brain methylation associated with maltreatment. Using a scarcity adversity paradigm of maltreatment outside the home cage, male and female Long-Evans rat pups were exposed to either nurturing care or maltreatment for 30 minutes per day during postnatal days 1-7. Prior to each exposure session, rats were given a systemic injection of vehicle or VPA (200 mg/kg). We replicate our previous observation of a significant effect of infant condition, such that both males and females exposed to maltreatment displayed higher levels of methylation in

the prefrontal cortex. VPA was ineffective at preventing the maltreatment-induced increase in methylation. Current work in the lab is exploring whether other doses of VPA or another HDACi are capable of normalizing the methylation, with future work aimed at determining whether this strategy can also normalize adult behavior associated with maltreatment.

Disclosures: N. Collins: None. **C. Zimmerman:** None. **T.S. Doherty:** None. **N.L.H. Phillips:** None. **T.L. Roth:** None.

Poster

767. Cellular Response to Stress

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 767.04/P3

Topic: F.04. Stress and the Brain

Support: NSERC

Title: The effects of prenatal testosterone on stress system development

Authors: *E. R. MARTIN[1], H. A. WILSON[2], N. J. MACLUSKY[2], E. CHOLERIS[1];
[1]Psychology, [2]Biomed. Sci., Univ. of Guelph, Guelph, ON, Canada

Abstract: Gonadal hormones, such as testosterone (T), act on the brain during critical periods of development to produce sexually dimorphic changes which result in sex differences in neuroendocrine function and behaviour later in life. Exposure to increased T levels during prenatal development has implications in various disorders such as Autism Spectrum Disorder, which is characterized by impairments in social behaviour and is often associated with anxiety disorders. A recent study assessed the effects of slightly elevated prenatal T exposure in mice and found increased aggression and anxiety-like behaviour as well as deficits in social recognition and social learning. The current study aims to determine the mechanisms underlying the lasting changes in behaviour caused by prenatal T. Prenatal T and glucocorticoid (GC) exposure produce similar effects on offspring behaviour and their transcriptional effects have been shown to interact, so we hypothesize that prenatal T and GC exposure might exert similar effects on brain development and stress responsivity. We assessed the effects of elevated prenatal T and dexamethasone (DEX; a synthetic GC) on the expression of stress sensitive genes and miRNAs during the neonatal period as well as hormone profiles and GC levels in mice in adulthood. Pregnant CD1 dams were subcutaneously injected with sesame oil (vehicle control), 10 μg T propionate, or 0.1mg/kg DEX on embryonic days 12, 14 and 16. The expression of stress sensitive genes and miRNAs were measured in the hippocampus (HPC) on the day of birth. We also measured T levels from 1-6 hours following birth in male pups. Plasma corticosterone (CORT) was measured in adulthood at 10 minutes, 1 hour, or 3 hours following a 30-minute restraint stress. Prenatal treatment had no effect on T levels on the day of birth;

however, miR-124 was selectively down-regulated in the HPC at this time. MiR-124 is a brain specific miRNA that negatively regulates the expression of both the GC receptor and mineralocorticoid receptor, which may result in changes in stress sensitivity. DEX had no effect on CORT responsivity in either sex but prenatal T reduced CORT responsivity to restraint stress in males, but not in females. Thus, low doses of prenatal T may specifically alter stress responsivity in males. These findings have implications for understanding sex differences in the prevalence of ASD.

Disclosures: E.R. Martin: None. **H.A. Wilson:** None. **N.J. MacLusky:** None. **E. Choleris:** None.

Poster

767. Cellular Response to Stress

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 767.05/P4

Topic: F.04. Stress and the Brain

Support: Arkansas Biosciences Institute

Title: Surgical disruption of corticotropin releasing hormone neurons in the nucleus of the hippocampal commissure reduces HPA axis activity in birds

Authors: *M. T. KIDD, Jr[1], H. J. KADHIM[2], S. W. KANG[1], W. J. KUENZEL[1];
[1]Poultry Sci., [2]Cell and Mol. Biol., Univ. of Arkansas, Fayetteville, AR

Abstract: The nucleus of the hippocampal commissure (NHpC) in previous studies has been proposed to be part of the hypothalamic-pituitary-adrenal (HPA) axis regarding its role in the neuroendocrine regulation of stress in birds. The objective of this study was to apply electrolytic lesions to the NHpC, effectively disrupting corticotropin releasing hormone (CRH) neurons in that structure, to determine if its disruption affects the normal activity of the HPA axis driven by CRH neurons within the paraventricular hypothalamic nucleus (PVN). Male chicks (BW 300-350g, 10-14 days of age) were used in this experiment and split into two groups; lesioned birds (LES) and sham operation controls (sCON), which are birds subjected to surgery including placement of the electrode within the brain, but with no electrical current applied. On day 5 post surgery, a 2-hour (2 h) food deprivation (FD) stress was applied to all birds. Brain and anterior pituitary (APit) were promptly taken at 2 h of FD. Brain samples from the NHpC and PVN were dissected for qRT-PCR. Gene expression of CRH and CRH receptor 1 (CRHR1) in the NHpC were measured as well as CRH and CRHR1 in the PVN, the major hypothalamic nucleus involved in stress responses of vertebrates. CRHR1 and proopiomelanocortin (POMC) mRNA were measured in the APit. All data were analyzed using a one-way ANOVA. CRH and CRHR1 mRNA in the NHpC were found significantly down due to lesion placement ($p<0.001$) in LES in

comparison to sCON. In the PVN, CRH was found significantly upregulated ($p<0.01$) in LES in comparison to sCON, while its receptor, CRHR1 was significantly downregulated ($p<0.05$) in LES compared to sCON. In the APit, POMC was found significantly downregulated ($p<0.001$) in LES in comparison to sCON while its receptor, CRHR1, was found upregulated ($p<0.001$) in LES. Evidence suggests that lesioning the NHpC including all or some of its CRH neurons disrupts food restriction related HPA stress responses due to APit downregulation of POMC. Although PVN upregulation of CRH is present, the upregulation could be a compensatory response caused by the lack of normal increased NHpC CRH expression due to surgical disruption. Even with upregulated expression of CRH in the PVN, downregulation of POMC and upregulation of CRHR1, illustrate a lack of HPA activation expected from an intact NHpC. Also, diminished POMC expression suggests a neural pathway from the NHpC to median eminence. In conclusion, lesioning NHpC CRH neurons disrupted the expected response of the avian HPA axis during FD stress adding evidence that the NHpC plays a role in the avian HPA axis. (Supported in part by an Arkansas Biosciences Institute Grant).

Disclosures: **M.T. Kidd:** None. **H.J. Kadhim:** None. **S.W. Kang:** None. **W.J. Kuenzel:** None.

Poster

767. Cellular Response to Stress

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 767.06/P5

Topic: F.04. Stress and the Brain

Support: Arkansas Biosciensces Institute

Title: Vasotocinergic system in septo-hypothalamic structures and anterior pituitary sustains HPA axis response in birds

Authors: *H. J. KADHIM[1], M. T. KIDD, Jr.[2], S. W. KANG[2], W. J. KUENZEL[2];
[1]Cell and Mol. Biol., Univ. of Arkansas Fayetteville, Fayetteville, AR; [2]Poultry Sci., Univ. of Arkansas, Fayetteville, AR

Abstract: Recently, we proposed that CRH neurons in the nucleus of hippocampal commissure (NHpC), located in the septum, functioned as a part of the traditional HPA axis in avian species. A major reason was greater activation of CRH mRNA in the NHpC compared to CRH mRNA in the paraventricular nucleus (PVN) following food deprivation (FD) stress. Therefore, we determined if FD stress also activates arginine vasotocin (AVT) neurons and their receptors, V1aR and V1bR, within HPA axis. AVT mRNA and its receptors were examined in the NHpC, PVN, and medial basal hypothalamus (MBH). Additionally, gene expression of V1aR and V1bR in the anterior pituitary (APit) and plasma corticosterone (CORT) concentration were determined. Male chicks, 14 days of age, were divided into six groups (10 birds/treatment) and

subjected to different times of FD (Control, 1 h, 2 h, 3 h, 4 h, and 8 h). For each bird, blood was first collected for measuring CORT by RIA. Brains and APits were sampled and immediately frozen for each group. Brains were cryosectioned. The NHpC, PVN, and MBH were microdissected for RT-PCR. Data were analyzed using one-way ANOVA followed by Tukey Kramer HSD test with significant level ($p<0.05$). Here, we provide novel evidence that not only AVT ($p<0.001$) and V1aR ($P< 0.001$) mRNA are expressed and increased significantly in the PVN during stress, but V1bR mRNA also appears to be expressed and upregulated ($p<0.001$) in the avian brain, particularly in the MBH. Data showed a positive feedback between AVT and receptors in the PVN starting at 3 h of FD. In contrast, significant downregulation of AVT mRNA occurred in the NHpC ($p< 0.001$) during FD perhaps due to the absence of AVT cell bodies in that structure as shown by immunohistochemistry, whereas its receptors were upregulated significantly after 3 h of FD. On the other hand, AVT mRNA in its nerve terminal fields located in the MBH were upregulated ($p<0.001$) at 2 h and continued throughout the last sampling point (8 h) along with upregulation of V1bR ($p<0.01$) and downregulation of V1aR ($p<0.01$). At the APit level, significant upregulation of V1bR ($p<0.001$) and downregulation V1aR ($p<0.001$) indicated that AVT differentially regulates receptors in the AP to regulate CORT release. Data show that upregulation of AVT mRNA in the PVN and V1bR in the APit sustained the significant increase of plasma CORT ($p<0.001$) at the end of the FD treatment. Taken together, continued FD stress is associated with increasing plasma CORT via upregulation of AVT mRNA not only in the cell bodies within the PVN but also in the terminal field including the MBH and median eminence responsible for differential activation of AVT receptors in brain structures and APit. Supported by AR Biosci Inst.

Disclosures: **H.J. Kadhim:** None. **M.T. Kidd:** None. **S.W. Kang:** None. **W.J. Kuenzel:** None.

Poster

767. Cellular Response to Stress

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 767.07/P6

Topic: F.04. Stress and the Brain

Support: NARSAD Young Investigator Grant

Title: Exploring the role of Egr1 in regulating hormone-dependent transcriptional programs and anxiety- and depression-related behavior in female mice

Authors: *D. ROCKS[1], I. JARIC[1], H. CHAM[2], A. HERCHEK[1], J. M. GREALLY[3], M. SUZUKI[3], M. KUNDAKOVIC[1];
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Abstract: Due to the prevalence of sex-bias in animal research of the brain and behavior, little is known about the mechanisms driving the two-fold increase in risk for anxiety and depression experienced by females. To address this gap in knowledge, we studied the role of ovarian hormone fluctuations and developmental stress in mediating sex-specific vulnerability to anxiety- and depression-like behavior as measured by behavioral tests (open field, elevated plus maze, sucrose preference, forced swim, n=80 females, 40 males). We found that females exposed to early-life stress in the form of maternal separation (MS) showed increased depression-like behavior compared to MS males. Within control females, the high-estrogenic stage of the cycle was associated with decreased anxiety- and depression-like behavior compared to the low-estrogenic stage. This protective effect of estrogen was disrupted by early-life stress, as high- and low-estrogenic MS females exhibited no difference in anxiety-indices in the open-field test. To understand the molecular basis of this phenomenon, we utilized targeted and genome-wide gene expression and epigenetic assays: qRT-PCR & Bisulfite-Pyrosequencing (n=12 females, 8 males), and ATAC-seq (n=12 females, 6 males) in the ventral hippocampus, a brain region relevant for anxiety and depression. Following early-life stress, we observed aberrant gene expression and DNA methylation in psychiatric-risk genes including *Nr3c1* and *Cacna1c*. Additionally, we found that neuronal chromatin organization in this brain region changes dynamically across the estrous cycle. A subsequent motif analysis identified Egr1, an estrogen-responsive transcription factor, as a predicted upstream regulator of genes with differential chromatin accessibility across the estrous cycle. Interestingly, the expression of *Egr1* fluctuates across the estrous cycle in control females and is disrupted by early-life stress in MS females. To validate a direct relationship between estrogen and Egr1 that is implicated in our observed phenotype, we utilized primary mouse hippocampal neurons. Preliminary data from these experiments reveal a dynamic pattern of *Egr1* expression following estradiol treatment that coincides with the expression of anxiety-related Egr1 target genes. Together, our results indicate an important role for sex hormone fluctuations in female-specific susceptibility to depression and anxiety disorders. Further, we present Egr1 as a candidate key regulator in driving transcriptional fluctuations across the estrous cycle which are likely contributors to increased female vulnerability to anxiety- and depression-related phenotypes.

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Poster

767. Cellular Response to Stress

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Support: NIH-NIMHD Grant G12MD007592

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NIH-NIDA Grant R25DA033613
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Title: Impaired proteostasis in response to early life stress in the adult and aged hippocampus

Authors: *J. A. SIERRA FONSECA[1], J. N. HAMDAN[2], A. A. COHEN[2,3], S. M. CARDENAS[2], S. SAUCEDO, Jr.[2], G. A. LODOZA[2], K. L. GOSSELINK[2,4];
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Abstract: Early-life stress (ELS) can persistently modify neuronal circuits and functions, and increase the expression of misfolded and aggregated proteins that are hallmarks of several neurodegenerative diseases (NDs), including Alzheimer's (AD). In order to maintain proteostasis, the healthy brain clears abnormal proteins through the actions of two main pathways: the autophagy-lysosomal pathway (ALP), which employs autophagosome fusion with the lysosome for recycling of cellular components, and the ubiquitin-proteasome system (UPS), which targets soluble, short-lived proteins with a specific ubiquitin signal for proteasomal degradation. Accumulating evidence indicates that these two systems become impaired in NDs, causing accumulation of abnormal proteins and ultimately leading to neuronal death. ELS is known to impact development and progression of NDs, yet the precise underlying mechanisms remain poorly understood. We therefore hypothesized that ELS disrupts proteostasis in the brain, leading to deficient clearance and the subsequent accumulation of abnormal proteins. Our analyses focused on the hippocampus (HIPP), given its critical roles in mediating the stress response and its involvement in the pathology of AD. Female and male Wistar rats underwent ELS in the form of maternal separation for 3h/d on postnatal days 2-14. Brain tissue was then harvested from adult (3 months) and aged (16 months) animals, and the HIPP was isolated and evaluated for expression of protein markers associated with the ALP (beclin-1, LC3 and p62), the UPS (20S proteasome, PSMC5, and K48-polyubiquitinated proteins), and AD (phosphorylated Tau, amyloid precursor protein and cleaving enzymes BACE1 and IDE) using Western blot. ALP markers in the adult HIPP were significantly increased by ELS in both sexes, whereas UPS marker expression displayed sex differences, with 20S proteasome and K48 polyubiquitinated protein expression increased in females but decreased in males. In the adult HIPP, phospho-Tau was increased significantly after ELS in females but decreased in males, and the cleaving enzymes BACE1 and IDE were increased by ELS in males only. In the aged HIPP, expression of the ALP marker p62 was increased by ELS in females, while the UPS protein PSMC5 was found to be increased in females and decreased in males. Levels of phospho-Tau were found to be decreased in the aged male HIPP, with the enzyme BACE showing decreased levels in ELS males. Collectively, our results indicate that ELS can persistently and selectively modify the proteostasis machinery in the HIPP in a sex- and age-dependent manner, which may consequently impact the development of NDs.

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Poster

767. Cellular Response to Stress

Location: Hall A

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Program #/Poster #: 767.09/P8

Topic: F.04. Stress and the Brain

Support: CONACYT NO. 256882

Title: Effect of chronic corticosterone treatment on tryptophan hydroxylase isoform expression and activity in rat adrenal glands

Authors: *N. SAROJ[1], J. TERRÓN SIERRA[1], S. ,,[2];
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Abstract: Chronic stress has been proposed as one of the key factors predisposing to endocrine disruption and the development of stress-related disorders. Recently chronic restraint stress (CRS) was shown to induce sensitization of stress-induced corticosterone (CORT) secretion via ACTH-independent mechanisms involving increased adrenal 5-HT levels and ectopic expression of adrenocortical 5-HT7 receptors. Tryptophan hydroxylase (TPH) is the rate-limiting enzyme in the biosynthesis of 5-HT and two isoforms of this enzyme encoded by different genes, TPH1 and TPH2, have been identified. In the present study we examined the effect of chronic CORT treatment on TPH isoform expression in rat adrenal glands, as determined by immunohistochemistry, Western blot and reverse transcription polymerase chain reaction (RT-PCR), respectively; in addition, TPH activity was also measured by a fluorometric HPLC technique. Male Wistar rats received chronic CORT (20 mg/kg, s.c.) and vehicle (VEH; 1 ml/kg, s.c.) treatments for 14 days. On day 15, animals of each group were anesthetized and perfused or decapitated for collection of tissues. Body weight gain, and relative adrenal and thymus weight were recorded. As compared to VEH, chronic CORT treatment notably increased TPH2 -but not TPH1- expression in the adrenals, as visualized by an increase of TPH2-like immunoreactivity in the adrenocortical zona glomerulosa and inner and outer zona fasciculata, as well as TPH2 protein and mRNA levels in whole adrenal glands. Furthermore, chronic CORT significantly increased adrenal 5-HT levels as compared to chronic VEH treatment. Results support the notion that the increase of adrenocortical levels of 5-HT in chronically stressed animals may be accounted for by ectopic expression and activity of THP2, and that these changes are corticosteroid-dependent.

Disclosures: **N. Saroj:** None. **J. Terrón sierra:** None. **S. ,,:** None.

Poster

767. Cellular Response to Stress

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Program #/Poster #: 767.10/P9

Topic: F.04. Stress and the Brain

Support: Ito Foundation For International Education Exchange

Title: Profiling m^6A RNA methylation in human postmortem brain tissue in individuals with depression

Authors: *H. MITSUHASHI[1,3], C. NAGY[3], Z. AOUABED[3], G. TURECKI[3,2];
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[3]McGill Group for Suicide Studies, Montreal, QC, Canada

Abstract: Introduction: Major Depressive Disorder (MDD) is one of the most common psychiatric disorders worldwide. Mounting evidence suggests there is an alteration of epigenetic mechanisms in response to stressful stimuli and environmental factors in the pathophysiology of MDD, yet little is known about the epitranscriptome in MDD. N6-methyladenosine (m^6A) is the most abundant and reversible RNA modification in mammalian mRNA. Given its high abundance and dynamic regulation in the brain, m^6A has been described to be crucial in brain development. Recent studies have found m^6A to be involved in stress response suggesting its importance in the development of stress-related psychiatric disorders. However, there are no human studies examining m^6A-seq in the brain and its role remains largely undescribed. The aim of this study is to describe the landscape of m^6A in the human brain and to identify changes that may occur in the context of MDD.
Methods: To examine the post-mortem stability of m^6A and the influence of age, RNA Integrity, and pH on m^6A levels, global m^6A levels were quantified using EpiQuik m^6A RNA Methylation Quantification Kit (Epigentek). To assess the small quantity of RNA extracted from post-mortem brain tissue, a low-input m^6A-seq protocol was optimized according to the published protocols and sequenced on the Illumina platform.
Results: Results suggest that PMI does not have a significant influence on global m^6A levels and m^6A is relatively stable in post-mortem brain. A significant number of peaks were detected using the low-input m^6A-seq protocol compared to a high-input m^6A-seq protocol.
Conclusions: The use of human postmortem brain could help us understand the role of m^6A in general brain function as well as provide greater insight into the etiopathogenesis of MDD.

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Poster

767. Cellular Response to Stress

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Program #/Poster #: 767.11/P10

Topic: F.04. Stress and the Brain

Support: DGAPA-PAPIIT IA205218
DGAPA-PAPIIT IN215218
DGAPA-PAPIIT IN217918

Title: Oxytocin and CB2 receptors in rats subjected to maternal separation and social isolation

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Abstract: Early experiences during perinatal life may be a factor of vulnerability to develop psychiatric disorders such as depression, and substance abuse. Maternal separation (MS) in male rats increase the consumption of alcohol in adulthood. MS also induces decreased expression of cannabinoid receptor 1 (CB1R) in the PFC. On the other hand, high levels of oxytocin are associated with social bonds. The objective of this study is to describe the changes in the oxytocin and endocannabinoid systems and the affective state (anxiety and depression) generated by family and / or social exclusion, in adult male Wistar rats. as well as to analyze the potential environmental protection effect social during adolescence. Four groups of Wistar rats, non-MS /Socialized, non-MS/Isolated, MS (PND2-15)/ Socialized (PND24-60) and MS/ Isolated (PND24-90) were utilized. They were evaluated in the elevated plus maze test. Oxytocin and CB2 receptors were estimated in PFC, Amygdala, NAcc, by means of immunofluorescence. Results. Social isolation facilitated the expression of like-anxiety behaviors. Socialization during adolescence reversed MS effects on the anxiety-like behaviors. Regarding the findings of Oxytocin and CB2R will be discussed. Key words: Cannabinoid receptor 2, oxytocin receptor, maternal separation, socialization

Disclosures: Y.A. Alvarado Ramirez: None. **D.A. Rangel Rangel:** None. **A.E. Ruiz-Contreras:** None. **O. Prospero-Garcia:** None. **M. Mendez Diaz:** None.

Poster

767. Cellular Response to Stress

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 767.12/P11

Topic: F.04. Stress and the Brain

Support: conacyt 256882

Title: Chronic stress-induced increase of adrenocortical serotonin transporter expression in rats: A glucocorticoid-dependent phenomenon

Authors: S. „[1], J. TERRON SIERRA[2], P. LOPEZ SANCHEZ[2], N. SAROJ[3];
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Abstract: Chronic restraint stress (CRS) has been shown to magnify acute stress-induced corticosterone (CORT) secretion in rats through a mechanism involving 5-HT7 receptors, and to increase the amount of 5-HT7 receptors and serotonin (5-HT) in the adrenal cortex. Since chronic stress has also been demonstrated to increase the expression of the 5-HT transporter (SERT) in the central nervous system, the purpose of the present study was to investigate whether SERT expression is also increased in the adrenal glands as a result of CRS exposure, specifically at the level of adrenocortical cells involved in glucocorticoid secretion. In addition, we asked the question whether potential CRS-induced changes in adrenocortical SERT expression might be glucocorticoid-dependent. We examined the effects of CRS (20 min/day) as compared to control (CTRL) conditions for 14 days on SERT-like immunoreactivity (SERT-LI) in adrenal gland sections, and SERT mRNA and protein levels in whole adrenal glands as determined by immunohistochemistry, reverse-transcription polymerase chain reaction (RT-PCR) and Western blot assays, respectively. On the other hand, the effects of a chronic 14-day treatment with CORT (20 mg/kg, s.c. per day) as compared to vehicle (20% CBD; 1 mL/kg, s.c. per day) on SERT-LI, SERT mRNA and protein levels in adrenal glands as well as on acute 30 min restraint-induced ACTH and CORT secretion were analyzed. Exposure to CRS augmented SERT expression in adrenal glands as suggested by a remarkable increase of SERT-LI in the adrenal cortex along with a significant increase in the amount of SERT mRNA and protein in whole adrenals. Like CRS, chronic CORT treatment induced an increase of 5-HTT-LI in the adrenal cortex as well as in the amount of SERT mRNA and protein in whole adrenal glands as compared to vehicle. In contrast to the reported changes in acute stress-induced secretion of ACTH (i.e. decrease) and CORT (i.e. magnification) as a result of CRS exposure, chronic CORT treatment produced significant blunting of restraint-induced secretion of ACTH and CORT. The present data reveal an interesting association between chronic stress exposure and SERT expression in adrenocortical cells, which seems to be a glucocorticoid-dependent phenomenon.

Disclosures: S. „: None. **J. terron sierra:** None. **P. Lopez Sanchez:** None. **N. Saroj:** None.

Poster

767. Cellular Response to Stress

Location: Hall A

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Program #/Poster #: 767.13/P12

Topic: F.04. Stress and the Brain

Support: The Inoue Enryo Memorial Grant,TOYO University

Title: Oxidative stress modifies extracellular vesicles in HT22 murine hippocampal cells

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Abstract: It has been well established that neuronal cells secrets several proteins in response to oxidative stressors. For example, we recently identified that the secretions of progranulin (PGRN) and BDNF were increased by hydrogen peroxide (H_2O_2) treatment in HT22 cells or PC12 cells. On the other hand, whether the other secreted factors, such as nucleic acids, lipids, and extracellular vesicles, are also involved in this process has not been well understood. Among these factors, we focused on extracellular vesicles (EVs), which contain proteins and small nucleic acids, and transfer these molecules by fusing with the other cells. EVs seem to play important roles in causing pathological changes that are typically observed in some neurological diseases which are induced by oxidative stress (i.e. Alzheimer disease). In this study, therefore, we investigated whether and how the quantity and quality of EVs are modified by oxidative stress in HT22 cells.Initially, we purified EVs from HT22 cell culture supernatant by the sequential ultracentrifugation method, which were confirmed by electron microscopic analysis, dynamic light scattering (DLS) analysis, and the expression of specific exosome marker proteins assessed by western blotting. We then analyzed the effects of H2O2 on the secretion of EVs. Briefly, HT22 cells are cultured with or without different concentration of H2O2 for 48 hours and the EVs were purified from the collected supernatant, followed by DLS analysis. The amounts of EVs release significantly increased by oxidative stress without affecting the size distribution of EVs. The induction of PGRN gene expression by oxidative stress was tightly correlated with this enhancement of EV release, which is consistent with recent reports; however, exogenous PGRN treatment did not affect the EV release, which suggested the “intracellular” PGRN induction by oxidative stress may control the secretion of EVs. Moreover, we comparatively analyzed the protein profiles in EVs with or without H2O2 treatment, and found that the amounts of three proteins in EVs were significantly reduced by oxidative stress. By utilizing MALDI/TOFMS analysis, we identified two proteins are related to membrane

trafficking.In conclusion, oxidative stress clearly affects the quantity and quality of EVs released from HT22 murine hippocampal cells. We speculate that this modification may alter the EV-dependent cell-cell communications in central nervous system.

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Poster

767. Cellular Response to Stress

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 767.14/P13

Topic: F.04. Stress and the Brain

Title: Hippocampal regulation of BDNF and Sonic hedgehog- Gli1 signaling cascade via naringenin in a rat model of depressive-like behavior

Authors: *M. TAYYAB[1], S. FARHEEN[1], M. M. P.M[1], N. KHANAM[1], M. M. HOSSAIN[1,2], M. H. SHAHI[1];
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Abstract: Background: Brain-derived neurotrophic factor (BDNF) is a highly abundant neurotrophin and one of the principal neural growth factors. It is involved in adult hippocampal neurogenesis, neural plasticity and in various mental disorders including depression. In addition to BDNF, Sonic hedgehog (Shh) is also a powerful regulator of embryonic as well as adult hippocampal neurogenesis. Recently, studies have delineated a significant role of Shh in various neurological diseases including brain tumor and depressive disorders. In our study, we concentrated on antidepressant and neuroprotective effects of naringenin (NAR) pretreatment via BDNF and Shh signaling pathways in a rat model of chronic stress-induced depressive-like behavior.
Method: Twenty-four male Wistar rats were randomized into four groups namely; Control (saline), Naringenin (NAR 50mg/kg), chronic unpredictable mild stress (CUMS) and CUMS+NAR for 28 days including 1-week pre-treatment with NAR. Forced swim test (FST), open field test (OFT) and Morris water maze (MWM) were performed. The rats' brains were harvested for histopathological examination and for the analysis of mRNA expression of BDNF, Shh, its downstream signaling component GLI1 and its homeodomain transcription factors NKX2.2 and PAX6.
Results: We observed that NAR reversed depressive behavior as well as CUMS associated cognitive deficits and morphological anomalies. The mRNA expression of BDNF, Shh, GLI1, NKX2.2 and PAX6 were decreased in CUMS, and these decreased levels were recovered by

NAR. In conclusion, we suggest that BDNF and Shh signaling pathways might play an important role in the pathophysiology of depression and in providing NAR mediated antidepressant effects.

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Poster

767. Cellular Response to Stress

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 767.15/P14

Topic: F.04. Stress and the Brain

Support: NSERC Grant 071611
Ontario Veterinary College Scholarship

Title: Mouse hippocampal G-protein coupled estrogen receptor (GPER) protein expression and functional signalling is regulated by glucocorticoids

Authors: *K. C. NICHOLSON[1], E. R. MARTIN[2], A. L. MENDELL[1], C. E. CREIGHTON[1], N. J. MACLUSKY[1];
[1]Biomed. Sci. - Ontario Vet. Col., [2]Psychology, Univ. of Guelph, Guelph, ON, Canada

Abstract: Estrogens exert neuroprotective and neurotrophic effects on the hippocampus, modulating hippocampal-dependent learning and memory. The primary female sex steroid 17β-estradiol binds to the G-protein coupled estrogen receptor (GPER), rapidly enhancing hippocampal dendritic spine density, learning, and memory in female rodents via a mechanism involving phosphorylation of c-jun N-terminal kinase (JNK). However, in response to acute behavioural stressors, estradiol-mediated neurotrophic and memory-enhancing effects are dramatically impaired in the female hippocampus. The mechanisms underlying stress-induced impairment of rapid estrogen effects on the brain remains unclear. This study tested the hypothesis that stress-induced glucocorticoid release might affect hippocampal GPER expression and GPER-mediated cellular responses. Novel mHippoE-14 (female-derived) and mHippoE-18 (male-derived) immortalized mouse hippocampal cell lines (Gingerich et al., Neuroscience. 2010;170:54-66) were characterized for mRNA expression of stress hormone, gonadal steroid, and neurotransmitter receptors through conventional PCR (n=10). Amplicons were validated with sequencing. Given the concurrent expression of the glucocorticoid receptor (GR) and GPER, cells were treated with vehicle or the synthetic glucocorticoid dexamethasone (DEX; 10nM) for 10 minutes, 1 hour, 10 hours, 24 hours, and 48 h. GPER protein levels determined using Western blot analysis were significantly downregulated at 24 h after treatment with 10 nM DEX (n=5). To characterize functional GPER responses, cells were treated with 10 nM of the synthetic GPER agonist G-1 for 10 minutes, 1 hour, or 4 hours. To characterize functional GPER

antagonism, cell lines were pretreated with 10 nM of the synthetic GPER antagonist G-15 for 1 hour followed by 10 nM G-1 for 10 minutes, 1 hour, or 4 hours. Western blot analyses show G-1 induced phosphorylation, while G-15 inhibited phosphorylation of both 54 and 46 kDa JNK isoforms (n=4-6). To investigate glucocorticoid regulation of GPER signalling, mHippoE-14s were given a 24-hour 10 nM DEX or vehicle pretreatment, followed by a vehicle or 10 nM G-1 treatment for 10 minutes, 1 hour, or 4 hours. Western blot analyses indicate that G-1 induced phosphorylation of both JNK isoforms was blocked by prior treatment with 10 nM DEX (n=4). Since GPER mediates some of the rapid neurotrophic, neuroprotective and memory enhancing effects of estradiol, these findings may explain why the female hippocampus is particularly vulnerable to the detrimental effects of stress (Supported by NSERC and the Ontario Veterinary College).

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Poster

767. Cellular Response to Stress

Location: Hall A

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Topic: F.04. Stress and the Brain

Support: NSERC Grant 071611
Ontario Veterinary College Scholarship

Title: Time course of acute surgical stress and the role of testosterone in the post-operative recovery of dendritic morphology in adult male rats

Authors: *L. K. ISAACS, E. M. LAWTON, A. L. MENDELL, N. J. MACLUSKY; Biomed. Sci. - Ontario Vet. Col., Univ. of Guelph, Guelph, ON, Canada

Abstract: Gonadal and stress steroids dramatically alter dendritic morphology in the hippocampus (HC) and medial prefrontal cortex (mPFC). These changes may contribute to altered cognitive function, as well as the development of neuropsychiatric disorders. Our laboratory has shown that orchidectomy (ORCH) results in the rapid expansion of apical dendrites in the cornu ammonis 3 (CA3) subfield of the HC lasting for up to 2-months following surgery. The time-course of the effects of surgical stress following ORCH and the role of testosterone (T) in modulating these effects have yet to be completely elucidated. We hypothesized that even brief surgical stress might result in remodeling of hippocampal and mPFC apical dendrites, while T enhances recovery. To test this hypothesis, we determined the time-course of the effects of surgical stress and glucocorticoid (GC) treatment in young adult male Sprague-Dawley rats (60-70 days old). Rats were given drinking water containing

1.5ug/mL of dexamethasone for 16-hours and sacrificed 1-, 3- and 10-days later. Brains were stained using the Golgi Cox method. Three-days following treatment CA3 apical dendrites showed decreased dendritic branching similar to that seen in rats who received a sham-orchidectomy (SHAM). No effects were seen in CA1 or the mPFC. To determine the role of T in the modulation of dendritic morphology following surgery, young adult male Sprague-Dawley rats received either ORCH with T replacement (ORCH+T), ORCH with cholesterol replacement (ORCH+C), SHAM or left intact and were sacrificed 1- or 2-months later (n=4-5). At 1-month, ORCH+C rats showed similar expansion of CA3 apical dendrites previously seen at 10-days and 2-months. While the ORCH+T and intact rats had similar CA3 apical dendritic branching, SHAM rats displayed decreased CA3 apical branching. At 2-month following surgery, SHAM rats appeared to be almost completely recovered. However, all operated animals had dramatically reduced the maximal apical dendritic length in CA3, even at 1- and 2-months following surgery. No effects were seen in CA1 or the mPFC. These results suggest that surgical stress causes the rapid remodeling of CA3 apical dendrites, which is at least partially mediated by glucocorticoid action, while T may modulate the subsequent recovery of dendritic morphology.
Acknowledgments: Supported by NSERC and the Ontario Veterinary College.

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Poster

767. Cellular Response to Stress

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 767.17/P16

Topic: F.04. Stress and the Brain

Support: CEEHRC Phase II Impact Grant

Title: Purine salvage deficiency drives energy deficits and impairs dopaminergic cell development in humans

Authors: *S. C. BELL, H. PENG, M. JEFRI, C. ERNST;
McGill Univ., Montreal, QC, Canada

Abstract: Lesch-Nyhan Syndrome (LNS) is a purine recycling disorder caused by mutations in *HPRT1* and includes features such as dystonia and self-aggressive behaviour. Human studies have repeatedly implicated midbrain dopamine dysfunction in LNS, however, it remains unclear how mutations in *HPRT1* lead to disease. We made isogenic knock-outs of *HPRT1* in human induced pluripotent stem cells and simultaneously differentiated these cells to a forebrain and midbrain fate. HPRT deficient midbrain cells showed a clear deficiency in all markers of dopaminergic development including tyrosine hydroxlase, a result recapitulated in cells derived

from nine different LNS patients. Analysis of glycolytic rate and oxygen consumption showed that HPRT deficient cells have compromised energy dynamics, while midbrain cells show particular deficits in oxidative phosphorylation, a result absent in forebrain cells deficient in HPRT. Metabolomic analyses showed that HPRT-deficient midbrain cells have increased levels of metabolites specific to *de novo* purine synthesis, likely depleting intracellular glucose pools normally used in OXPHOS and glycolysis. Additionally, HPRT deficient midbrain cells show a significant reduction in MTORC1 signalling, a integrator of cell nutritional state and developmental programing. We propose that loss of purine salvage leads to profound loss of ATP required for proper dopaminergic development through an MTOR-mediated mechanism. Our results describe an unexpected link between purine salvage and metabolic rate in human midbrain progenitor cells. We further reveal a surprising need for high energy flux for proper dopaminergic development in humans. These results have important implications for LNS and other disorders of the dopaminergic system, including Parkinson's disease.

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Poster

767. Cellular Response to Stress

Location: Hall A

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Program #/Poster #: 767.18/P17

Topic: F.04. Stress and the Brain

Support: NIH Grant MH108286
NIH Grant MH099910
NIH Grant MH104184
NIH Grant ES028202

Title: Extracellular vesicle payloads: Delivering stress experience via sperm to the next generation of mice and men

Authors: *C. P. MORGAN[1], J. C. CHAN[4], A. SHETTY[2], S. A. AMENT[3], M. KANE[5], C. N. EPPERSON[6], T. L. BALE[7];
[2]Inst. for Genome Sci., [3]Inst. for Genome Sci. and Dept. of Psychiatry, [1]Univ. of Maryland Sch. of Med., Baltimore, MD; [4]Biomed. Sci., Perelman Sch. of Med., Philadelphia, PA; [5]Pharmaceut. Sci., Univ. of Maryland Sch. of Pharm., Baltimore, MD; [6]Psychiatry, Univ. of Pennsylvania Perelman Sch. of Med., Philadelphia, PA; [7]Pharmacol., Univ. of Maryland Baltimore, Baltimore, MD

Abstract: Extracellular vesicles (EVs) are a unique mode of intercellular communication capable of incredible specificity in transmitting signals involved in cellular function. One example of this is the essential role EVs secreted by epithelial cells lining the lumen of the

reproductive tract play in the post-spermatogenic maturation of sperm. EVs released by these epididymal epithelial cells (EECs) transport bioactive cargoes including small non-coding RNA (sncRNA), proteins and lipids that are required for sperm to develop essential properties, including the ability to swim and fuse with the ovum. Here we demonstrate that this fundamental process also plays a causal role in the somatic-to-germline transmission of information regarding paternal stress experience capable of altering fetal development in a preclinical model. In our model, paternal preconception stress produces lasting histone and transcriptomic alterations in mouse EECs, with corresponding persistent changes in the miRNA, proteomic, and lipid composition of secreted EVs. Using the *in vitro* fertilization technique, intracytoplasmic sperm injections, we demonstrate sperm that had been incubated with EVs collected from stress-treated EECs produce offspring with significant changes in neurodevelopment and adult stress reactivity. To determine whether these findings had a potential translational relevance, we developed a broad framework to assess the composition of sperm sncRNAs (including miRNA, piRNA, tRNA, and rRNA) in healthy human subjects. Utilizing within and between subject comparisons of sperm samples and perceived stress reports collected repeatedly over six months, we were able to detect a distinct sncRNA expression pattern that largely grouped subjects according to their recent stress experience, similar to that of our mouse model. In addition, by implementing complex modeling of the relationship between individual sncRNA and perceived stress state in these data, we have identified specific populations of sperm sncRNA that are responsive to the dynamics of stress experience. These studies establish a novel precedent that intergenerational transmission does not require propagation of germ cell epigenetic marks through gametogenesis and provides broad mechanistic insight into the translational importance of parental lifetime stress experiences and exposures on offspring development.

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Poster

767. Cellular Response to Stress

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 767.19/P18

Topic: F.04. Stress and the Brain

Support: NRF Grant 2016M3C7A1905385

Title: A study on the temporal variability of acute stress response in mice using proton magnetic resonance spectroscopy

Authors: *Y. HWANG[1], M. LEE[2,3], W. KIM[1], C. YUN[1], Y. KIM[4], H. BAEK[4], B. HAN[1], D. KIM[1];

[1]Yonsei Univ., Wonju, Korea, Republic of; [2]Children's Hosp. of Michigan, Detroit, MI; [3]Wayne State Univ. Sch. of Med., Detroit, MI; [4]Gachon Univ., Incheon, Korea, Republic of

Abstract: A proton magnetic resonance spectroscopy (^{1}H-MRS) has been broadly used in the study for the stress and provide the neurochemical information for the brain of a living animal. The acute stress (AS) response is the complex process that activates the neuroendocrine and metabolic systems for homeostasis. A study on the stress responses is important to understand the process by which an organism adapts to the stress for survival. Up to now, most studies have focused on the chronic stress responses and there are few studies for the AS. They have analyzed the changes of brain metabolites at a particular time after AS. In this study, we explored the temporal variations of the brain metabolites in the hippocampi of mice after receiving AS response using ^{1}H-MRS. We used 24 male C57BL/6N mice from 6-7 weeks that weigh from 18g to 25g and randomly divided into two groups, control group (10 mice) and AS group (12 mice). Two from the control group were removed by the outlier occurring at all times. To evaluate the temporal variability of the AS response, all mice in the AS group were physically restrained for 2 hours in a 50mL conical tube. Then, MRS data for the two groups were acquired with 9.4T Bruker MRI/MRS equipment using PRESS with the following parameters: TR/TE = 4000/10ms, NEX = 512, voxel size = 1.8 x 3.4 x 1.8mm^3. MRS data measurements were repeated four times without inter-scan interval. MRS data were analyzed using LCModel with a simulated basis-set including 17 metabolites. In order to compare and identify the temporal variability between two groups, MRS data for control group and AS group were statistically analyzed using two-way repeated-measure analysis of variance. We found that the effect of time that is a repetition factor for intra-group significantly exists ($P < 0.05$) on the concentration of Glutamate (Glu) and Alanine (Ala). The effect of stress between groups is presented in Ala ($P < 0.05$), but not in Glu ($P = 0.094$). As shown in Figure 1, the concentrations of Glu and Ala in the stress group are higher than those in the control group at all time points and the temporal variability for concentration of Glu and Ala showed a decreasing tendency over time. The decreasing tendency of concentrations of Glu in control group is similar to previous studies. In addition, our study suggests that Ala as well as Glu is related with AS. The result of our study can provide a deeper understanding of AS responses and consider the utility as a biomarker of AS response.

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Poster

768. Preclinical and Human Studies in Neurovascular Coupling Mechanisms

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 768.01/DP11/P19

ControlExtraData.DynamicPosterDisplay:
Dynamic Poster

Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Support: NIH Grant R01NS108407

Title: Quantitative micro neurovasculature mapping across the whole brain in young and old mice

Authors: *Y.-T. WU, U. CHON, Y. KIM;
Penn State University, Col. of Med., Hershey, PA

Abstract: The structure of the brain's microvasculature provides the extraordinary surface needed for a high level of energy exchange and clearance of metabolic wastes. Small vessel pathologies are involved in cognitive decline associated with aging and many brain disorders. Mounting evidence suggests that the 3D regional distribution of small vessels is heterogeneous in different circuits, which may undergo differential changes during aging. To quantitatively understand the underlying neurovascular mechanisms affected in health and pathological conditions, we are creating a precise 3D map of micro vessels in the entire mammalian brain using the mouse as a model. We used FITC conjugated fluorescent albumin gel perfusion to label the micro vessel in the whole brain from young (2 months old) and old (18 months old) mice. Then, we used serial two-photon tomography to acquire high resolution 3D brain images at resolution 1 x 1 x 5um (x,y,z), which is sufficient to visualize even smallest micro vessels. We are developing computational pipeline to precisely stitch the terabyte size imaging data, detect and track fluorescently labeled the vasculature information. We used image registration to map our signal in a standard reference brain to quantify vasculature signals (e.g., density, connectivity) in over 200 different anatomical regions across the whole brain. Our preliminary finding suggests significant difference in vascular density and 3D geometry across different brain regions, which can be linked with different vulnerability of brain regions in pathological conditions. We envision that our work provides a foundation for further studies of neurovascular architectures supporting normal cognitive function and their changes in various neuropathologies.

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Poster

768. Preclinical and Human Studies in Neurovascular Coupling Mechanisms

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 768.02/P20

Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Title: Aroma effects on hemodynamic modulation in the prefrontal lobe measured using fNIRS

Authors: *T. MATSUMOTO[1], T. KOHAMA[1], Y. TAKIKAWA[1], S. KANJIYAMA[2], H. YOSHIDA[2];
[1]Kindai Univ., 930 Nishimitani, Kinokawa, Wakayama, Japan; [2]KIndai Univ., 930 Nishimitani, Kinokawa, Wakayama, Japan

Abstract: Aromatherapy has begun to attract attention as a treatment for depression. In particular, the aroma of lavender is suggested to have a sedative effect (Ueda & Ikeda 2007). Previous studies have shown effects of the perception of smell measured using functional near-infrared spectroscopy (fNIRS) on prefrontal lobe activities. However, the studies had limitations such as those of lengthy stimulation or incomplete removal of skin blood flow artefacts in fNIRS signals. In this study, to objectively evaluate the effects of aroma stimulation on prefrontal activity, we used fNIRS. Four healthy college students (2 men and 2 women) participated in the experiment. We used a block design approach with an aroma stimulation of 2 seconds and an interstimulus interval of 20 seconds. The aroma stimuli were Lilium japonicum, lavender, grapefruit, and the control was odorless air. The stimuli were presented in this order 8 times in each trial. We also examined another condition applying 30 seconds of stimulation and 30 seconds of interval, for comparison with previous studies. An fNIRS device with 22 channels (WOT-100, Hitachi medical Co.) was used to measure the subjects' prefrontal activity. We analyzed the fNIRS signals with the following steps: (1) Separate into brain function and systemic components based on a hemodynamic modality separation method (Yamada et al. 2012); (2) Eliminate long-term trend using a high-pass filter; and (3) Subtract the average during the stimulus presentation section for baseline correction. A difference in the responses of aroma stimuli and odorless air was observed only when the subjects underwent stimulations for 2 seconds. When the aroma stimuli were presented for 30 seconds, no differences between the stimuli and odorless air were found in any subject. However, large individual differences were observed, but no clear differences were seen in the responses of the three aroma stimuli. These results suggest that the perception of smell influences the hemodynamic responses of the prefrontal lobe. Furthermore, it indicates that a short duration of stimulation is effective when measuring the effect of aroma stimuli using fNIRS.

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Poster

768. Preclinical and Human Studies in Neurovascular Coupling Mechanisms

Location: Hall A

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Program #/Poster #: 768.03/P21

Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Title: Three dimensional imaging reveals exercise induced alteration of vascular morphology in the rat primary motor cortex

Authors: *M. E. STEVENSON[1], C. C. MILLER[1], A. S. NAZARIO[1], B. S. LARSON[1], Y. S. GREENBERG[1], H. A. OWEN[2], R. A. SWAIN[1];
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Abstract: Exercise is beneficial to brain health, and, historically, the advantageous effects of exercise on the brain have been attributed to neuronal plasticity. However, it has become clear that the brain vascular system also exhibits plasticity in response to exercise, and these changes contribute to the beneficial health outcomes exercise produces in the brain. Increased blood vessel density following exercise is well replicated in brain regions involved in movement, like the primary motor cortex. Still remaining ambiguous is the form of vascular plasticity that underlies these increases in blood vessel density. Specifically, is increased blood vessel density due to a permanent expansion of existing vessels or sprouting of new vessels (angiogenesis)? This experiment aimed to answer this question by employing vascular corrosion casting and scanning electron microscopy, methods not standardly used to characterize vascular plasticity following exercise. These methods provide a high-resolution, three-dimensional view of vessel architecture that cannot be obtained using traditional light microscopy. In this experiment, one group of rats engaged in five-weeks of voluntary wheel running while a second group remained sedentary. Animals were then euthanized and, during perfusions, a resin was infused into each animal's vascular system. Brains were removed and the surrounding tissue was macerated, leaving only the vascular corrosion cast, a replica of the brain vasculature. The primary motor cortex region on each vascular corrosion cast was imaged on the scanning electron microscope. For each animal, vessel diameters were measured and number of new vessel sprouts was counted. Preliminary data suggest rats that engaged in voluntary exercise had wider microvessels (vessels categorized as less than 20 μm in diameter) and more new capillary sprouts than sedentary controls. This indicates both the expansion of existing vessels and angiogenesis contribute to exercise-induced vessel remodeling.

Disclosures: **M.E. Stevenson:** None. **C.C. Miller:** None. **A.S. Nazario:** None. **B.S. Larson:** None. **Y.S. Greenberg:** None. **H.A. Owen:** None. **R.A. Swain:** None.

Poster

768. Preclinical and Human Studies in Neurovascular Coupling Mechanisms

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 768.04/P22

Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Support: F31NS106724
R01AR063772

Title: The contribution of cortical tachykinin receptor 1 inhibitory interneurons to neurovascular coupling

Authors: *C. F. RUFF[1], J. J. COUEY[1], B. M. HOOKS[1], A. L. VAZQUEZ[2], S. E. ROSS[1];
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Abstract: The brain lacks energy reserves and depends on the blood for a constant supply of oxygen and glucose. To meet energy demands, cerebral blood flow parallels changes in brain activity by a mechanism known as neurovascular coupling (NVC). Although NVC is critical to normal brain function and its dysfunction is reported in many neuropathologies, the underlying neural basis remains unclear. Here, we describe a tachykinin receptor 1 (Tacr1)-CreER knock-in mouse that selectively labels a subset of cortical inhibitory neurons that are ideally suited to regulate cerebral blood flow. Using this genetic tool, in combination with two photon imaging, electrophysiology, optogenetic techniques and in vivo laser Doppler flowmetry we explore the role of Tacr1 neurons in the regulation of cerebral blood flow. Our data suggests that Tacr1 cortical interneurons are a specific population of long-range projecting neurons that receive local excitatory input. Moreover, optogenetic activation of this distinct inhibitory population is sufficient for a local cerebral blood flow response. Together, these findings suggest that Tacr1 cortical inhibitory interneurons act as local integrators of neural activity to mediate NVC, providing important insight into this unique population of long-range projecting neurons and the circuitry of NVC.

Disclosures: C.F. Ruff: None. **J.J. Couey:** None. **B.M. Hooks:** None. **A.L. Vazquez:** None. **S.E. Ross:** None.

Poster

768. Preclinical and Human Studies in Neurovascular Coupling Mechanisms

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 768.05/P23

Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Title: Proinflammatory cytokine contributes to the effects of angiotensin II on neurovascular coupling

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Abstract: Angiotensin II (Ang II), a hormone involved in the development and maintenance of arterial hypertension, alters neurovascular coupling (NVC). NVC is the dynamic link between neuronal activity and local blood flow supply. NVC impairment induces cerebral homeostasis disruption and have been associated with increased susceptibility to strokes and

neurodegenerative diseases. We have recently demonstrated that Ang II induces brain inflammation. This inflammation can be induced by modulation of T cell activity involving an increase in the production of the proinflammatory cytokine IL-17A. Thus, our hypothesis states that IL-17A is involved in the induction of neurovascular decoupling by Ang II. NVC was tested by monitoring the cerebral blood flow (CBF) response to whiskers stimulation by laser-Doppler flowmetry in anesthetized C57BL/6J mice. Our results show a significant reduction in NVC in mice with chronic Ang II administration by osmotic pump (600 ng / kg / min, for 14 days) compared to the control group (14.4% and 18.6%, $p < 0.01$, $n = 10-12$). The depletion of IL-17A by intraperitoneal injections of a neutralizing antibody, anti IL-17A (0.5 μg / μL) normalizes NVC and demonstrates a response comparable to the values obtained for the control groups (17.6% and 18.6%, $n = 10-12$). Treatment with the IL-17A antibody also reduces Ang II induced oxidative stress in the hippocampus ($p <0.05$, $n = 7-12$) and the somatosensory cortex ($p < 0.05$, $n = 7-12$). Finally, the effects of IL-17A depletion on NVC is accompanied by a partial prevention of about 10 mm Hg of the increase in systolic blood pressure in mice receiving Ang II ($p <0.05$ at day 7 and $p <0.001$ at day 14, $n = 12-20$). These results suggest that IL-17A plays a crucial role in the effects of Ang II on NVC. Therefore, therapy using antibody against IL-17A could prevent cerebrovascular dysfunction in hypertensives patients and reduce the incidence of strokes and neurodegenerative diseases associated with high blood pressure.

Disclosures: J. Youwakim: None. **D. Vallerand:** None. **H. Girouard:** None.

Poster

768. Preclinical and Human Studies in Neurovascular Coupling Mechanisms

Location: Hall A

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Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

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Foundation Leducq, reference no. 16 CVD 05.

Title: Acute brain-wide pericyte ablation leads to rapid neurovascular uncoupling

Authors: *K. KISLER, A. M. NIKOLAKOPOULOU, M. D. SWEENEY, Z. ZHAO, B. V. ZLOKOVIC;
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Abstract: Pericytes are perivascular mural cells that grow along capillaries. Pericytes help maintain blood brain barrier integrity at the capillary level and play a role in neurovascular coupling (NVC), the regulation of cerebral blood flow (CBF) to match the demands of neuronal functional activity. We have previously shown that congenital loss of pericytes driven by genetic knockout of one copy of PDGFRβ resulted in dysregulation of NVC. However, in this model it remains unclear what the developmental impact of embryonic loss of PDGFRβ signaling may be on the vascular phenotype in the adult brain. To address this, we generated an inducible pericyte-specific Cre line employing a double promoter strategy using both *Pdgfrb* and *Cspg4* promoters, which are genes enriched in pericytes relative to other brain cell types. The resulting pericyte-specific Cre line was crossed to mice carrying Cre-dependent human diphtheria toxin receptor (iDTR). Diphtheria toxin (DT)-induced pericyte ablation in adult mice led to rapid reduction in stimulus-induced CBF response measured with laser Doppler flowmetry and intrinsic optical signal imaging, suggesting defects in NVC. Voltage sensitive dye imaging indicated no neuronal deficit at the time of NVC failure, implicating pericyte dysfunction and loss driving changes to NVC. This has implications in neurodegenerative disorders where pericyte loss and CBF changes are observed such as Alzheimer's disease and stroke.

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Poster

768. Preclinical and Human Studies in Neurovascular Coupling Mechanisms

Location: Hall A

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Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Support: NIH Grant K99AG058780
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Title: Pericyte contractility by optogenetics regulates capillary diameter and blood flow

Authors: *A. R. NELSON, M. A. SAGARE, Y. WANG, K. KISLER, Z. ZHAO, B. V. ZLOKOVIC;
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Abstract: Pericytes are vascular mural cells that wrap around capillaries and are essential for blood-brain barrier formation and maintenance, and perform multiple functions at the neurovascular unit including regulation of **a)** BBB permeability and bulk flow fluid transcytosis, **b)** capillary diameter, **c)** cerebral blood flow (CBF) velocity, **d)** angiogenesis, subsequent microvascular stability and network architecture, **e)** clearance of toxic metabolites from the CNS,

f) pro-inflammatory responses, and **g)** multipotent stem cell activity. However, whether or not pericytes are contractile cells has been a continuous debate dating back to 1873 when Rouget first described them. Here, we test the hypothesis that capillary level pericytes are contractile cells, and that their contractility is altered by amyloid-beta. We used a novel pericyte-specific Cre mouse using a double-promoter approach with both the *Pdgfrβ* and *Cspg4* promoters, and crossed to a Cre-dependent channelrhodopsin (ChR2) mouse with a YFP reporter gene, termed *Pericyte-ChR2*, or crossed to a Cre-dependent archaerhodopsin (ArchT) mouse with a YPF reporter gene, termed *Pericyte-ArchT*. Furthermore, we are testing the impact of amyloid-beta on pericyte contractility. First, we confirmed that ChR2 and ArchT are only expressed in pericytes by performing immunofluorescent staining with anti-CD13 antibody and which colocalized with the YFP reporter gene. Using the *Pericyte-ChR2* mice, we performed optogenetics experiments *in vivo* and found that stimulation of ChR2 caused pericytes to contract, the underlying capillary to constrict and restricted blood flow. Using *Pericyte-ArchT* mice, we performed optogenetics experiments *in vivo* and measured changes to pericyte contractility and underlying capillary diameter, and are assessing whether amyloid-beta alters contractility. Pericytes are contractile cells. Discovering the functional role of pericytes will have important implications for pathological conditions and neurodegenerative diseases in which pericytes degenerate including Alzheimer's disease, amyotrophic lateral sclerosis, Parkinson's disease and Huntington's disease.

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Poster

768. Preclinical and Human Studies in Neurovascular Coupling Mechanisms

Location: Hall A

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Program #/Poster #: 768.08/P26

Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Support: NIH NINDS R35 NS097265
HHMI

Title: Toward the whole murine brain angiome

Authors: *X. JI[1], T. A. FERREIRA[2], B. FRIEDMAN[1], H. LIECHTY[1], E. BAS[2,3], J. V. CHANDRASHEKAR[2], D. KLEINFELD[1];
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Abstract: The brain vascular network provides a stable supply of energy and oxygen to support neural activity. To quantify and understand the network through which blood flows, we prepared

whole brains from 2 month old mice in which every vessel lumen was filled with a cross-linked fluorescent gel (Tsai et al, J Neurosci 2009) and imaged with block-face serial two photon microscopy at 0.3 x 0.3 x 1.0 μm^3 voxel resolution (Economo et al, Elife 2016). We implemented a computational pipeline to reconstruct the vascular network and, further, extracted the graphical representation of the network. The reconstruction contains more than 300 meters of interconnected vessel segments. Preliminary analysis suggests that the microvasculature is fully interconnected across the entire brain, i.e., the dominant cluster of the connectivity matrix contains at least 96 % of all microvessels. Interestingly, the density of the microvasculature varies across different regions of the brain, with a mean volume fraction of 0.011 but a range of 0.005 to 0.016 for 95 % of the sample. In agreement with past data on microvasculature in parietal neocortex (Blinder, Tsai et al, Nat Neuro 2013), some topological and geometrical features of the microvascular network across all parts of the brain are rather uniform, i.e., 97% ± 3 % of the nodes are of degree 3, the median number of microvessels that comprise the shortest loops is 8.8 ± 1.5 (mean ± SD), and the median tortuosity of the microvessels, i.e., the ratio of actual length to end-to-end length, is 1.25 ± 0.07. We are working on precise vectorization of the entire brain vascular network with combined experimental and computational approaches.

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Poster

768. Preclinical and Human Studies in Neurovascular Coupling Mechanisms

Location: Hall A

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Program #/Poster #: 768.09/P27

Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Support: IBS-R015-D1
NRF-2014H1A2A1020612
NRF-2017R1A2B4009350
NRF-2018H1A2A1062942

Title: Real-time *in vivo* two-photon imaging study reveals alterations in capillary blood flow and blood-brain barrier permeability in the post-ictal state

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Abstract: Epilepsy is characterized by recurrent seizures that involve the most dramatic neuronal activation. It has long been known that, following the termination of a seizure, individuals often experience an extended period of behavioral abnormalities from hours to days, such as sensory, cognitive, or motor dysfunction according to brain regions that are affected by the seizure. Recently, it has been suggested that the negative consequences of seizure can be attributed to prolonged hypoxic condition during the post-ictal state which accompanies pathological hypoperfusion. In this realm, hypoperfusion in the post-ictal state could impair proper local network functions, i.e., brain tissue oxygen levels are not normally maintained. Recent studies suggested that the post-ictal hypoxia is mediated by the hypoperfusion due to vasoconstriction and that a structural disruption of neurovascular units during seizure events could affect blood flow regulation. However, a detailed examination of cerebrovascular system has not been carried out yet to clarify what causes the post-ictal hypoperfusion. In this study, we conducted real-time *in vivo* two-photon microscopic imaging with an injection of fluorescence-conjugated dextran for a detailed investigation of functional and structural cerebrovascular changes during the post-ictal state. Acute mouse seizure model induced by a 4-aminopyridine (4-AP) injection was used as we could designate the seizure focus in the experimental setting, mimicking focal seizures in human brain. Around the seizure focus after the cessation of recurrent seizures, resting blood flow was measured by red blood cell (RBC) velocity, and structural changes were assessed by vessel diameter and blood-brain barrier (BBB) function. Our results show changes in the mean RBC flow in capillary beds and BBB permeability, depending on the severity of seizures that were induced. Therefore, epilepsy is not solely a neurological disorder that disrupts neuronal network, but also can result in long-lasting consequences of vascular dynamics and function. Our study can provide insights to better understand the underlying mechanisms of the post-ictal state brain malfunctions and evidence for a potential therapeutic target.

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Poster

768. Preclinical and Human Studies in Neurovascular Coupling Mechanisms

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 768.10/P28

Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Title: Two photon imaging dramatically affects brain temperature blood flow and oxygenation

Authors: *M. ROCHE[1], E. CHAIGNEAU[3], R. RUNGTA[1], D. F. BOIDO[2], B. WEBER[4], S. CHARPAK[5];
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Abstract: Two-photon phosphorescence lifetime microscopy is the new emerging technique for high-resolution measurements of oxygen partial pressure in vessels and tissue of brain and other organs. However, previous studies (including ours: Parpaleix et al. 2013, Lyons et al. 2016) have disregarded that imaging through a cranial window lowers brain temperature, an effect known to change neuronal excitability and susceptible to affect cerebral blood flow, the properties of the oxygen sensors and thus brain PO2. Here, we investigated the relationship between temperature, blood flow parameters and oxygenation in the olfactory bulb of awake and anesthetized mice. We first show that in awake mice chronically implanted with a thermal sensor below the glass window, or a thinned-skull surface, the postsurgical decrease of brain temperature takes several days to recovers. In both animal preparations, imaging with a water immersion objective at room temperature decreases brain temperature by ~ 2-3°C, causing resting capillary blood flow and Po2, hemoglobin saturation and tissue Po2 to drop. These adverse effects are corrected by heating the immersion objective or avoided by imaging through a dry air objective, allowing the establishment of truly physiological values of brain oxygenation in awake mice.

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Poster

768. Preclinical and Human Studies in Neurovascular Coupling Mechanisms

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Program #/Poster #: 768.11/P29

Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Support: Grant-in-Aid for Scientific Research (KAKENHI) 16K10716

Title: Improvement of vasoactive dysfunction on rat cerebral penetrating arterioles in early vascular injury after subarachnoid hemorrhage

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Abstract: Early brain injury (EBI) after rupture of rupture inducing subarachnoid hemorrhage (SAH) represents one of the most important contributors to poor outcome in patients with SAH. EBI is characterized by a severe reduction in cerebral blood flow suggesting alterations on the level of cerebral small vessels. The early vascular injury in small vessels after SAH demonstrated a rapid change in structure, however, vasoactive dysfunction via potassium

channels is unclear. This study was therefore conducted to clarify whether SAH induced immediate potassium channels dysfunction in rat experimental SAH model, and free radical scavenger restored potassium channels dysfunction. The institutional animal ethics committee in Shinshu University School of Medicine approved all experimental protocols for this study. In this study, SAH was induced using a blood injection method into the cisterna magna of male rat, and saline injection models were also made. Sham surgery rats as control received the same surgical procedures except for the injection. Rats were sacrificed at 1 hour after SAH, saline injection and sham surgery. The penetrating arterioles from the middle cerebral artery were isolated, cannulated and pressurized. Vessel diameters were recorded by computer-aided videomicroscopy. After development of vascular tone, to investigate the ATP-sensitive potassium channels function, the activator pinacidil was applied with or without free radical scavenger. The penetrating arterioles from SAH models developed significantly more tone compared with the arterioles from sham. The ATP-sensitive potassium channels activator significantly dilated the penetrating arterioles from sham surgery rats. The vasodilatory responses to the activator were attenuated in SAH rats but not saline injection and sham surgery rats. Free radical scavenger-treated arteriolar dilatory response to ATP-sensitive potassium channels activator was partially restored compared with non-treated arteriolar response. In conclusion, ATP-sensitive potassium channels may inactivate immediately after SAH, and the dysfunction may be induced by free radical due to acute increased intracranial pressure. These results provide a background to understand the early vascular injury after SAH.

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Poster

768. Preclinical and Human Studies in Neurovascular Coupling Mechanisms

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 768.12/P30

Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Support: EMBO

Title: Spatial-temporal dynamics of functional hyperemia and mural cell calcium signals from the synapse to the pia

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Abstract: Objectives: Functional hyperemia, a regional increase of blood flow triggered by local neural activation, is used to map brain activity in health and disease. Despite its vast importance for functional imaging, the spatial-temporal dynamics of functional hyperemia, as well as its site of initiation remain unclear. Furthermore, the dynamics of mural cell (pericyte and

smooth muscle cell) Ca^{2+} signals in different vascular compartments remain elusive. **Methods:** *In vivo* two-photon calcium imaging of neuron, oligodendrocyte precursor cell, pericyte and smooth muscle cell responses to sensory stimulation in combination with vessel diameter and red blood cell velocity measurements in NG2-creERT2;GCaMP6f mice (both anesthetised and awake). First, by exploiting the unique neural-vascular anatomy of the olfactory bulb we are able to map out these responses along the entire vascular arbour, from juxta-synaptic capillaries back to the upstream pia. Second, these dynamics are investigated in the primary somatosensory cortex. **Results:** In the olfactory bulb, we first show that activation of oligodendrocyte precursor cells is a reliable marker of synaptic input and precedes (by ~300 ms) a synchronous Ca^{2+} drop in upstream pericytes and smooth muscle cells enwrapping the vessels that feed the activated synapses. Despite this simultaneous activation of mural cells, the resulting hemodynamics varied dramatically but precisely in terms of timing, amplitude and direction according to the vascular compartment. The most rapid dilation occurs with indistinguishable onset at the parenchymal arteriole and proximal first-order capillary and is paradoxically associated with a local decrease or delayed increase in blood velocity. In contrast, a slower dilation associated with a rapid velocity increase occurs in the upstream pial arteriole and downstream capillaries. Proportionally, the largest velocity increase occurs in juxta-synaptic capillaries. Interesting similarities and differences in these OB dynamics were observed in the somatosensory cortex. **Conclusions:** These results establish the precise temporal and spatial dynamics of blood volume and velocity changes essential for the interpretation of blood flow based imaging techniques such as BOLD-fMRI.

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Poster

768. Preclinical and Human Studies in Neurovascular Coupling Mechanisms

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Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

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DP3DK108248
R01EY029121
R01EY028304
R01HL064774
T32EY25202

Title: Real time visualization of vascular remodeling in ischemic stroke using visible light optical coherence tomography

Authors: *N. A. NADKARNI[1], L. BECKMANN[2], A. BATRA[1], D. P. SULLIVAN[3], W. A. MULLER[3], X. ZHANG[2], H. ZHANG[2];
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Abstract: Background: Stroke is a leading cause of death in the USA. Angiogenesis, the formation of new capillaries from blood vessels, is a key area of interest in neurorehabilitation. The ability to track microvascular remodeling after stroke *in vivo* is necessary to better understand future therapeutic targets. We have pioneered a system using visible-light optical coherence tomography (vis-OCT), a 3-dimensional anatomical and functional imaging modality with microscopic resolution, integrated with chronic cranial window-embedded microprism to visualize vessels 1mm in depth from the cortical surface *in vivo* for up to 60 days after ischemic stroke. Methods: A Vis-OCT microscope system for brain imaging was developed using a supercontinuum laser with a center wavelength of 560nm and bandwidth of 100nm as the light source. We created cranial windows by attaching a 1-mm right angle aluminum coated microprisms to two concentric coverslips of different diameter. Six wild-type C57Bl/6 mice around 3 months age underwent craniotomy, durotomy, and subsequent insertion of the cranial window apparatus with ultimate adhesive seal. After 15 days for healing, a mouse underwent a transient middle cerebral artery occlusion (tMCAO) for 60 minutes to recreate the ischemic penumbra. Results: The microprism provided a deep view with an additional 1000µm×750µmx250µm cortical volume in addition to standard 250 µm surface view without microprism. After microprism insertion, bleeding was observed on Vis-OCT on day 2 and day 3 but almost completely resorbed by day 7 with no evidence of blood on day 15. By day 60, the window and glue were stable with consistent image quality in optical microscopy. There were no behavioral deficits noted as a result of the microprism surgery. After tMCAO, severe reduction of capillary density was noted in the deep view image on day 1 with minimal capillary density change at the surface view. On day 30 and day 60, vessel diameters were smaller in both views than at the acute stage with a robust increase of vessel density in the deep view. Conclusions: Vis-OCT, in combination with a chronic cranial window embedded-microprism, is a novel modality to longitudinally study *in vivo* vessel changes as a consequence of stroke. Further investigations will focus on better understanding these changes to inform us to new outcome measures for patients with stroke.

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Poster

768. Preclinical and Human Studies in Neurovascular Coupling Mechanisms

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Program #/Poster #: 768.14/P32

Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Support: NIH Grant F31

Title: Neurovascular coupling in the diabetic brain

Authors: *A. R. NIPPERT, P.-P. CHIANG, E. A. NEWMAN;
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Abstract: Diabetes mellitus is associated with vascular pathologies in the periphery and central nervous systems. Decreases in cognitive function have been described in patients with both type 1 and type 2 diabetes. These declines in cognitive function may be due to vascular dysfunction in the brain. Studies in the retina, which is damaged by diabetic retinopathy, demonstrate that functional changes in the vasculature occur before structural damage or overt cellular pathology. Specifically, there is a decrease in neurovascular coupling, the active dilation of vessels in response to increased neuronal activity. While some evidence exists suggesting reduced vessel responses in the brain in diabetes, it is unknown how neurovascular coupling is altered. In this study, simultaneous measurements of neuronal activity and blood flow were taken longitudinally from mice before and after the induction of diabetes with streptozotocin, a within subject design. Due to sex differences in diabetes induction, results are from male mice only. Using a cranial window implanted over the whisker barrel cortex with an implanted electrode, blood flow and neuronal activity were simultaneously measured, with laser Doppler flowmetry and local field potential recordings, respectively. Whisker stimulation with an air puff elicited changes in blood flow and neuronal activity. All measurements were taken from awake, head-fixed mice over a two month period, including a two week period prior to induction of diabetes. Results indicate a reduction in neurovascular coupling after induction of diabetes. A decrease in neurovascular coupling occurred immediately after induction of diabetes and continued to decline over the next two months. Future experiments will examine how acute hyperglycemia alters neurovascular coupling and if the decline in neurovascular coupling seen in diabetes can be reversed with the iNOS inhibitor aminoguanidine, which reverses the loss of neurovascular coupling in the retina.

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Poster

768. Preclinical and Human Studies in Neurovascular Coupling Mechanisms

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

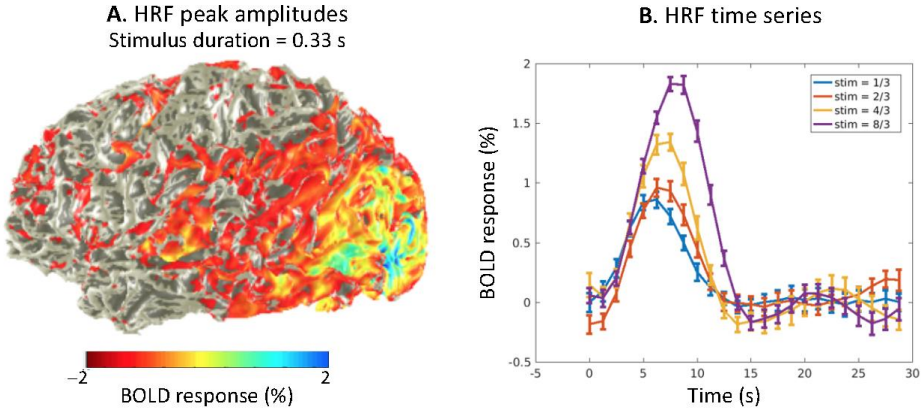
Program #/Poster #: 768.15/P33

Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Title: Exploring the non-linearity of the BOLD response through varied stimulus timing

Authors: *K. B. XI, X. ZOU, J. KIM, D. RESS;
Neurosci., Baylor Col. of Med., Houston, TX

Abstract: Introduction: Functional magnetic imaging (fMRI) is based on the hemodynamic response function (HRF) elicited by a brief (2—4 s) period of neural activation, the stereotypical blood oxygen level dependent (BOLD) response that depends on competition between cerebral blood flow (CBF) and oxygen consumption. The shift-invariant linearity of the BOLD HRF is a critical feature of fMRI. However, for briefer stimuli (<2 s), the HRF exhibits non-linearity that is poorly understood. We measured HRF and CBF responses with high spatiotemporal resolution using BOLD fMRI and arterial spin labeling (ASL), respectively, with variable stimulus durations. We will fit measured HRF and CBF with BOLD models to investigate the non-linearity. **Methods**: A speeded audiovisual sequence-detection task was used to evoke strong HRFs over a large portion of cerebral cortex. On each run, stimulus duration was fixed at one value in the range of 0.33, 0.67, 1.33, or 2.67 s, in a slow event-related design with a 30-s inter-stimulus interval and 12 stimuli/run. HRFs were measured using a SMS-accelerated acquisition that covered the whole brain with 2-mm cubic voxels and TR = 1.25 s on a 3T scanner. Initial analysis was carried out in early visual areas discerned using population receptive field mapping methods applied to separate imaging sessions. **Results**: Strong HRFs were evoked across most of visual cortex by all stimulus durations (Fig **A**). Example HRFs from primary visual cortex (Fig **B**) show the strong non-linearity of the HRFs. In particular, peak amplitude has a sub-linear dependence on stimulus duration, while time-to-peak increases monotonically in a complex fashion. Processing of CBF measurements and BOLD modeling are in progress. **Discussion**: Our variable-duration stimulation approach permits the investigation of BOLD non-linearity in many brain regions. Evoked HRFs show clear non-linearity, which we expect to be the consequence of weak transmural oxygen transport competing with more effective longitudinal oxygen transport by blood flow, as indicated by our previous modeling work (Kim & Ress, 2016).



Disclosures: **K.B. Xi:** None. **X. Zou:** None. **D. Ress:** None. **J. Kim:** None.

Poster

768. Preclinical and Human Studies in Neurovascular Coupling Mechanisms

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 768.16/P34

Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Support: R01AG033106
R01HL102457

Title: Impact of common carotid artery compliance on cerebrovascular resistance in amnestic mild cognitive impairment

Authors: ***C. CHILES**, T. TOMOTO, J. SUGAWARA, B. CURTIS, E. PASHA, R. ZHANG; Insitute For Exercise and Envrn. Med., Dallas, TX

Abstract: Objective: Increased cerebrovascular resistance (CVR) associated with brain hypoperfusion is a potential risk factor for the progression of Alzheimer's disease (AD). However, the underlying pathophysiological mechanisms are unknown. Increased arterial stiffness augments cerebral blood flow (CBF) fluctuations which may cause cerebrovascular damage and a subsequent increase in CVR. However, the relation between arterial stiffness and CVR is unclear. This study investigated the correlation between arterial stiffness and CVR for patients with amnestic MCI (aMCI), a prodromal stage of AD.
Methods: Fifty-four amnestic aMCI patients and twenty-four cognitively normal (NC) subjects underwent measurements of CVR and arterial compliance, an inverse index of arterial stiffness. CVR was calculated as the ratio of mean arterial pressure measured via applanation tonometry to total CBF. Total CBF was calculated from CBF velocities and diameters at the bilateral internal carotid and vertebral arteries using Duplex ultrasonography. Arterial compliance at the common

carotid artery was calculated as the ratio of carotid pulse pressure to the vessel diameter changes. **Results:** Compared to the NC, total CBF was lower (MCI = 585 ± 66, NC = 636 ± 66 ml/min) and CVR higher (MCI = 0.156 ± 0.023, NC = 0.143 ± 0.019 mmHg/ml/min, P = 0.015) in aMCI. Arterial compliance (MCI = 8.57 ± 2.10, NC = 9.27 ± 1.64 mm^2/mmHg*100, P = 0.151) was not different between groups. Decreased arterial compliance was correlated with higher CVR in aMCI (R = -0.505, P < .001) but not in NC (R = -0.321, P = 0.126). When controlling for age, sex, and BMI, the correlation maintained in aMCI (R = -0.431, P = 0.002) but not in NC (R = -0.204, P = 0.377).
Conclusions: Patients with aMCI had a higher CVR and lower CBF when compared to cognitively normal adults. Additionally, higher arterial stiffness was associated with higher CVR in aMCI. These results suggest arterial stiffening may contribute to the increased CVR in patients with aMCI.

Disclosures: C. Chiles: None. **T. Tomoto:** None. **J. Sugawara:** None. **B. Curtis:** None. **E. Pasha:** None. **R. Zhang:** None.

Poster

768. Preclinical and Human Studies in Neurovascular Coupling Mechanisms

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 768.17/P35

Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Title: Simultaneous 2-color imaging of vascular and neural activity using 2-photon microscopy

Authors: *E. M. KLEIN, C. I. MOORE;
Neurosci., Brown Univ., Providence, RI

Abstract: Cerebral blood vessels (CBVs) form a dense and interconnected network that exists in close proximity to neurons. Dynamics across neurovascular networks are functionally interconnected, most notably, as increases in neural activity predict local vascular dilations. The reciprocal impact of vascular dynamics on neurons is, however, a largely under-explored question. To explore cellular activity dynamics between these networks, we have developed a strategy for 2-color calcium imaging of CBV endothelial cells and neurons. Head-bars, and cortical imaging windows were implanted in adult mice (*N*=5 Tie2:CaMP6f, and *N*=5 WT). To explore Ca^{2+} dynamics in primary somatosensory cortex CBVs, we imaged Tie2:GCaMP6f mice using 2-photon microscopy. Imaging of CBV Ca^{2+} activity was tested in pial arteries and supragranular vessels. Vascular dilation and constriction was recorded from these vessels. To observe the cellular activity of CBVs and of perivascular neurons, *N*=3 Tie2:GCaMP6f mice were injected with adeno-associated virus transducing jRGECO1a under control of the hSyn promoter. Tie2:GCaMP6f/hSyn-jRGECO1a mice were imaged during and between tactile vibrissa stimulation to compare spontaneous and functional hyperemia epochs of neurovascular

activity. Imaging data was preprocessed to cancel motion and noise. Vessel walls were traced in images when possible - to record dilation and constriction. Fluorescence data were segmented into spatiotemporal components using constrained non-negative matrix factorization (Pnevmatikakis et al., 2016, Giovannucci et al.,2019) and deconvolved to infer Ca^{2+} transients. Analysis of the data indicates that Ca^{2+} activity in CBVs can be segregated into distinct spatiotemporal components. Transients in these components occurs both during and in absence of vessel motion. Cross correlation and event triggered averages revealed lead-lag relationships where neural activity is synchronized to, leads or lags vascular activity. Ca^{2+} transients occurring during bouts of vascular constriction or dilation indicate that endothelial Ca^{2+} is an important signaling pathway for cerebrovascular regulation. The manifestation of multiple lead-lag temporal dynamics between vascular and neural activity suggests a bi-directional, rather than exclusively feed-forward relationship between perivascular neural, and cerebrovascular activity. These data are consistent with prior and ongoing studies being conducted in our lab in parallel with the imaging described here, in which optogenetic stimulation of vascular elements has been associated with changes in local neural activity.

Disclosures: E.M. Klein: None. **C.I. Moore:** None.

Poster

768. Preclinical and Human Studies in Neurovascular Coupling Mechanisms

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 768.18/P36

Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

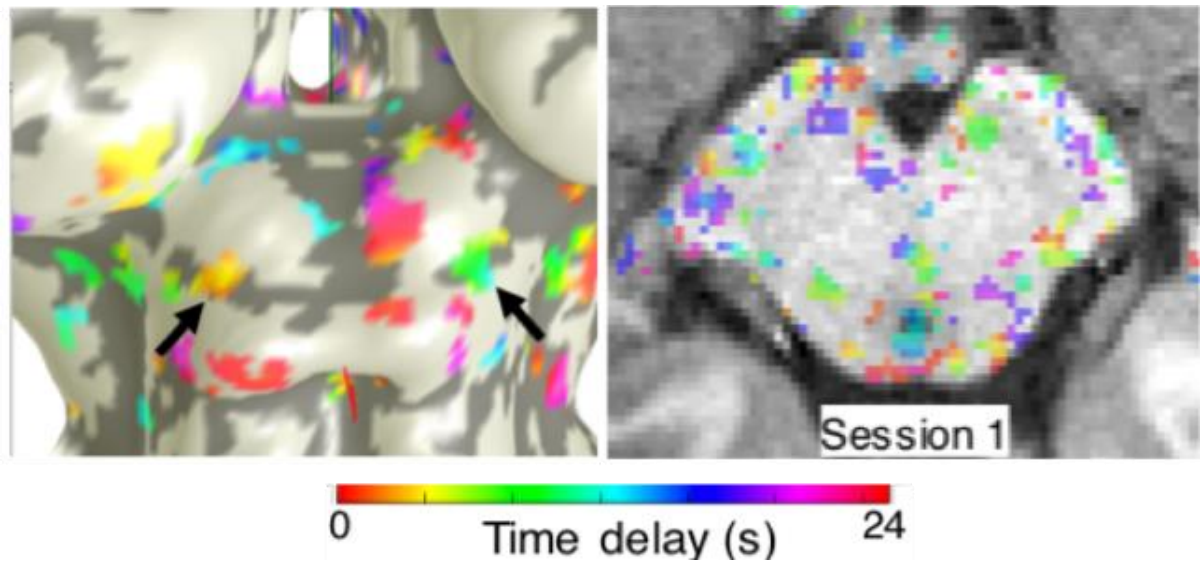
Support: NIH R01 EB027586

Title: Somatosensory responses in the deep layers of superior colliculus

Authors: *A. QURESHI[1], R. GOEL[1], J. KIM[1], N. M. DE LA ROSA-RIVERA[2], M. HIMMELBACH[3], G. HAGBERG[4], K. SCHEFFLER[5], D. RESS[1];
[1]Neurosci., Baylor Col. of Med., Houston, TX; [2]Univ. of Massachusetts Amherst, Amherst, MA; [3]Hertie-Institute For Clin. Brain Res., Tuebingen, Germany; [4]Biomed. Magnetic Resonance, University Hospital Tübingen, Germany; [5]Univ. of Tuebingen, Tuebingen, Germany

Abstract: Introduction: Neurons in the deep layers of superior colliculus (SC) respond during somatosensory input, so we expected that deep-layer responses would be evoked by a somatovisual integration task. Based on animal experiments, we also expected the deep-layer activation to correspond to the retinotopic position of the hands for the subject. Methods: Visual stimuli were 4 square grids of red and green dots, with patterns changing every 0.5 s. Usually, the dot patterns were random. Each grid was 3° on a side, and offset 2.5° in both x and y from fixation. Subjects fixated on a central dot, and were cued to attend to the left or right pair of grids

by tactile stimulation with a train of air puffs delivered alternately to the index and ring fingers of the current hand. Every few seconds, subjects (N = 2) were cued to attend either the upper or lower grid in the current hemifield by a double air puff to one of the two fingers. After a variable delay, the dot pattern took on either a x or + shape. Only occurrences of the rarer + shape were counted by the subject, and reported at the end of each run. The left-right alternation occurred every 30 s and repeated 8 times in each 4-min run. During each run, fMRI data was collected on a 3T scanner using a dual-echo spiral sequence (1.4-mm voxels) on 13 quasi-axial slices that covered SC. Results: We observed two regions of significant responses (Figure attached). Early responses (~3-s lag with respect to right stimulation onset) on the left SC, and later responses (~18-s lag) on the right SC. They are located near the caudo-lateral edges of both SCs. Activations extend ~5 mm within SC, but also include more superficial responses in the same region. Discussion: The somatovisual integration task successfully evoked strong lateralized responses that included the deep layers of SC. The results confirm the expected retinotopic organization of deep layer neuronal responses for hand stimulation: strongly caudal because hand position is at high eccentricity, and at the lateral margins of SC because of their position in the lower visual field. Future experiments are planned at 9.4T to extend these results.



Disclosures: **A. Qureshi:** None. **R. Goel:** None. **J. Kim:** None. **N.M. De La Rosa-Rivera:** None. **M. Himmelbach:** None. **G. Hagberg:** None. **K. Scheffler:** None. **D. Ress:** None.

Poster

768. Preclinical and Human Studies in Neurovascular Coupling Mechanisms

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 768.19/P37

Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Support: PP-1709-29160 (NMSS)
RG150704951 (NMSS)
R01AG 029523 (NIH)

Title: Neural-vascular uncoupling in the hippocampus of multiple sclerosis patients: Could it explain multiple sclerosis-related memory deficits?

Authors: *B. P. RYPMA[1], **D. SIVAKOLUNDU**[4], K. WEST[2], M. D. ZUPPICHINI[3], G. BATCHALLI MARUTHY[5], D. H. ABDELKARIM[6], M. P. TURNER[6], Y. ZHAO[1], R. ROMERO[5], S. RAO[5], D. OKUDA[7];
[1]Univ. of Texas At Dallas, Richardson, TX; [2]Ctr. for BrainHealth, [3]Zuppichini, Univ. of Texas At Dallas, Dallas, TX; [4]Dept. of Biol. Sci., Univ. of Texas at Dallas, Dallas, TX; [5]Univ. of Texas at Dallas, Richardson, TX; [6]Sch. of Behavioral and Brain Sci., Univ. of Texas at Dallas, Dallas, TX; [7]Univ. of Texas Southwestern Med. Ctr., Dallas, TX

Abstract: Introduction:
Cognitive impairment occurs in about 70% of Multiple Sclerosis (MS) patients. Neural-vascular uncoupling, sub-optimal blood flow increases following neural activity have been postulated to explain cognitive impairment in MS. Effective coupling requires coordinated and optimal functioning of the neural, glial, and the vascular system.
Objective:
We sought to assess the integrity of the neural-vascular coupling system in the hippocampus of MS patients. We hypothesized that neural-vascular uncoupling in the hippocampus contributes to memory deficits in MS.
Methods:
We conducted a single-blind case-control study comparing MS patients and healthy controls (HC). We studied neural-vascular coupling under basal and constricted vascular tone using caffeine as a vasoconstrictor. Each participant underwent 2 calibrated fMRI sessions following caffeine and placebo administration. MRI scans were performed on a Philips 3T MRI. A dual-echo MRI sequence permitted measurements of cerebral blood flow (CBF) and blood-oxygen level dependent signal (BOLD). During each session, participants performed two scans. In one scan, participants periodically inhaled room-air and a hypercapnic gas mixture for calculation of cerebral metabolic rate of oxygen ($CMRO_2$). In a second scan, participants learned face-name pairs, while judging whether or not the face and name fit together well or poorly. We calculated task-evoked changes in BOLD, CBF and $CMRO_2$ in the hippocampus following caffeine and placebo intake. The effect of caffeine on the task-evoked changes in BOLD, CBF and $CMRO_2$ was studied by comparing the changes following placebo administration.
Results:
Following caffeine intake, MS patients had significantly lower task-evoked BOLD, CBF and $CMRO_2$ compared to healthy controls in the hippocampus. Neural-vascular coupling ratio was calculated as the ratio of task-evoked CBF to $CMRO_2$. Neural-vascular coupling ratio was significantly lower in the hippocampus of MS patients compared to healthy controls, following caffeine administration.
Conclusion:

Our results suggest that there is neural-vascular uncoupling in the hippocampus of MS patients. Such uncoupling differences becomes more apparent under constricted vascular tone (i.e., following caffeine intake). This result suggests that underlying glial-vascular dysfunction might contribute to neural-vascular uncoupling in the hippocampus and would have implications for cognitive performance in MS.

Disclosures: B.P. Rypma: None. **D. Sivakolundu:** None. **K. West:** None. **M.D. Zuppichini:** None. **G. Batchalli Maruthy:** None. **D.H. Abdelkarim:** None. **M.P. Turner:** None. **Y. Zhao:** None. **R. Romero:** None. **S. Rao:** None. **D. Okuda:** F. Consulting Fees (e.g., advisory boards); received lecture fees from Acorda, Genzyme, and TEVA Neuroscience, consulting, advisory board fees from EMD Serono, Genentech, Genzyme, Novartis, TEVA Neuroscience, and research support from Biogen.

Poster

768. Preclinical and Human Studies in Neurovascular Coupling Mechanisms

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 768.20/P38

Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Support: NIH Grant NS080675
NSF Grant DGE-1745038
NIH Grant MH106253

Title: Traveling waves coordinate brain-wide activity in awake, adult humans

Authors: *R. V. RAUT, A. MITRA, A. Z. SNYDER, M. E. RAICHLE;
Washington Univ. In St. Louis, St Louis, MO

Abstract: Brain function requires communication among functional units at a range of spatial scales. At the macroscale, function is organized into anatomically distributed systems, such as the cortico-subcortical components of the motor and visual systems. It is presently unclear how the activity of such large-scale systems is coordinated. Increasingly slow fluctuations in excitability synchronize neural populations of increasing spatial scale. Thus, infra-slow activity (<0.1 Hz) as measured using resting-state functional magnetic resonance imaging (rsfMRI) signals may shed light on brain-wide coordination. In particular, the global fMRI signal, computed as the mean signal across the brain, is positively correlated across the entire brain; however, this global information is typically discarded to reduce artifact and increase spatial specificity. Here, using a cohort of 1,100 healthy adult humans, we show that latency patterns of the rsfMRI global signal demonstrate the presence of traveling waves within cortex, striatum, thalamus, and cerebellum. In cortex, propagation is topographically organized and results in a temporal sequence of large-scale functional networks that begins with the somatomotor-sensory

system and ends with the distributed regions of the default mode network. Importantly, we find that this network sequence is largely recapitulated separately within the striatum, thalamus, and the cerebellum. We show that the spatial arrangement of functional networks in relation to the motor system, which is roughly consistent within each of these structures, enables such network sequences to arise from traveling waves. Finally, we demonstrate that activity within each functional system begins in the cortex and subsequently appears in the striatum, thalamus, and finally, the cerebellum. Findings were highly consistent across sub-samples of the studied cohort. The observed patterns suggest that infra-slow activity may propagate via cortico-subcortical loops. Moreover, previously demonstrated arousal state-dependence of the global signal suggests that these waves may reflect the widespread broadcasting of motor state. In sum, spontaneous, low-frequency, cortically- and subcortically-organized traveling waves may provide a scaffolding for the ongoing coordination of brain-wide activity.

Disclosures: R.V. Raut: None. **A. Mitra:** None. **A.Z. Snyder:** None. **M.E. Raichle:** None.

Poster

768. Preclinical and Human Studies in Neurovascular Coupling Mechanisms

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 768.21/P39

Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Title: Using the cross-wavelet transform to measure functional connectivity in BOLD fMRI reveals frequency-specific effects of anesthesia in mice

Authors: *G. DESROSIERS-GRÉGOIRE[1], G. A. DEVENYI[4,2], J. GRANDJEAN[5,6], M. CHAKRAVARTY[4,1,2,3];
[1]Integrated Program in Neurosci., [2]Dept. of Psychiatry, [3]Biol. & Biomed. Engin., McGill Univ., Montreal, QC, Canada; [4]Cerebral Imaging Ctr., Douglas Mental Hlth. Univ. Inst., Montreal, QC, Canada; [5]Dept. of Radiology and Nuclear Med. & Donders Inst. for Brain, Cognition, and Behaviour, Donders Inst., Nijmegen, Netherlands; [6]Agency for Science, Technol. and Res., Singapore Bioimaging Consortium, Singapore, Singapore

Abstract: Introduction
In functional magnetic resonance imaging (fMRI) research, considerable efforts are targeted at understanding how functional connectivity (FC) regulates brain function. While FC is typically computed using temporal correlation in blood oxygen-level dependent (BOLD) signal between regions, electrophysiological recordings suggests that neural communication may operate through frequency-specific oscillatory coherence in activity. We investigated whether similar oscillatory structure is driving BOLD FC using the cross-wavelet transform (xWT), a technique measuring oscillatory coherence.
Methods

We used fMRI data from 100 subjects of the Human Connectome Project (HCP), and a mouse fMRI dataset acquired in a previous study by Grandjean et al., where mice were anesthetized under either isoflurane 1% (Iso group, n=8), medetomidine 0.2 mg/kg/h (Med group, n=6), or a combination of both anesthetics at half dosages (MI group, n=8). Regions of interest (ROI) were defined with independent component analysis (ICA) and timeseries were extracted from 50 (humans) or 46 (mice) components. Each timeseries was decomposed with the wavelet transform to measure oscillations across frequencies (Fig. 1A). FC between two timeseries was assessed across time and frequencies by measuring the "phased xWT" (Fig. 1B).

Results

We found that taking the mean of the phased xWT reproduces a FC matrix essentially identical to the correlation FC matrix (r=0.938) (Fig. 1C). Then, we found that the frequency signature of xWT is strikingly different across mouse groups (Fig1. D), in accordance with differences in the BOLD frequency spectrum previously reported by Grandjean et al. Finally, the differences across anesthetic groups were much greater when measuring temporal variability in FC using xWT than using sliding-window correlations (Fig. 1E).

Conclusion

For the first time, we demonstrate how the xWT can not only recapitulate correlation-derived FC, but also highlight how this technique improves mechanistic interpretability and differentiation between states of brain dynamics.

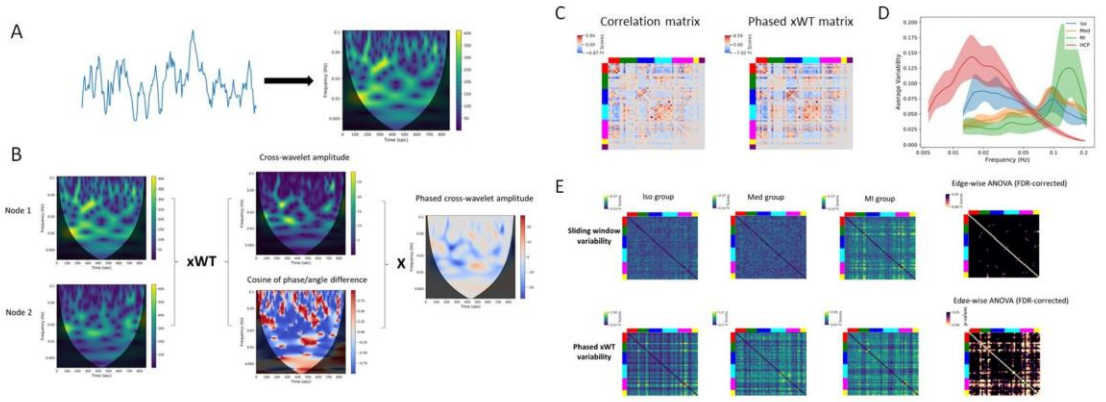


Figure 1: A) Decomposition of a BOLD timeseries (left) using the wavelet transform demonstrates frequency composition of the signal and computes oscillatory amplitude (right) and phase across frequencies (Shading areas represents time windows incompletely captured, due to incomplete phase). **B)** The cross-wavelet transform (xWT) measures oscillatory coherence between two signals decomposed by the wavelet transform (estimates the two signals' shared oscillatory amplitudes and their phase lags). The "phased xWT" is then computed by multiplying xWT amplitude with the cosine of the phase lag to map positive and negative coupling. **C)** Comparison of a brain-wide FC matrix derived from correlations (left) to a FC matrix measured by the phased xWT averaged across time and frequencies (right). ROI order was arranged based on k-means clustering (color labels on the side of the matrices). **D)** Comparison of the frequency profile of FC temporal variability in the phased xWT in humans (HCP) and across mouse anesthesia groups. The anesthesia groups are isoflurane (iso), medetomidine (med), or a combination of the two (MI). The FC variability by the temporal standard deviation, and the average was taken across all ROIs to map which frequencies are dominant for oscillatory coherence. **E)** Comparison between the sliding-window correlations (mapping changes in correlations over time) and the phased xWT in measuring the influence of anesthesia on FC temporal variability. On the right, p-values for group effects on FC was measured with one-way ANOVA and the matrices were corrected for false discovery rate (FDR).

Disclosures: G. Desrosiers-Grégoire: None. **G.A. Devenyi:** F. Consulting Fees (e.g., advisory boards); GAD performs consulting services for MIAC AG. **J. Grandjean:** None. **M. Chakravarty:** None.

Poster

768. Preclinical and Human Studies in Neurovascular Coupling Mechanisms

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 768.22/P40

Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Support: NIH-NIA K01 AG044467
R01 AG057962

Title: Common neural mechanisms underlie contralateral and ipsilateral negative bold responses in human primary visual cortex

Authors: *N. ETTEHADI[1], Q. RAZLIGHI[2];
[1]Biomed. Engin., Columbia Univ. in the City of New York, New York, NY; [2]Neurol., Columbia Univ. Med. Ctr., New York, NY

Abstract: The task-evoked positive BOLD response (PBR) due to a unilateral visual stimulus is often accompanied by robust and sustained contralateral as well as ipsilateral (relative to the stimulus) negative BOLD responses (NBRs) in the human primary visual cortex. Little is known about the origins and characteristics of these two types of NBRs, their relationship with one another, and with the accompanying PBR. Hence, in this study, we used a unilateral visual task to stimulate human primary visual cortex during fMRI acquisition to investigate the properties of the two task-evoked NBRs. Using 42 healthy and right handed participants, we first demonstrated that the magnitude of both NBRs linearly increase with the stimulus duration, providing evidence of rough linearity. Then, we extracted the shape of the hemodynamic response functions (HRFs) of the two NBRs and demonstrated that the two are very similar in both overall shape and timings (figure 1). However, the amplitude and timing of the HRF for contralateral NBR (cNBR) and ipsilateral NBR (iNBR) were significantly different from the PBR. While both NBRs showed a delayed onset time ($\Delta t=-1.05\pm1.81$ sec, $p<0.0009$), they both reached their peaks faster ($\Delta t=0.42\pm0.72$ sec, $p<0.006$), and also fell back to their baselines quicker ($\Delta t=1.4\pm3.88$ sec, $p<0.0005$) than PBR. Additionally, we showed that the subject-wise amplitude of the cNBR is tightly associated with that of iNBR ($r=0.96$, $p<5.6x10^{-26}$) which is much higher than their relationship with PBR (cNBR: $r=-0.507$, $p<0.00062$; iNBR: $r=-0.364$, $p<0.018$). Furthermore, we showed that unlike the PBR, neither of the NBRs were correlated with task performance. Finally, we demonstrated that unlike the PBR both NBRs are independent of attention. Our findings suggest that the visually evoked cNBR and iNBR are most likely generated through a common underlying neural and/or vascular mechanism(s).

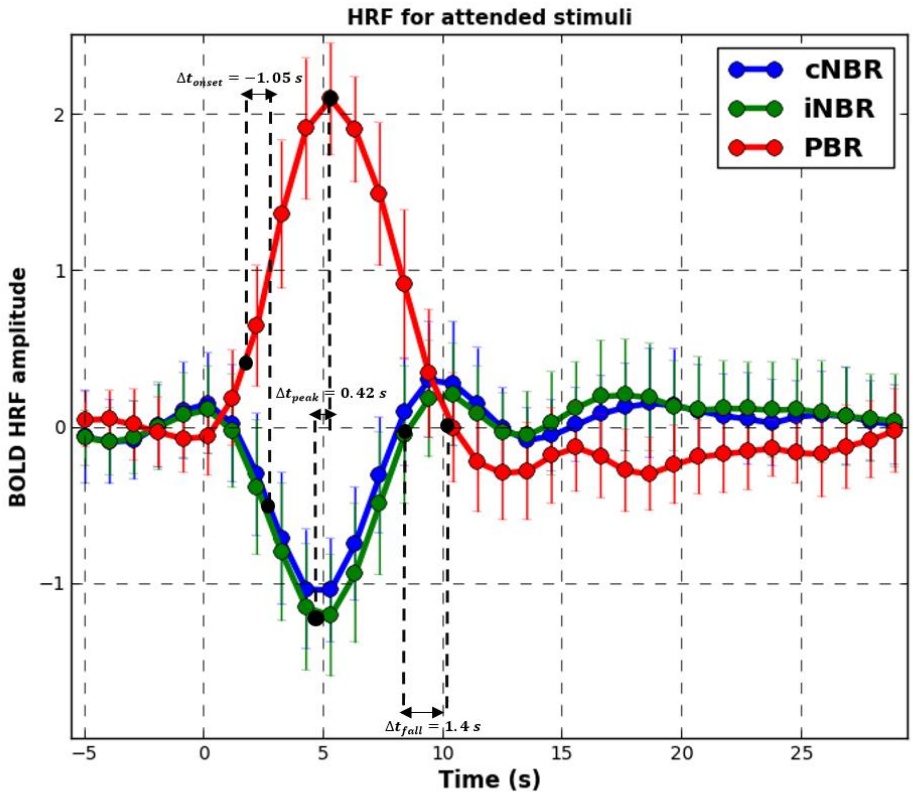


Figure 1. HRFs of PBR, cNBR, and iNBR for unilateral attended visual stimulation

Disclosures: **N. Ettehadi:** None. **Q. Razlighi:** None.

Poster

768. Preclinical and Human Studies in Neurovascular Coupling Mechanisms

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 768.23/P41

Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Support: European Research Council (ERC- 2013-AD6; 339513)
Agence Nationale de la Recherche (ANR/NSF 15-NEUC-0003- 02
Agence Nationale de la Recherche (NR-16-RHUS-0004 [RHU TRT_cSVD])
Fondation Leducq Transatlantic Networks of Excellence program (16CVD05)
NIH 2018 R01 EB CRCNS: US-French Research Proposal: Neurovascular coupling-democracy or oligarchy?

Title: Transfer function between activated neurons and local and regional vascular responses: A two-photon and functional ultrasound imaging study in a single voxel

Authors: *D. F. BOIDO[1], A.-K. AYDIN[1], W. D. HASELDEN[2], Y. GOULAM HOUSSEN[3], R. L. RUNGTA[4], C. POUZAT[3], P. J. DREW[5], S. CHARPAK[6];
[1]INSERM U1128, Paris, France; [2]The Pennsylvania State Univ., University Park, PA; [3]Paris Descartes Univ., Paris, France; [4]Lab. of Neurophysiol. and New Microscopies, INSERM U1128, Paris, Paris, France; [5]Dept. Engin. Sci. and Mechanics, Pennsylvania State Univ., University Park, PA; [6]INSERM 1128 Paris Descartes Univ., Paris cedex 06, France

Abstract: Imaging techniques based on blood flow dynamics are commonly used to study sensory processing in the human brain. However, these techniques do not directly measure neuronal activation, reporting instead functional hyperemia, a delayed increase of blow flow that irrigates a volume larger than that of the activated neurones. This raises the question of how maps of brain activation with a mesoscopic spatial resolution report local cellular and vascular responses measured with microscopic resolution. Using the olfactory bulb as a model, we combined two-photon microscopy and fast ultrasound imaging (fUS) in the same mouse. We computed the transfer functions (TFs) between the cellular and vascular microscopic responses, as well as the TF between microscopic and mesoscopic (fUS) responses. The TF from neuronal calcium and capillary red blood cell (RBC) velocity responses were robust across mice and a large range of odor duration and concentration. However, this TF required fine adjustments to predict correctly responses to brief stimuli (elicited by a single sniff of the odor) or very high odor concentrations. Co-alignment of the fUS and two-photon imaging apparatus enabled us to establish a TF between the fUS signal from single voxel and microscopic responses from the responsive glomerulus comprised in the same voxel. This first “hemodynamic response function” (HRF) for fUS data, was robust with respect to the stimulation duration and intensity, and faster than the canonical BOLD fMRI HRF. When applied to standard statistical mapping analyses (GLM), the TF improved the precision of fUS olfactory bulb activation maps. In conclusion, this new TF provides a new tool to compare quantify neurovascular coupling in control and pathological animal models.

Disclosures: D.F. Boido: None. **A. Aydin:** None. **W.D. Haselden:** None. **Y. Goulam Houssen:** None. **R.L. Rungta:** None. **C. Pouzat:** None. **P.J. Drew:** None. **S. Charpak:** None.

Poster

768. Preclinical and Human Studies in Neurovascular Coupling Mechanisms

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 768.24/P42

Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Support: DFG

Title: Resting state BOLD signal, functional connectivity, and neural dynamic modeling

Authors: *M. E. ARCHILA-MELENDEZ, C. SORG, C. PREIBISCH;
Dep. of Diag. and Interventional Neuroradiology, Klinikum rechts der Isar, Fakultät für Medizin, Technische Univ. München, Munich, Germany

Abstract: Introduction Blood oxygenation level dependent (BOLD) signal's ability to reflect underlying neuronal activity (NeuA) relies on the assumption of tight coupling between NeuA and vascular-hemodynamic processes. This neurovascular coupling (NC) depends on changes in cerebral blood flow (CBF) and cerebral metabolic rate of oxygen ($CMRO_2$). The precision with which the ongoing NeuA is reflected by the BOLD signal during rest is not completely understood. In this study, we aimed to investigate the influence of CBF and $CMRO_2$ amplitude changes on the BOLD signal and intrinsic functional connectivity (iFC) at rest.
Methods BOLD signals were simulated (S_{BOLD}) using a dynamic model based on the balloon model assuming tight coupling[1,2] for different combinations of normalised CBF and CMRO2 amplitude changes, f1 (1.0-1.75) and m1 (1.0-1.375), respectively. NeuA was modeled as dynamic amplitude-amplitude coupling between gamma, alpha and ultra-slow oscillations[3]. Different SNR levels (1000-125) were modeled by adding random noise to the S_{BOLD}. We calculated correlation coefficients (CC) between S_{BOLD} with different f1 and m1 for all SNR levels to quantify the interaction between vascular components influencing the BOLD signal (Fig1).
Results S_{BOLD} reflected the amplitude modulation in power generated by ultra-slow oscillations. S_{BOLD} evolved from negative responses for all $CMRO_2$ amplitudes (m1=1.0-1.375) at constant CBF, i.e., f1=1.0, to positive responses for all $CMRO_2$ amplitudes at max. CBF change amplitude, f1=1.75 (Fig2). The CC varied between negative and positive values for different SNR levels (Fig3). For SNR between 150 and 250, CC ranged between 0.4 and 0.3, as commonly found in iFC analyses.
Conclusion Accurate modeling of the NC can provide insights on the interplay between vascular-hemodynamic components, which should be considered when estimating iFC, especially in patients with potential vascular pathologies.
References 1.Simon and Buxton, NeuroImage, 2015; 2.Chu NeuroImage, 2018; 3.Michalareas, Neuron, 2016

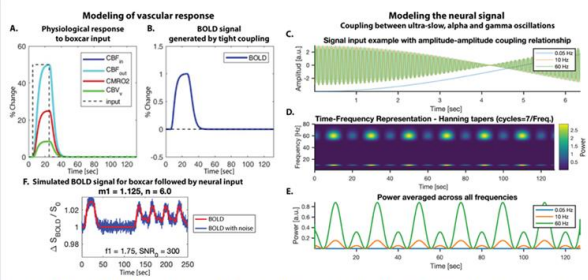


Fig.1. A) Physiological response. B) BOLD signal. C) Simulated neural signal input. D) Time-frequency representation. E) Power used as the input for the BOLD simulations. F) BOLD signal for boxcar followed by neuronal input with and without noise.

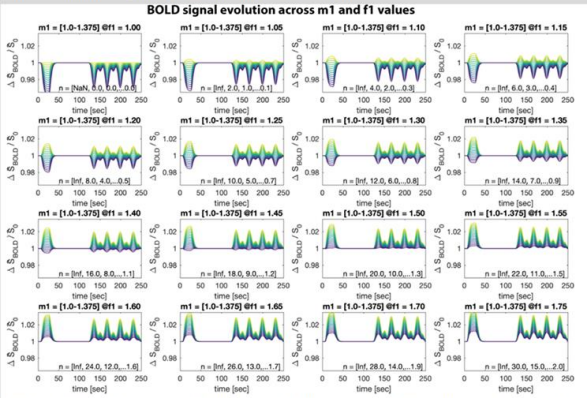


Fig.2. Evolution of the simulated BOLD signal for different m1 and f1 combinations. Each plot shows the BOLD signal for all values of m1 at a fixed value of f1. The BOLD signal varied from all negative (top left) to all positive (bottom right).

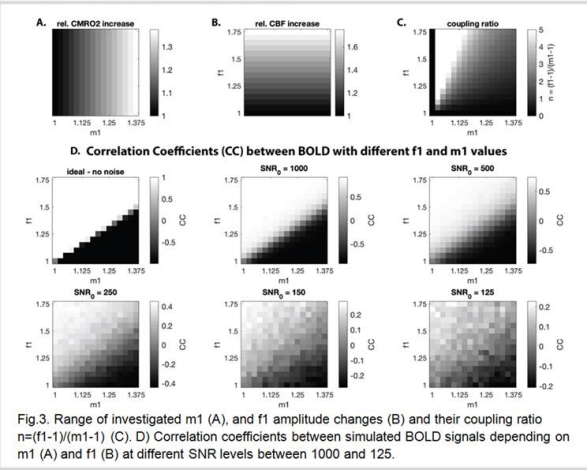


Fig.3. Range of investigated m1 (A), and f1 amplitude changes (B) and their coupling ratio n=(f1-1)/(m1-1) (C). D) Correlation coefficients between simulated BOLD signals depending on m1 (A) and f1 (B) at different SNR levels between 1000 and 125.

Disclosures: M.E. Archila-Melendez: None. **C. Sorg:** None. **C. Preibisch:** None.

Poster

768. Preclinical and Human Studies in Neurovascular Coupling Mechanisms

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 768.25/Q1

Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Support: NMSS Grant No RG150704951

Title: Reduced arterial compliance along the cerebrovascular tree predicts cognitive impairment in multiple sclerosis: Evidence for neural-vascular uncoupling hypothesis

Authors: *D. SIVAKOLUNDU[1], K. WEST[3], G. MARUTHY[1], M. D. ZUPPICHINI[4], M. P. TURNER[2], D. H. ABDELKARIM[2], Y. ZHAO[1], J. SPENCE[1], H. LU[6], D. OKUDA[7], B. P. RYPMA[5];
[1]Univ. of Texas at Dallas, Richardson, TX; [2]Sch. of Behavioral and Brain Sci., Univ. of Texas at Dallas, Dallas, TX; [3]Ctr. for BrainHealth, [4]Zuppichini, [5]Behavioral & Brain Sci., Univ. of Texas At Dallas, Dallas, TX; [6]Johns Hopkins Univ., Baltimore, MD; [7]Univ. of Texas Southwestern Med. Ctr., Dallas, TX

Abstract: Background: Cognitive impairment occurs in almost 70% of multiple sclerosis (MS) patients. The pathophysiology of this impairment is unknown. Loss of vascular compliance along the cerebrovascular tree (i.e., vascular network extending from superficial pial arteries to deep penetrating arteries) would result in suboptimal vasodilation upon neural stimulation, providing insufficient nutrients and oxygen to active neurons. This process is called neural-vascular uncoupling and we hypothesized this uncoupling would result in cognitive impairment.
Objective: To assess vascular compliance along the cerebrovascular tree and its relationship to MS-related cognition.
Methods: We conducted a cross sectional study investigating healthy controls, cognitively-normal and -impaired MS patients. Participants were scanned on a Philips 3T MRI scanner using a dual-echo fMRI sequence while they periodically inhaled room-air and hypercapnic gas-mixture (5% CO_2 and 95% room air). We assessed vascular compliance along the cerebrovascular tree by dividing cerebral cortex into nested-layers. Arterial and venous cerebrovascular reactivity (CVR) was calculated from both cerebral blood flow (arterial) and blood-oxygen-level-dependent signal (venous) increases per unit increase in end-tidal CO_2.
Results: Arterial CVR exponentially reduced from the superficial to deep portions of the cerebrovascular tree for healthy controls ($p=0.0014$) and cognitively-normal MS patients ($p=0.0005$). No such reductions were observed in cognitively-impaired MS patients ($p=0.7244$). These arterial CVR changes were fit to exponential functions, the decay-constant (arterial compliance index; ACI) of which was associated with individual subjects' cognitive performance ($p=0.01$) and accounted for 20.3% of variability in their performance in MS patients. Furthermore, ACI significantly explained an additional 11.7% of the cognitive-performance variability in MS after controlling for age, disease duration, lesion volume, EDSS, brain atrophy, and cortical grey and white matter volume ($p=0.003$).
Conclusion: ACI is a novel biomarker reflecting the degree of injury along the cerebrovascular tree. This index might provide a platform for MS disease surveillance, development of targeted cognitive therapies, and a method for distinguishing between MS patients who are prone to develop cognitive impairment and those who are not.

Disclosures: D. Sivakolundu: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Has a patent pending related to the work presented here. **K. West:** E. Ownership Interest (stock, stock

options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Has a patent pending related to the work presented here. **G. Maruthy:** None. **M.D. Zuppichini:** None. **M.P. Turner:** None. **D.H. Abdelkarim:** None. **Y. Zhao:** None. **J. Spence:** None. **H. Lu:** None. **D. Okuda:** F. Consulting Fees (e.g., advisory boards); Received lecture fees from Acorda, Genzyme, and TEVA Neuroscience, consulting and advisory board fees from EMD Serono, Genentech, Genzyme, Novartis and TEVA Neuroscience, and research support from Bi. **B.P. Rypma:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Has a patent pending related to the work presented here.

Poster

768. Preclinical and Human Studies in Neurovascular Coupling Mechanisms

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 768.26/Q2

Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

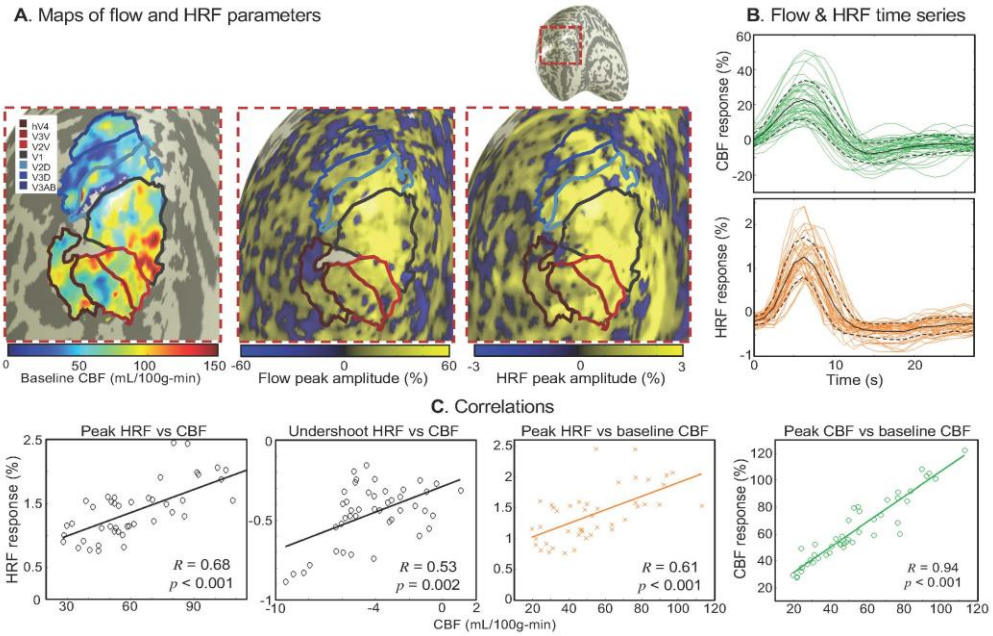
Support: NIH R01 NS095933
NIH K25 HL131997

Title: High spatiotemporal resolution measurements of blood flow evoked by brief neural activity

Authors: *D. RESS[1], A. TAYLOR[1], X. ZOU[1], D. J. J. WANG[2], J. KIM[1];
[1]Neurosci., Baylor Col. of Med., Houston, TX; [2]Steven Neuroimaging and Informatics Inst., USC, Los Angeles, TX

Abstract: Introduction: FMRI relies on a stereotypical response to brief neural activation called the hemodynamic response function (HRF) that largely depends on competition between cerebral blood flow (CBF) and oxygen metabolism. The detailed dynamics of the CBF response are poorly understood. Standard arterial spin labeling (ASL) experiments to measure transient CBF suffer from low temporal sampling (≥5 s). We used a dithering scheme to obtain 1.25-s sampling of the CBF evoked by brief stimulation, as well as baseline CBF. **Methods**: An audiovisual sequence-detection task was used to evoke the HRF broadly across visual cortex in 7 subjects. CBF was measured in 5 runs using ASL with PICORE/Q2TIPS tagging, TR = 2.5 s, and 2-mm voxels. Stimulus onset times were 4:1 dithered, with onset delayed in 1.25-s steps from event-to-event. Dithering was compensated by upsampling and shifting each event time series. The fMRI HRF was measured in 2 runs using SMS-accelerated EPI, TR = 1.25 s, 2-mm voxels, without dithering. Data were transformed into a 0.7-mm MP-RAGE anatomy and analysis restricted to gray matter voxels. Retinotopic mapping was done in separate sessions to discern visual areas V1—3, V3AB, and hV4. CBF and HRF data were averaged across these visual areas to obtain 44 measurements. **Results**: Strong CBF and HRF response were obtained across visual cortex

(Fig A). Stimulation created an initial CBF peak followed by an undershoot (Fig B). Peak was reliable in all measurements and undershoot significant in 33/44 measurements. Peak and undershoot were significant in all HRF measurements. There were significant moderate-to-strong correlations among HRF, CBF responses, and baseline CBF (Fig C). **Discussion**: Our dithering approach allowed detailed characterization of flow dynamics with satisfactory contrast-to-noise ratio. CBF dynamics were similar to HRF dynamics, and the CBF was at least partly responsible for the HRF undershoot. The correlation of CBF and HRF peak responses with baseline CBF indicated that fMRI signals may be strongly modulated by perfusion, a notable nuisance effect for fMRI analysis.



Disclosures: D. Ress: None. **A. Taylor:** None. **X. Zou:** None. **D.J.J. Wang:** None. **J. Kim:** None.

Poster

768. Preclinical and Human Studies in Neurovascular Coupling Mechanisms

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 768.27/Q3

Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Support: NIH Grant R01NS078168
NIH Grant R01NS101353

Title: Arousal-state dependence of bilateral hemodynamic signals in the mouse

Authors: *K. L. TURNER[1], P. J. DREW[2];
[1]Dept. Biomed. Engin., [2]Dept. Engin. Sci. and Mechanics, Pennsylvania State Univ., University Park, PA

Abstract: Hemodynamic signals in the brain are used to infer neural activity, and bilateral correlations in hemodynamic signals have been observed in the absence of any overt stimulus or task. However, recent studies have suggested that the nature and strength of hemodynamic signals depend on arousal state. Here, we monitored neural activity and hemodynamic signals in un-anesthetized, head-fixed mice to understand how sleep and wake states impact cerebral hemodynamics. In parallel with electrophysiological recordings, we used intrinsic optical signal imaging to measure bilateral changes in cerebral blood volume (CBV). We concurrently monitored body motion, whisker movement, muscle EMG, and cortical LFP to classify the arousal state of the mouse into awake, NREM sleep, or REM sleep. We found that mice regularly fell asleep for a few minutes at time during imaging. During both NREM and REM sleep, mice showed large increases in CBV relative to the awake state. During NREM sleep, the amplitude of bilateral low-frequency oscillations in CBV increased markedly. Bilateral correlations in neural activity and CBV were highest during NREM sleep, and lowest in the awake state. Our results show that hemodynamic signals in the cortex are strongly modulated by arousal state and emphasize the importance of behavioral monitoring during studies of spontaneous activity.

Disclosures: K.L. Turner: None. **P.J. Drew:** None.

Poster

768. Preclinical and Human Studies in Neurovascular Coupling Mechanisms

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 768.28/Q4

Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Support: CRCNS Grant R01EB021703

Title: Simulations of nitric oxide diffusion show spatial dynamics of degradation can drive vasomotion and post-stimulus constriction

Authors: *W. D. HASELDEN[1], R. KEDARASETTI[2], P. J. DREW[3];
[1]The Pennsylvania State Univ., State College, PA; [2]Ctr. for Neural Engin., The Pennsylvania State Univ., University Park, PA; [3]Dept. Engin. Sci. and Mechanics, Pennsylvania State Univ., University Park, PA

Abstract: Nitric oxide (NO) is a gaseous signaling molecule that plays an important role in neurovascular coupling. NO produced by neurons diffuses into smooth muscle surrounding

arterioles, driving vasodilation. However, the rate of NO degradation in hemoglobin is orders of magnitude higher than in brain tissue, though how this might affect NO signaling is not completely understood. Using computer simulations, we investigated how the spatial and temporal patterns of NO generation and degradation impacted arterial dilations. We found that NO production that was localized near the arteriole was markedly more effective than spatially extended NO production. Because of the higher degradation of NO in the blood, the size of the arteriole exerted an effect on NO signaling in our simulations, with smaller vessels being more sensitive to NO than larger ones. When we implemented a model with dynamic NO production, degradation and vasodilation, we found that the increased degradation of NO created by vasodilation drove emergent dynamics. In this dynamic model, large dilations were followed by a post-stimulus constriction, similar to the post-stimulus undershoot seen in fMRI experiments. The dynamic model also generated oscillations in arterial diameter around the 0.1-0.3 Hz range, reminiscent of vasomotion. Vasomotion could also be enhanced by increasing the free hemoglobin in the plasma, as happens with certain diseases. Thus, our simulations suggest that many common arterial dynamics may be emergent phenomenon generated by the dynamics of NO degradation by the blood.

Disclosures: W.D. Haselden: None. **R. Kedarasetti:** None. **P.J. Drew:** None.

Poster

768. Preclinical and Human Studies in Neurovascular Coupling Mechanisms

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 768.29/Q5

Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Support: NIH 2018 R01 EB CRCNS: US-French Research Proposal: Neurovascular coupling-democracy or oligarchy?
European Research Council (ERC- 2013-AD6; 339513)
Agence Nationale de la Recherche (ANR/NSF 15-NEUC-0003- 02)
Agence Nationale de la Recherche (NR-16-RHUS-0004 [RHU TRT_cSVD])
Fondation Leducq Transatlantic Networks of Excellence program (16CVD05)

Title: Transfer function computation of neurovascular coupling: Advantages and pitfalls

Authors: *A.-K. AYDIN[1], D. F. BOIDO[2], W. D. HASELDEN[3], Y. GOULAM HOUSSEN[4], R. L. RUNGTA[5], C. POUZAT[4], P. J. DREW[6], S. CHARPAK[7];
[2]Neurophysiol. and New Microscopies Lab., [1]INSERM U1128, Paris, France; [3]The Pennsylvania State Univ., University Park, PA; [4]Paris Descartes Univ., Paris, France; [5]Lab. of Neurophysiol. and New Microscopies, INSERM U1128, Paris, Paris, France; [6]Dept. Engin. Sci. and Mechanics, Pennsylvania State Univ., University Park, PA; [7]INSERM 1128 Paris Descartes Univ., Paris cedex 06, France

Abstract: Multimodal brain imaging of neuronal and blood flow dynamics in the same animal allows the quantitative analysis of the causal relationship between neuronal activation and functional hyperemia. Given the complexity of the many mechanisms involved during neurovascular coupling (NVC), we adopt a model-free approach, using the transfer function (TF), whose convolution with neuronal signals, will provide an estimation of expected vascular responses. We first established a database of cellular and vascular responses to odor. We measured with microscopic resolution using two-photon imaging, and with a mesoscopic resolution using functional ultrasounds (fUS), in the same mice. A direct approach to determine TFs is the deconvolution, either working on the frequency domain, or calculating the Toeplitz matrix. Both these methods produced estimates that were extremely sensitive to noise, and did not give robust TFs. We then used a machine learning optimization algorithm working on known functions, such as the gamma functions, and were able to build up a set of TFs recapitulating NVC at the microscopic resolution (from neuronal calcium to capillary red blood cell velocity responses) or at the mesoscopic level (from neuronal calcium to single fUS voxel responses). After having evaluated the effect of regularization and cross-validated the robustness of the TFs across mice, we challenged the best TF by modulating the stimulation parameters: this first "hemodynamic response function" for fUS data, was fast and robust over a large range of odor durations and intensities. Our approach sets some guidelines for efficient computations and validations of a TF that can predict NVC in control and pathological animal models.

Disclosures: A. Aydin: None. **D.F. Boido:** None. **W.D. Haselden:** None. **Y. Goulam Houssen:** None. **R.L. Rungta:** None. **C. Pouzat:** None. **P.J. Drew:** None. **S. Charpak:** None.

Poster

768. Preclinical and Human Studies in Neurovascular Coupling Mechanisms

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 768.30/Q6

Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Support: NIH Grant R01NS101353

Title: Arousal state-associated hemodynamic changes occlude stimulus-evoked neurovascular coupling in the somatosensory cortex of the juvenile mouse

Authors: *K. W. GHERES, K. L. TURNER, P. J. DREW;
Pennsylvania State Univ. Univ. Park, University Park, PA

Abstract: In juvenile rodents and humans, neurovascular coupling associated with sensory stimulus can be weak, absent, or inverted. Using Intrinsic Optical Signal (IOS) imaging, two photon microscopy, and in vivo extracellular electrophysiology, we investigated how neurovascular coupling in somatosensory cortex is affected by arousal state throughout the

juvenile period. In adult mammals, the diurnal sleep-wake cycle is characterized by long bouts of wakefulness followed by periods of sleep which is accompanied by large, global, increases in blood volume. However, in juvenile mice, sleep and wake periods occur sporadically and in quick succession on the time scale of seconds to minutes. We find that in juvenile mice, sleep onset is accompanied by a large increase in cerebral blood volume (CBV) in the somatosensory cortex. After eye opening (~P14), whisker stimulation will awaken the mice, resulting in large decreases in blood volume. This arousal state-related change in CBV obscures any sensory-evoked neurovascular relationship. Finally, we use cell type specific optogenetics to investigate how the neurovascular hemodynamic response is affected by sleep state independent of sensory stimuli. These results suggest that careful monitoring of arousal state is essential to prevent confounding of stimulus evoked hemodynamic responses with large global changes in blood volume driven by sleep-wake state transitions.

Disclosures: K.W. Gheres: None. **K.L. Turner:** None. **P.J. Drew:** None.

Poster

769. Cardiovascular Regulation I

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 769.01/Q7

Topic: F.07. Autonomic Regulation

Support: TCMRC-P-107002

Title: Regulation by central estrogen receptors of ethanol-induced tachycardia in female rats

Authors: *C.-C. LAI[1,2], J. SITUMORANG[2], H.-H. LIN[3];
[1]Dept. of Pharmacol., [2]Master and PhD Programs in Pharmacol. and Toxicology, [3]Dept. of Physiol., Tzu Chi Univ., Hualien, Taiwan

Abstract: Several ethanol-related diseases are gender-dependent; females are more sensitive than males to the effects of ethanol (alcohol). Our previous study showed that nitric oxide synthase (NOS) and nitric oxide (NO) signaling in the medulla of the brain might play an important role in mediating ethanol-induced tachycardia during ethanol exposure. Studies showed that estrogen or estrogen receptors might regulate NOS/NO signaling in the brain. The role of estrogen receptors in the brain in ethanol-induced tachycardia remains unclear. This study examined the role of central estrogen and estrogen receptors in the changes in blood pressure (BP) and heart rate (HR) induced by acute ethanol administration in ovariectomized (OVX) and sham-control (SHAM) female SD rats weighing 250-300g. The responses of BP and HR in conscious rats were measured by the tail-cuff method. Ethanol (3.2 g/kg) and saline (as control) were given by oral gavage. Oral administration of ethanol increased HR with little changes in BP in both SHAM and OVX rats. Compared to SHAM rats, however, OVX rats showed a

significantly higher HR response in 60, 90, and 120-minute post ethanol administration. Intraperitoneal (IP) injection of Tamoxifen (a selective estrogen receptor modulator) augmented ethanol-induced tachycardia in SHAM rats. Intracerebroventricular (ICV) infusion of estrogen α or β receptor antagonists potentiated ethanol-induced tachycardia effect in SHAM rats. ICV infusion of Estradiol (E2, an estrogen receptor agonist) attenuated the ethanol-induced tachycardia effects in OVX rats. These results suggest that estrogen and estrogen receptors in the CNS play a role in the regulation of ethanol-induced tachycardia in female rats. The changes in the NOS activity and NO contents will be determined in several brain nuclei related to autonomic control to clarify the role of NOS/NO signaling in estrogen regulation of ethanol-induced tachycardia.

Disclosures: C. Lai: None. **J. Situmorang:** None. **H. Lin:** None.

Poster

769. Cardiovascular Regulation I

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 769.02/Q8

Topic: F.07. Autonomic Regulation

Support: HL36520
HL098351

Title: Estrogen receptor beta agonists block slow-onset angiotensin II hypertension and reduce NMDA receptor-signaling in paraventricular neurons in female mice at an early stage of accelerated ovarian failure

Authors: *T. A. MILNER[1], N. H. CONTOREGGI[2], F. YU[2], M. A. JOHNSON[2], G. WANG[2], E. M. WATERS[3], B. S. MCEWEN[3], M. J. GLASS[4];
[2]Feil Family Brain and Mind Res. Inst., [1]Weill Cornell Med., New York, NY; [3]Lab. of Neuroendocrinology, Rockefeller Univ., New York, NY; [4]Feil Family Brain and Mind Res. Inst., Weill Cornell Med. Col., New York, NY

Abstract: Men are more susceptible to hypertension than women from early adulthood to mid-life; however, when women transition to menopause (perimenopause), their risk for hypertension increases and approaches that of men. Animal models suggest that differences in hypertension susceptibility in males and females may involve sex-dependent divergences in estrogen signaling in cardiovascular regulatory brain areas, including the hypothalamic paraventricular nucleus (PVN). Our studies have begun to elucidate the mechanisms for these sex differences using the 4-vinylcyclohexene diepoxide (VCD) mouse model of accelerated ovarian failure (AOF), which recapitulates hormonal changes in peri-menopause (peri-AOF). In peri-AOF mice, slow-pressor angiotensin II (AngII) increases blood pressure. This is accompanied by redistribution of the

GluN1 NMDA receptor subunit from the cytoplasm to the plasmalemma in PVN estrogen receptor beta (ERβ) containing dendrites, a process that would promote sympathoexcitation (Marques-Lopes et al., 2017). Here, we report that cyclic administration of diarylpropionitrile (DPN; 1mg/kg, I.P.), ERB041 (20mg/kg, I.P.), or liquiritigenin (30mg/kg, I.P.), which represent three different classes of ERβ agonists, blocked the increase in blood pressure by AngII in peri-AOF females but not age-matched males. Dual-label electron microscopy revealed that the reduction of blood pressure in DPN-administered peri-AOF females was paralleled by a decrease in GluN1 near the plasmalemma, in the cytoplasm and in total in ERβ-containing dendrites in the PVN. In contrast, the trafficking of GluN1 in ERβ-containing dendrites in DPN-administered hypertensive males was unaltered. Physiological studies are in progress analyzing the NMDA-receptor mediated excitatory signaling in PVN ERβ-expressing neurons from AngII mice with DPN agonists. These results suggest that heightened NMDA receptor signaling in ERβ-expressing PVN neurons contributes to the susceptibility of peri-AOF mice to the hypertensive actions of AngII. These findings provide preclinical evidence supporting a therapeutic window of opportunity for estrogen-based management of hypertension as women transition through menopause.

Disclosures: T.A. Milner: None. **N.H. Contoreggi:** None. **F. Yu:** None. **M.A. Johnson:** None. **G. Wang:** None. **E.M. Waters:** None. **B.S. McEwen:** None. **M.J. Glass:** None.

Poster

769. Cardiovascular Regulation I

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 769.03/Q9

Topic: F.07. Autonomic Regulation

Support: HL135498
HL136520

Title: Estrogen receptor beta activity contributes to a reduction in tumor necrosis factor alpha-induced reactive oxygen production in the hypothalamic paraventricular nucleus and to the resistance to angiotensin II-dependent hypertension in cycling female mice

Authors: *M. J. GLASS, C. WOODS, N. H. CONTOREGGI, T. A. MILNER, G. WANG; Weill Cornell Med., New York, NY

Abstract: Before the start of menopause women have a lower incidence of hypertension when compared to age-matched men. However, the mechanisms influencing sex-differences in hypertension susceptibility are not well understood. Males and females differ with respect to essential processes that affect blood pressure, including neurogenic factors, inflammation, and oxidative stress. In a mouse model of neurogenic hypertension induced by low-dose angiotensin

II (AngII) infusion males show an increase in blood pressure that involves both tumor necrosis factor alpha (TNFα) and reactive oxygen species (ROS) signaling in the hypothalamic paraventricular nucleus (PVN), an important central coordinator of cardiovascular regulation. However, the role of TNFα signaling in reactive oxygen production and blood pressure in response to AngII administration in females is uncertain. These issues were addressed using a combination of *in situ* hybridization, high-resolution electron microscopic immunohistochemistry, and *in vitro* dihydroethidium microfluorography. We found that cycling female mice given chronic (14-day) infusion of AngII did not show an increase in blood pressure, a finding consistent with previous reports. In addition, female mice infused with AngII or vehicle did not differ either in the expression or the subcellular localization of the TNFα receptor type 1 (TNFR1) in the PVN. In contrast to what is typically seen in males, TNFα exposure resulted in only a modest production of Nox2-mediated ROS in isolated PVN neurons. Significantly, blocking estrogen receptor beta (ERß) with the antagonist PHTPP resulted in a robust increase in TNFα-dependent ROS production in isolated PVN cells from female mice. Moreover, administration of PHTPP during chronic AngII infusion was associated with an increase in blood pressure in females. These results indicate that ERß signaling in PVN neurons contributes to the reduced sensitivity of female mice to cytokine-induced free radical production and AngII-dependent hypertension.

Disclosures: M.J. Glass: None. **C. Woods:** None. **N.H. Contoreggi:** None. **T.A. Milner:** None. **G. Wang:** None.

Poster

769. Cardiovascular Regulation I

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 769.04/Q10

Topic: F.07. Autonomic Regulation

Support: NIH Grant R15HL127739

Title: Changes in neuropeptide expression, responses, and receptors in parasympathetic neurons following chronic myocardial infarction

Authors: *L. LOISELLE, P. GALVIN, K. HUTTON, J. C. HARDWICK;
Biol., Ithaca Col., Ithaca, NY

Abstract: Myocardial infarction (MI) induces significant remodeling in both cardiac muscle and the neuronal systems that control the heart. Previous studies have demonstrated significant increases in activity of the sympathetic nervous system following MI. The current study looked at changes in postganglionic parasympathetic neurons in the cardiac plexus and autonomic neurons of the nodose and stellate ganglia in guinea pigs 4-6 weeks following a chronic MI. MI

was surgically-induced in both male and female guinea pigs by ligation of coronary vessels branching off the LAD. Animals were then allowed to recover for 4-6 weeks. Intracellular voltage recordings from neurons within whole mounts of the intrinsic cardiac plexus were used to assess physiological changes in parasympathetic neuronal responses to peptide application. Intracardiac neurons from MI animals showed a decrease in sensitivity to NPY. NPY application (in the bath or by local pressure ejection) accelerated the rate of return to resting membrane potential of the afterhyperolarization of a single action potential. A dose response curve (1 nM - 100 nM NPY) of control neurons vs. neurons from MI animals showed a 10-fold increase in the EC_{50} for NPY with MI. Specific agonists for Y1 and Y5 receptors demonstrate that the response in these neurons is due to primarily to activation of Y1 receptors. Western Blot analysis of homogenized cardiac ganglia showed no significant change in Y1R protein at 6 weeks post MI, indicating that the decrease in sensitivity is not due to reduced protein content. In addition to postganglionic neurons, we also examined the neurons that innervate these cells, including the nodose ganglion and the stellate ganglion. Examination of cryostat sections of fixed nodose ganglia showed little to no NPY expression in neurons within the ganglion in control or MI tissues, but did show a significant increase in expression of galanin-immunoreactivity, and nNOS in neurons with MI, along with an increase in neuronal size. Examination of stellate neurons, whose fibers also innervate this cardiac plexus, showed an increase in NPY expression and cell size with MI, consistent with findings in other species. This data demonstrates that chronic heart disease, such as MI, induces phenotypic and functional remodeling in both the sympathetic and parasympathetic neurons innervating the heart.

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Poster

769. Cardiovascular Regulation I

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 769.05/Q11

Topic: F.07. Autonomic Regulation

Support: FAPESP (2017/06645-4)
CNPq
PROPE/FUNDUNESP

Title: Participation of brain angiotensin type 1 receptor in the anti-hypertensive effects of catalase blockade in spontaneously hypertensive rats

Authors: *M. R. LAUAR, D. S. A. COLOMBARI, L. A. DE LUCA JR, P. M. DE PAULA, E. COLOMBARI, C. A. F. ANDRADE, J. V. MENANI;
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Abstract: The spontaneously hypertensive rat (SHR), a genetic model of neurogenic hypertension, has increased sympathetic activity, a hyperactive brain renin-angiotensin system and high density of angiotensin II (ANG II) type 1 receptors (AT-1r) centrally. Activation of brain AT-1r enhances NAD(P)H oxidase activity and formation of reactive oxygen species, such as the superoxide anion (O_2^-). The O_2^- is dismutated to hydrogen peroxide (H_2O_2) by the enzyme superoxide dismutase. Previous studies have shown that intracerebroventricular (icv) injection of H_2O_2 or the catalase inhibitor 3-amino-1,2,4-triazol (ATZ) reduces the pressor response to icv ANG II in SHR. In addition, the subcutaneous (sc) administration of ATZ acutely reduces mean arterial pressure (MAP) in SHR. In the present study, we evaluated the participation of brain AT-1r in the changes of MAP produced by sc injection of ATZ in SHR. Male SHR (280-350 g, n=4-7/group) with stainless steel guide-cannulas implanted in the lateral ventricle were used. After a baseline period of MAP and heart rate (HR) recording, rats received icv injection of saline (1 µl) or losartan (100 ng/1 µl) 30 min prior to sc injections of ATZ (300 mg/kg of body weight). The sc injection of ATZ reduced MAP (ATZ: 157 ± 6, vs. baseline 186 ± 7 mmHg) and HR (ATZ: 374 ± 24 bpm, vs. baseline: 425 ± 49 bpm) in SHR that received saline icv. Losartan icv abolished the reduction in MAP (185 ± 3 mmHg) and HR (448 ± 15 bpm) produced by sc injection of ATZ. Losartan alone produced no change in MAP and HR. The results suggest that the anti-hypertensive effects of ATZ depend on AT-1r activity which produces O_2^- that is dismutated to H_2O_2 in the brain. Blocking catalase, ATZ might increase the availability of H_2O_2 produced endogenously in the brain, thereby reducing MAP and HR in SHR.

Disclosures: M.R. Lauar: None. **D.S.A. Colombari:** None. **L.A. De Luca Jr:** None. **P.M. De Paula:** None. **E. Colombari:** None. **C.A.F. Andrade:** None. **J.V. Menani:** None.

Poster

769. Cardiovascular Regulation I

Location: Hall A

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Program #/Poster #: 769.06/Q12

Topic: F.07. Autonomic Regulation

Support: Italian Ministry of Health, GR-2011-02350132

Title: The glycoprotein Dickkopf-3: A new player in the central and peripheral regulation of blood pressure

Authors: *C. L. BUSCETI[1], A. CARRIZZO[1], F. BIANCHI[1], M. DE LUCIA[1], A. DAMATO[1], M. AMBROSIO[1], P. DI PIETRO[2], R. P. GINERETE[1], M. COTUGNO[1], R. STANZIONE[1], S. MARCHITTI[1], V. BRUNO[1,3], G. BATTAGLIA[1,3], F. FORNAI[1,5], M. VOLPE[1,4], S. RUBATTU[1,4], C. VECCHIONE[1,2], F. NICOLETTI[1,3];
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Salerno, Italy; [3]Dept. of Physiol. and Pharmacol., [4]Dept. of Clin. and Mol. Med., Univ. Sapienza, Roma, Italy; [5]Dept. of of Human Morphology and Applied Biol., Univ. of Pisa, Pisa, Italy

Abstract: Dickkopf3 (Dkk-3) is a secreted glycoprotein known for its proapoptotic and angiogenic activity. We have shown that Dkk-3 induces vascular endothelial growth factor (VEGF) in astrocytes and endothelial cells (Busceti et al., Front. Pharmacol., 2017; Front. Cell. Neurosci., 2018), raising the possibility that Dkk-3 may regulate vascular homeostasis. Here, we report that genetic deletion of Dkk-3 in mice enhanced systolic blood pressure and impaired endothelium-dependent relaxation of mesenteric arteries. Endothelial function in Dkk-3$^{-/-}$ mice was rescued by incubating mesenteric arteries with the human recombinant VEGF peptide. In addition, *i.v.* injection of a lentiviral vector encoding for Dkk-3 caused anti-hypertensive effects in Dkk-3$^{-/-}$ mice, demonstrating a role for Dkk-3 in the systemic control of blood pressure. At CNS level, immunohistochemical analysis showed a high Dkk-3 immunoreactivity in brainstem nuclei that are involved in the baroreceptor reflex, such as the area postrema, the nucleus of the solitary tract, and the nucleus ambiguous. Interestingly, *i.c.v.* infusion of the lentiviral vector encoding for Dkk-3 could also lower blood pressure in Dkk3$^{-/-}$ mice, but did not rescue endothelial function in isolated mesenteric arteries (as opposed to the *i.v.* injection of the vector). Central infusion of the vector encoding for Dkk-3 enhanced VEGF protein levels and increased endothelial nitric oxide synthase (eNOS) phosphorylation in the brainstem of Dkk-3$^{-/-}$ mice, and Dkk-3 overexpression was unable to reduce blood pressure in eNOS$^{-/-}$ mice. We extended the analysis to spontaneously hypertensive rats (SHR) as a genetic model of neurogenic hypertension. Interestingly, Dkk-3 gene maps inside a WKY/SHR (Wistar Kyoto/Spontaneously hypertensive rat) chromosome 1 QTL (Quantitative Trait Locus) included between D1Mit3 and D1Rat57 markers and linked to the hypertensive phenotype. In SHR rats, i.c.v. infusion of the vector encoding for Dkk-3 lowered systolic blood pressure, whereas Dkk-3 silencing produced the opposite effect. Taken together, these findings demonstrate that the molecular Dkk-3/VEGF/eNOS axis acts as peripheral and central regulator of vascular homeostasis under both physiological and pathological conditions.

Disclosures: C.L. Busceti: None. **A. Carrizzo:** None. **F. Bianchi:** None. **M. De Lucia:** None. **A. Damato:** None. **M. Ambrosio:** None. **P. Di Pietro:** None. **R.P. Ginerete:** None. **M. Cotugno:** None. **R. Stanzione:** None. **S. Marchitti:** None. **V. Bruno:** None. **G. Battaglia:** None. **F. Fornai:** None. **M. Volpe:** None. **S. Rubattu:** None. **C. Vecchione:** None. **F. Nicoletti:** None.

Poster

769. Cardiovascular Regulation I

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 769.07/Q13

Topic: F.07. Autonomic Regulation

Title: Heart rate in myalgic encephalomyelitis/chronic fatigue syndrome: A review revisited

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Abstract: ME/CFS is a heterogeneous, medically unexplained illness characterized by fatigue lasting at least 6 months. A recent meta-analysis (1) summarized the data from peer-reviewed journals regarding heart rate (HR) response to exercise in ME/CFS patients. A main conclusion was that "smaller or reduced increases in HR during CPET (cardiopulmonary testing) are consistently observed in ME/CFS" compared to controls. However, a casual review of the data presented in Table 1 suggests that substantially lower mean peak HRs in ME/CFS patients were found mainly in studies that had no control group and generally not seen in studies with one. We conducted a re-analysis of the meta-analysis data to better understand if there were methodological differences between the controlled and uncontrolled studies. First, we used the observed mean peak HR in patients with ME/CFS from the studies listed in the meta-analysis (Table 1), but separated the data depending on whether the study was controlled or not. A significant difference ($p < .001$) in HR was seen in patients in studies without a control group (144+- 8) compared to patients with one (162 +- 14). This strongly suggests that methodological issues rather than disease-specific issues are driving the finding of blunted HR responsiveness. Further, 7 of 34 papers were written by the same group (peak HR 147 vs 157 in other studies), none of which used a control group. Two of these 7 papers (2, 3) state their data were "re-analyzed", making it likely the same data was included more than once in the meta-analysis, further weighing the results toward a low mean patient peak HR. Furthermore, the patients in the 7 studies were 94% women (85% in the other studies), who tend to have slightly lower peak HRs (4). In addition, HR may be affected by anticipation of or actual pain/stress due to invasive drawing of blood (5, 6). We saw that 9 of the 34 studies included invasive blood draws during or immediately after the exercise test and found that mean peak HR in each group (patient and control) was significantly higher when blood was drawn around the time of exercise than when it was not. This suggests another potential confound, as a higher percentage of controls (37%) received blood draws than patients (27%) in the meta-analysis. HR is an important variable in models for exercise tolerance (7) in ME/CFS. While HR is an objective measure, the methods and circumstances around its measurement can affect it and should be taken into account when comparing HR across groups. In addition, while meta-analyses have more statistical power to detect significant effects than do small, individual studies, careful attention must be made to the data that are included and the conclusions drawn.

Disclosures: K.M. Knutson: None.

Poster

769. Cardiovascular Regulation I

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 769.08/Q14

Topic: F.07. Autonomic Regulation

Title: Effect of exercise timing on sleep duration, sleep quality, and HRV-based recovery for collegiate female athletes

Authors: B. FLEMMING, **N. NARVAEZ**, *R. E. JOHNSON;
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Abstract: The physiological stresses that athletes experience during training must be balanced with adequate recovery. Recovery allows the body to reach a maximum athletic potential, which allows athletes to perform at higher levels. Recovery is affected by many factors, and in this work we focused on the timing of vigorous exercise. Our previous study found that training sessions after 8pm decreased recovery in collegiate women soccer players [1]. We hypothesized that late training sessions negatively affects sleep, but the literature on how timing of exercise affects sleep shows mixed results. This study investigates the relationship between timing of vigorous exercise, sleep, and recovery for collegiate female athletes.
Specifically, we studied how the timing of games affected sleep duration, sleep quality, and recovery for players on an NCAA Division I women's soccer team during the fall 2017 season. Games that started at or after 7pm were considered late, whereas games that started before 7pm were considered normal. Sleep duration and sleep quality were measured using a qualitative survey completed by players each day [as in 2]. Recovery was estimated using heart rate variability (HRV) by having each player record 5 minutes of their heart rate data each day upon waking up. This HRV data was then used to calculate a Recovery Index [3]. Higher HRV generally indicates better recovery, a process governed largely by the autonomic nervous system. We found that sleep duration remained similar for late and normal games (8 hours for both normal and late games); however, sleep quality decreased by 20% for late games (80% for normal games and 60% for late games). The median recovery index decreased by 6.1 percent for days after late games (52.7 % for normal games and 46.6 % for late games). In summary, we found that vigorous activity in the form of in-season games for a collegiate women's soccer team resulted in lower sleep quality and a lower recovery index when games occurred late in the evening as compared to games in the morning or early afternoon.
[1] 2018 Grotelueschen et al., Proc of ASB.
[2] 2010 Myllymaki et al., Eur Sleep Res Soc.
[3] 2017 Nuuttila et al., Int J Sports Med.

Disclosures: R.E. Johnson: None. **B. Flemming:** None. **N. Narvaez:** None.

Poster

769. Cardiovascular Regulation I

Location: Hall A

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Program #/Poster #: 769.09/Q15

Topic: F.07. Autonomic Regulation

Support: NIH Grant T32GM007592
NIH Grant RF1AG059867
NIH Grant R01AG048108

Title: Irregular sleep-wake schedules and their relationship to psychological and physical symptoms of poor mood

Authors: *C. HU[1], P. LI[1,2], P. M. WONG[3], F. A. J. L. SCHEER[1,2], C. LIN[4], M.-T. LO[4], K. HU[1,2], L. GAO[1,5];
[1]Div. of Sleep and Circadian Disorders, Brigham and Women's Hosp., Boston, MA; [2]Div. of Sleep Med., Harvard Med. Sch., Boston, MA; [3]Dept. of Psychology, Univ. of Pittsburgh, Pittsburgh, PA; [4]Inst. of Translational and Interdisciplinary Med., Natl. Central Univ., Taoyuan, Taiwan; [5]Dept. of Anesthesia, Massachusetts Gen. Hosp., Boston, MA

Abstract: Sleep-wake regularity (SWR) is often disrupted in college students and mood disorders are rife at this age. Disrupted SWR can cause repetitive and long-term misalignment between environmental and behavioral cycles and the circadian system which may then have psychological and physical health consequences. We previously showed that SWR was independently associated with mood, as measured using the Beck Depression Inventory (BDI) in a healthy adult cohort. However, it remained unclear whether this was driven by psychological complaints (e.g. guilt, sadness, or satisfaction) versus physical symptoms (e.g. appetite, libido, or tiredness). We studied 42 college students over a 3-week period using daily sleep-wake diaries. Neuropsychiatric wellbeing and mood was assessed weekly using the Beck Depression Inventory-II. Linear mixed effects models were used to account for repeated weekly measures. When we adjusted for age, sex, race, physical activity, chronotype, and mean sleep duration, prior week SWR was strongly predictive of the subsequent week's psychological symptom score component of BDI ($p = 0.0003$), whereas this was weaker for physical symptoms ($p = 0.02$); in fact, this observation was no longer significant once we accounted for the sleep question in BDI ($p = 0.053$). Further work is needed to understand the implications of poor psychological versus physical symptoms in those with low mood and irregular sleep-wake cycles.

Model		Psychological score (BDI)			Physical (BDI)		
		b	95% CI	*P*- value	b	95% CI	*P*- value
1a	SWR	-8.86	(-13.4 to 4.29)	**0.0003*** **	-3.14	(-5.74 to 0.56)	**0.02***
1b	SWR	-7.10	(-12.0 to -2.20)	**0.005** **	-0.06	(-0.14 to 0.02)	0.13
	Chronotype (MEQ)	-0.11	(-0.23 to 0.02)	0.08	0.05	(-0.004 to 0.10)	0.07
1c	SWR	-6.89	(- 12.4 to - 1.33)	**0.016***	-2.28	(-5.45 to 0.89	0.15
	Chronotype (MEQ)	-0.11	(- 0.23 to 0.02)	0.09	-0.03	(- 0.11 to 0.05)	0.49
	Delayed-bedtime	0.008	(- 0.08 to 0.10)	0.86	0.02	(- 0.04 to 0.08)	0.51

Table 1. Linear mixed effects models accounting for age, sex, race, physical activity, chronotype, and mean sleep duration for SWR prediction of psychological and physical components of BDI

Disclosures: **C. Hu:** None. **P. Li:** None. **P.M. Wong:** None. **F.A.J.L. Scheer:** None. **C. Lin:** None. **M. Lo:** None. **K. Hu:** None. **L. Gao:** None.

Poster

769. Cardiovascular Regulation I

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 769.10/Q16

Topic: F.07. Autonomic Regulation

Support: 5T32GM007592-40
RF1AG059867
R01AG048108

Title: Neuropsychiatric wellbeing and the daily/circadian rhythm of autonomic regulation in young adults

Authors: *L. GAO[1,2], H.-W. YANG[3], P. LI[1,4], C. HU[5], P. WONG[6], F. A. J. L. SCHEER[1,4], C. LIN[3], M.-T. LO[3], K. HU[1,4];
[1]Div. of Sleep and Circadian Disorders, Brigham & Women's Hosp., Boston, MA; [2]Dept. of Anesthesia, Massachusetts Gen. Hosp., Boston, MA; [3]Inst. of Translational and Interdisciplinary Med., Natl. Central Univ., Taoyuan, Taiwan; [4]Div. of Sleep Med., Harvard Med. Sch., Boston, MA; [5]Div. of Sleep and Circadian Disorders, Brigham and Women's Hosp., Boston, MA; [6]Dept. of Psychology, Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Disruption to sleep/wake regularity is perhaps most significant during college than at any other stage in life, and not surprisingly, mood disorders are rife. Repetitive and long-term misalignment between environmental/behavioral cycles and the circadian rhythm has been suggested as a potential mechanism leading to poor neuropsychiatric wellbeing, as well as

physical health consequences, likely through its influence on autonomic regulation. We hypothesized that the daily/circadian rhythm of high frequency heart rate variability (HF-HRV) was significantly altered in those with reporting poor mood in a healthy adult cohort.
We studied 42 college students over a 3-week period using daily sleep-wake diaries and continuous electrocardiogram (ECG) recordings from which hourly HF-HRV was derived. Neuropsychiatric wellbeing and mood was assessed weekly using the Beck Depression Inventory-II. We quantified the daily/circadian rhythm using cosinor model fitting in which both fundamental 24-h and 1st harmonics were included. We established a clear 24-h rhythm for HF-HRV ($p < 0.01$) across the study period. We found significantly increased HF-HRV across the habitual sleep-wake cycle ($p = 0.0002$) and a 36.7% increase in the 24-h fundamental rhythm ($p = 0.0003$) for those with poor mood (upper half of mean BDI), leading to more pronounced group difference during typical sleep periods (see Figure 1). In addition, the group difference in the daily/circadian rhythm was more pronounced in those with highly irregular sleep/wake cycles ($p = 0.0015$). Further work is needed to understand the implications of elevated daily/circadian HF-HRV rhythm in those with low mood and irregular sleep-wake cycles.

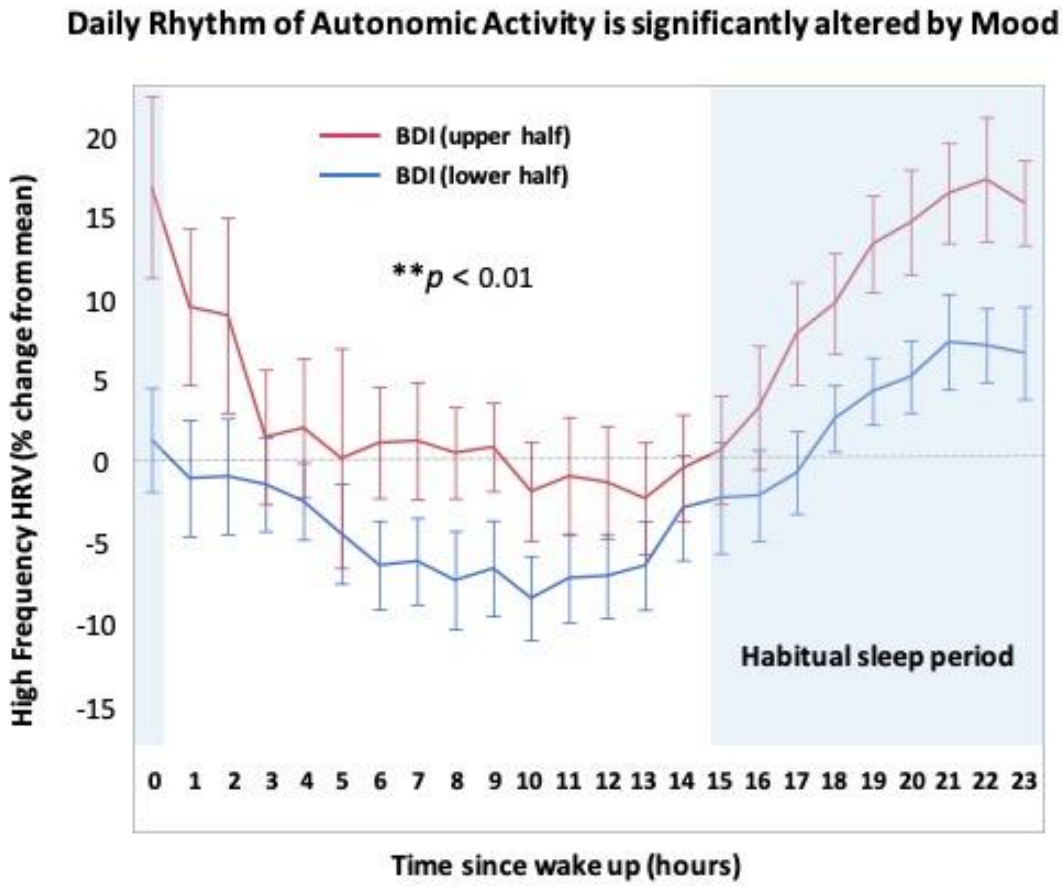

Figure 1. Daily rhythm of high frequency HRV (heart rate variability) is significantly different in those reporting higher weekly BDI (Beck Depression Inventory; upper half) scores versus lower BDI (lower half). Data (mean +/- 95% confidence interval) binned by hourly time since wake up, adjusted for each subject's habitual wake up time

Disclosures: **L. Gao:** None. **H. Yang:** None. **P. Li:** None. **C. Hu:** None. **P. Wong:** None. **F.A.J.L. Scheer:** None. **C. Lin:** None. **M. Lo:** None. **K. Hu:** None.

Poster

769. Cardiovascular Regulation I

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 769.11/Q17

Topic: F.07. Autonomic Regulation

Support: Internal funds from Battelle Memorial Institute

Title: Bioelectronic medicine for cardiovascular state control during spontaneous episodes of high blood pressure and myocardial ischemia

Authors: P. D. GANZER[1], S. ROOF[3], B. TENG[3], D. FRIEDENBERG[4], L. LIN[4], S. COLACHIS[1], R. HAMLIN[3], W. MUIR[3], D. J. WEBER[5], *G. SHARMA[2];
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Abstract: Bioelectronic medicine therapies are being developed as new treatments for a wide range of chronic diseases using peripheral nerve stimulation. Bioelectronic medicine can potentially be used to provide therapeutic benefit during many pathological states, including episodes of high blood pressure and myocardial ischemia. Prolonged periods of high blood pressure and myocardial ischemia can be life threatening in individuals with cardiovascular disease, potentially leading to myocardial injury, infarction, and other cardiovascular system damage. We first assessed the hypothesis that non-invasive stimulation of neural circuits can produce a robust and selective reduction in blood pressure without significant side effects. Experiments were performed in anesthetized rats and compared to an implanted cervical vagal nerve stimulation control. We recorded the electrocardiogram (ECG), arterial blood pressure (ABP), and the photoplethysmogram during systematic assessment of stimulation protocols. Our results support the hypothesis that selective control of ABP can be achieved via non-invasive stimulation (significant decreases up to ~35 mmHg), without significant side effects (e.g., no significant effect on heart rate, ECG waveform intervals, or breath rate). These results have potential implications for wearable bioelectronic medicine devices to treat pathological cardiovascular states, including periods of high blood pressure and myocardial ischemia. We next generated a model of spontaneous high blood pressure and myocardial ischemia using clinically relevant injectable cardiovascular agents in anesthetized rats. Agent injections induced prolonged periods of increased blood pressure and significant depression of the ECG S-T segment epoch, therefore modeling the attributes of clinical spontaneous myocardial ischemia.

We will present our results using non-invasive bioelectronic stimulation for reducing blood pressure and correlates of myocardial ischemia. In addition, we will present preliminary findings using machine learning to decode spontaneous episodes of myocardial ischemia at a sufficient prediction accuracy (> 80%, using non-linear support vector machines). These experiments assess the hypothesis that machine learning can be used to decode episodic cardiovascular pathology, and used to rapidly trigger reactive closed-loop neural stimulation for therapeutic benefit. Our eventual goal is to translate these findings to patients suffering from cardiovascular dysfunction, and develop wearable closed-loop bioelectronic medicines for treating an array of debilitating diseases.

Disclosures: P.D. Ganzer: None. **S. Roof:** None. **B. Teng:** None. **D. Friedenberg:** None. **L. Lin:** None. **S. Colachis:** None. **R. Hamlin:** None. **W. Muir:** None. **D.J. Weber:** None. **G. Sharma:** None.

Poster

769. Cardiovascular Regulation I

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 769.12/Q18

Topic: F.07. Autonomic Regulation

Support: Conacyt Grant 252702

Title: Effect of hydrogen sulfide on vascular dysfunction induced by fructose in rat thoracic aorta

Authors: *D. L. SILVA VELASCO[1], E. HONG[2], J. H. BELTRÁN-ORNELAS[1], A. SÁNCHEZ-LÓPEZ[1], C. B. GÓMEZ[1], S. HUERTA DE LA CRUZ[1], D. CENTURION[1]; [1]Pharmacobiology, [2]CINVESTAV, Mexico City, Mexico

Abstract: Hydrogen sulfide (H_2S) is a colorless, flammable and water-soluble gas characterized by a peculiar smell of rotten eggs. H_2S is a gasotransmitter synthetized from L-Cysteine by three enzymatic pathways namely cystathionine-ß-synthase (CBS), cystathionine- γ-lyase (CSE) and the tandem enzymes cysteine aminotransferase (CAT) and 3-mercaptopyruvate sulfurtransferase (3-MST). CSE predominates in the cardiovascular system, especially the myocardium and vascular smooth muscle cells (VSMCs). The aim of this study was to determine the effect of chronic administration of sodium hydrosulfide (NaHS; inorganic H_2S donor), L-Cysteine (L-Cys; H_2S producing enzymes substrate) and DL-Propargylglycine (DL-PAG; CSE inhibitor) on the vascular dysfunction induced by fructose in thoracic aorta obtained from male Wistar rats. For that purpose, animals were divided into two main sets that received for 20 weeks: (1) tap water (Control group; n=6); and (2) 15% p/v fructose in drinking water (Fructose group; n=30). Then, the fructose group were divided into 5 subgroups (n=6 each) which received daily i.p.

injections during 4 weeks of: (1) nothing; (2) vehicle (PBS, 1 ml/kg); (3) NaHS (5.6 mg/kg); (4) L-Cys (300 mg/kg); (5) DL-PAG (10 mg/kg). After 20 weeks, metabolic (oral glucose tolerance test, insulin, and Matsuda index) and hemodynamics variables by tail-cuff method as well as vascular function by *in vitro* experiments were determined. We observed that insulin resistance induced by fructose leads to: (1) an increase in blood pressure (without affecting heart rate); (2) hyperinsulinemia; (3) a decrease in Matsuda index; and (4) a decrease in vasorelaxation to carbachol without effect on the contractile responses to noradrenaline compared to control group. Interestingly, after 4 weeks of treatment, NaHS y L-Cys decreased blood pressure and restored vasorelaxation to carbachol without modifying metabolic variables when compared to vehicle. On the other hand, DL-PAG induced a slightly increase in systolic and median blood pressure with any effect on the contractile to noradrenaline or relaxant responses to carbachol as well as metabolic variables compared to vehicle. Taken together, these results suggest that chronic treatment with NaHS and L-Cys improved vascular dysfunction and reduced hypertension produced by fructose-induced insulin resistance and may have a potential therapeutic application.
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Poster

769. Cardiovascular Regulation I

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 769.13/R1

Topic: F.07. Autonomic Regulation

Title: Heart rate variability in patients with trigeminal neuralgia

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Abstract: BACKGROUND:
Trigeminal neuralgia (TN) is a common neurological disorder characterized by intermittent events of acute, sharp pain confined to small areas of the face. Numerous studies suggest TN is associated with autonomic dysfunction. Assessing this dysfunction using Heart Rate Variability (HRV) technique is very limited. Hence the aim of the present study is to evaluate the heart rate variability(HRV) in patients with TN and to compare it with healthy controls.
METHODS:
This is a prospective comparative study. Twenty-two (12 males) TN patients and 22 (11 males) healthy controls were included in the study. Short term HRV of time and frequency domain

parameters were assessed by recording resting lead II ECG. Time domain parameters of interest were standard deviation of all RR intervals (SDNN), square root of the mean of the sum of the squares of differences between adjacent RR intervals (RMSSD), the number of pairs of adjacent RR intervals differing by more than 50ms in the entire recording (NN50), the percentage of NN50 counts (pNN50). Frequency domain parameters assessed were Total power (sum of all constituent frequencies), low-frequency power (LF) (0.04 to 0.15 Hz), high-frequency power (HF) (0.15 to 0.4 Hz) and LF/HF ratio. Independent Mann- Whitney U test was used to compare between the groups.

RESULTS:

The mean age (years) of the subjects with TN was 50.36 ± 7.3 and controls was 49.11 ± 5.5. The study results did not show any significant difference in the HRV parameters between groups. The LF power of the TN subjects shows a trend towards high sympathetic activity [Median (Q1-Q3)] of [173.24 (79.87, 248.2)] as compared to healthy controls [150.43 (98.37, 573.20)]. As this is an on-going study we are considering to increase the sample size, include self-perceived pain severity scales and to subgroup the TN patients based on the severity. Extensive statistical analysis will be performed later after including these parameters.

Conclusion:

The results suggest that TN may be linked with autonomic dysfunction by exhibiting a trend towards sympathetic dominance as compared to healthy controls. This altered ANS response observed in TN patients might be a consequence or cause for TN pain. Future studies are required to characterize autonomic dysfunction on pain severity and to describe its pathophysiology in patients with TN.

Keywords: Trigeminal neuralgia, Heart rate variability

Disclosures: G. Inbaraj: None. **T.N. Sathyaprabha:** None. **K. Udupa:** None.

Poster

769. Cardiovascular Regulation I

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 769.14/R2

Topic: F.07. Autonomic Regulation

Title: Effects of match temperature on heart rate for female soccer players

Authors: F. VAZQUEZ[1], ***M. YOUNG**[1], T. WADE[1], A. JOHNSON[1], R. E. JOHNSON[2], K. SCHMITT[1];
[1]Mathematics and Statistics, [2]Mechanical Engin. and Bioengineering, Valparaiso Univ., Valparaiso, IN

Abstract: In athletics, coaches and trainers are increasingly using heart rate data to optimize training and workload. One factor that is not often considered is ambient temperature. We know

that in general, the body works harder in higher temperatures, so heart rate should tend to be higher on those days. However, we do not know if this relationship is consistent enough to use to make real-time decisions on workload for athletes during training and matches. In this study we investigated the relationship between ambient temperature and intensity of a workout, and the effect that temperature has on heart rate. Temperature data was sourced from the National Oceanic and Atmospheric Association (NOAA) and athlete heart rate data was collected by Firstbeat activity trackers. 27 collegiate female soccer players participated in this experiment. Using Python, we created several multiple linear regression models to predict heart rate. Attributes such as intensity of activity, duration, and temperature were included in the models. All results for our study use data starting in the fall of 2017. We conclude that models built on individual players' data is more informative than models on the team as a whole. We made regression equations to produce an average and peak heart rate for each player. These individual models may help us predict if a player is over exerting themselves. If a player's heart rate increased past the average predicted value, then coaches may consider pulling the player from a game or strenuous practice to prevent longer recovery times.

Disclosures: **F. Vazquez:** None. **M. Young:** None. **T. Wade:** None. **A. Johnson:** None. **R.E. Johnson:** None. **K. Schmitt:** None.

Poster

769. Cardiovascular Regulation I

Location: Hall A

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Program #/Poster #: 769.15/R3

Topic: F.07. Autonomic Regulation

Support: Supported by Conacyt 243298
CA-UASLP 254

Title: The hypertensive effect of α-MSH in a rat model of metabolic syndrome

Authors: *R. C. SALGADO-DELGADO[1], A. BAEZ-RUIZ[1], R. M. BUIJS[2], N. SADERI[3]; [1]Facultad de Ciencias, UASLP, San Luis Potosí, Mexico; [2]Inst. De Investigacíones Biomedicas, Mexico DF, Mexico; [3]Facultad De Ciencias, UASLP, San Luis Potosí, Mexico

Abstract: Much of the understanding of how the hypothalamus controls body homeostasis regards the physiological properties of the alpha- melanocyte stimulating-hormone (α-MSH) in the Arcuate nucleus (ARC). Blood-borne and neural satiety signals activate α-MSH neurons in order to suppress food intake and stimulate energy expenditure, while the deficit of the melanocortin signaling results in obesity and other metabolic alterations. Previous studies about the hypertensive effects of the hormone leptin indicated that α-MSH might mediate the hyperactivation of the sympathetic nervous system (SNS) in on obese animals and human

subjects. For instance, leptin receptors-expressing cells in the ARC colocalize with the angiotensin II-receptor 1 (AT-1), leading to the hypothesis whether these AT-1-expressing cells are α-MSH neurons. To address this issue, we compared AT-1 and α-MSH immunoreactivity in male Wistar rats (n = 5) fed with a standard chow (controls: CTR) and fed with and high fat diet (HFD) containing about the 30% of fat for 12 weeks. Results showed that HFD promotes AT-1 expression, α-MSH cells activation and the co-localization of AT-1 with α-MSH. Then, to assess the contribution of α-MSH to obesity-related hypertension, we injected either the melanocortin antagonist SHU9119 or saline in the third ventricle of anesthetized CTR and HFD animals and found that it significantly decreases BP specifically in HFD rats. Finally, to identify the anatomical site of the α-MSH hypertensive effect, we evaluated c-Fos expression in the Paraventricular nucleus (PVN), which is one of the main hypothalamic area containing pre-autonomic neurons. We found that HFD increase the number of c-Fos - positive cells in the PVN, while SHU9119 administration decreases it. Finally, among the target of ARC projections to the PVN, we observed that the number of Tyrosine hydroxylase-containing neurons is significantly increased in HFD and these cells received dense α-MSH projections. All together, these results suggest that ARC - α-MSH underlie the abnormal autonomic response in obesity that leads to hypertension.

Disclosures: R.C. Salgado-Delgado: None. **A. Baez-Ruiz:** None. **R.M. Buijs:** None. **N. Saderi:** None.

Poster

769. Cardiovascular Regulation I

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 769.16/R4

Topic: F.07. Autonomic Regulation

Support: OT2OD023848

Title: Mapping of intrinsic cardiac neurons projecting to the sinoatrial node and the left ventricle of rats

Authors: *J. CHEN[1], S. TAPPAN[2], R. VADIGEPALLI[3], J. S. SCHWABER[3], Z. CHENG[1]; [1]Burnett Sch. of Biomed. Sci., Univ. of Central Florida, Orlando, FL; [2]R&D, MBF Biosci. - MicroBrightField Inc., Williston, VT; [3]Dept. of Pathology, Thomas Jefferson Univ., Philadelphia, PA

Abstract: Previously, we showed that multiple intrinsic cardiac ganglionated plexuses (ICGPs) are located on the dorsal surface of the left and right atria. However, it is not clear which populations of the intrinsic cardiac neurons (ICNs) project to the Sinoatrial Node (SAN) and ventricles. Our long-term goal is to determine the topographical organization of ICGPs

projecting to different cardiac targets. In this study, we specifically aimed to determine differential projection of the ICGP to the SAN and left ventricle (LV) of Sprague Dawley rats (male, 3-mo). The SAN and LV were focally injected with fluorescent tracer Fast DiI to retrogradely label ICNs which projected to these regions (2 %; 4-5 µl/SAN injection, 20 µl/ventricle injection; n=5/region). After DiI injection, the animals were returned to their cages for 14 days for tracer transportation. 4-5 days before sacrifice, Fluorogold (FG) was injected intraperitoneally to counterstain all ICNs, and at the end of the time point, animals were perfused and fixed through the heart. The left and right atria were cut open and prepared as whole mounts, and SAN cells were confirmed by immunostaining with HCN4, a pacemaker channel marker. The distribution of tracer-labeled ICNs in the whole mounts of the left and right atria were imaged, overlaid, and analyzed using the Neurolucida Tracing and Digitization System (n=5/region) . Consistent with our previous findings, we found that there are multiple ICGPs, and there is a large ICGP near SAN. DiI injection into the SAN region retrogradely labeled 72.8±17.53 (n=5) ICNs mainly in this large ganglion near the SAN. In contrast, DiI injection into the LV labeled 17.6±5.93 (n=5) ICNs in several spatially-separated ICGPs on the dorsal surface of the atria, with only a few DiI-labeled ICNs in this large ICGP near the SAN, if any. Thus, we propose that there are different populations of ICNs that separately project to the SAN and the LV. Our work contributes to the understanding of the topographical organization of ICN innervation of the heart. Furthermore, a 3-D representation of this topographical mapping in the heart will provide an anatomical substrate to integrate physiological, molecular, and pharmacological data in the future. Supported by the subaward to ZJC from NIH SPARC OT2OD023848 to UCLA (PD/PI Kalyanam Shivkumar).

Disclosures: J. Chen: None. **S. Tappan:** None. **R. Vadigepalli:** None. **J.S. Schwaber:** None. **Z. Cheng:** None.

Poster

769. Cardiovascular Regulation I

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 769.17/R5

Topic: F.07. Autonomic Regulation

Support: Stichting Technische Wetenschappen 14901

Title: Multimodal non-invasive monitoring of cardiovascular responses to postural changes

Authors: *A. MOL[1], A. B. MAIER[2], R. J. A. VAN WEZEL[3], C. G. M. MESKERS[4];
[1]VU Amsterdam, Amsterdam, Netherlands; [2]The Univ. of Melbourne, Melbourne, Australia;
[3]Radboud University, Donders Inst. for Brain, Cognition and Behaviour, Nijmegen, Netherlands;
[4]VUmc, Amsterdam, Netherlands

Abstract: Background: Orthostatic hypotension (OH, i.e. a blood pressure (BP) drop after standing up) is a prevalent condition in older adults and is associated with poor health outcome such as falls. However, its underlying pathophysiological mechanisms are largely unknown. Current clinical assessment based on intermittent blood pressure measurements is insufficient due to lack of sensitivity and presence of compensatory physiological systems. Baroreflex sensitivity (BRS, i.e. increased heart rate as a response to BP drops), cerebral autoregulation (CAR, i.e. cerebral vasodilation as a response BP drops to keep cerebral blood flow constant) and peripheral vasoconstriction are likely to play a key role. There is a need for understanding of above-mentioned mechanisms and their reliability and validity in clinical practice. **Methods:** We used a combination of photoplethysmography (PPG, applied to wrist and finger), ECG, bifrontal near infrared spectroscopy (NIRS) and continuous blood pressure (Finapres) for measurements during postural changes varying in center of mass displacement, speed and leg muscle use in 34 healthy young (median age 25 years, inter quartile range 22-45; 10 female) and 31 healthy older adults (median age 77 years, inter quartile range 74-83; 18 female). Reliability and validity were defined as the correlation between repeats and the correlation with BP, respectively. Peripheral vasoconstriction was assessed using pulse wave velocity (PWV, measured from heart to wrist and finger). **Results:** BRS and CAR had fair to excellent validity in healthy young adults. Pearson correlation of finger PPG with BP during rapid standing up was 0.95 in healthy young adults and 0.55 in healthy older adults. After standing up, PWV showed a significant rise in healthy young adults, but not in healthy older adults. **Conclusion:** Non-invasive measurement of BRS and CAR using PPG-ECG-NIRS signals is reliable in healthy young adults. PPG might be used to estimate BP, but it has a lower correlation with BP in healthy older adults compared to young adults. The upper ertremity arteries demonstrate significant vasoconstriction in healthy young adults after standing up, but not in healthy older adults. The results highlight the potential clinical value of PPG-ECG-NIRS signals to assess BRS, CAR and vasoconstriction in patients with OH.

Disclosures: A. Mol: None. **A.B. Maier:** None. **R.J.A. Van Wezel:** None. **C.G.M. Meskers:** None.

Poster

769. Cardiovascular Regulation I

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 769.18/R6

Topic: F.02. Behavioral Neuroendocrinology

Support: JST CREST JPMJCR14E4

Title: Pre-competitive physiological state affects performance in snowboard jump competitions

Authors: *S. MATSUMURA, K. WATANABE, N. SAIJO, T. KIMURA, M. KASHINO; NTT Communication Sci. Labs., Kanagawa, Japan

Abstract: An athlete's pre-competitive mental state has a major influence on competitive performance. Several studies have reported that mental state affects the performance of simple motor tasks in experimental environments where mental state control is limited. However, little is known about the relationship between pre-competitive mental state and complex movements requiring high skills in practical situations. We examined the relationship between the pre-competitive physiological state as index of mental state and competitive performance in an actual snowboard jump competition. Forty-four expert snowboarders participated in this competition. There were three sessions, practice, qualifying and final. As in regular professional competitions, three professional snowboarders scored the jump performance in terms of completion. The top twenty jumpers in the qualifying session advanced to the final session and the champion won a prize. During the competition, as physiological indices, electrocardiograms (ECGs) and the electrodermal activity (EDA) of all the participants were measured for 140 seconds during the 10 minutes before the start of each jump. The mean heart rate (HR) and the natural logarithm of the high frequency power (lnHF) of the heart rate variability were calculated from the ECGs as an index of sympatho-vagal balance and parasympathetic nerve activity, respectively. The skin conductance level (SCL) was also acquired from the EDA as an index of sympathetic nerve activity. The twenty finalists were divided into the top and bottom ten, to analyze the dependence of the difference in physiological state on skill level. To compare the physiological indices in the qualifying and final sessions with those in the practice session, they were standardized with those in the practice session. The top group showed a significant increase in mean HR (1.12 ± 0.03, $p = 0.009$) and SCL (1.31 ± 0.11, $p = 0.037$) and a significant decrease in lnHF (0.93 ± 0.02, $p = 0.009$), while the bottom group did not. These results indicate that the sympathetic nerve activity of a skilled snowboarder increases prior to the jump. Since the bottom group did not exhibit such activity changes, highly skilled athletes may appropriately control their mental states to realize high-level performance. Interestingly, additional analysis of the top-group data showed a correlation between the judges' scores and the physiological indices. Since these judgments were related to a complex whole-body movement, this result may indicate that the pre-competitive mental state affects the motor coordination of whole-body movement.

Disclosures: S. Matsumura: None. **K. Watanabe:** None. **N. Saijo:** None. **T. Kimura:** None. **M. Kashino:** None.

Poster

769. Cardiovascular Regulation I

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 769.19/R7

Topic: F.03. Neuroendocrine Processes

Title: Subjective effects of a gambling challenge in recreational gamblers versus gambling naive individuals

Authors: *L. C. MILLER, A. SÖDERPALM GORDH, B. SÖDERPALM;
Neurosci. and Physiol., Gothenburg Univ., Gothenburg, Sweden

Abstract: Pathological gambling shares many similarities with drug addiction in terms of clinical phenomena (e.g. craving, tolerance, compulsive use and loss of impulse control) plus heritability. Pathological gamblers also show a similar arousal and reward sensitivity during gambling probably mediated by the mesolimbic dopamine system well known to the field of drug addiction. We hypothesize that recreational gamblers show extra sensitivity to the rewarding effects of gambling in comparison to gambling naive individuals.
Eighty-two healthy participants (36 no gamblers, 46 gamblers) were recruited. Self-reported questionnaires as The Profile of Mood States questionnaire (POMS), The Biphasic Alcohol Effects Scale (BAES), The Addiction Research Centre Inventory (ARCI), The Drug Effect Questionnaire (DEQ) and objective measures (cortisol and blood pressure) were used to assess mood states and subjective drug effects described sensitive to the effects of a variety of psychoactive drugs at baseline and post test.
Once participants had completed baseline measures, they gambled for 10 min on a laboratory casino slot machine that was set up on a laptop which gave them 'wins', 'jackpots' and 'loosing streaks. The participants were unaware of the length of time for which they gambled for. No money was paid out to the participants which was disclosed before the trial commenced. Once the gambling had finished each participant answered the post test questions and cortisol and blood pressure was taken a second time.
Our first aim was to study changes in the subjective, neuroendocrine, and physiological responses to an acute gambling situation in recreational gamblers and in those who never gambled before. This study would improve and allow a better understanding of the complexity of an individual's gambling behaviour. We compared recreational gamblers to those who never gambled before.

Disclosures: L.C. Miller: None. **A. Söderpalm Gordh:** None. **B. Söderpalm:** None.

Poster

769. Cardiovascular Regulation I

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 769.20/R8

Topic: F.02. Behavioral Neuroendocrinology

Support: JST CREST JPMJCR14E4

Title: The across-player correlation of the physiological change reflecting the fight-or-flight response in esports

Authors: *K. WATANABE, N. SAIJO, M. KASHINO;
NTT Communication Sci. Labs., Kanagawa, Japan

Abstract: It is well known that a fight-or-flight response is generated when one has to fight enemies or quickly escape a threat. In fighting sports, for example, it may occur when one player tries to beat or to defend against another. However, the relationship between the responses of two opponents remains unclear. In this study, we observed the changes in the physiological states of two opponents who played an esports fighting game. Nine professional esports players participated in this study. In the fighting game, one player controls a game character and fights an opponent in a virtual world. We measured the electrocardiograms (ECGs) of the participants when they were playing the game. First, the participants were measured when in a resting state. Then, they played against a computer for 5 minutes. After that, the participant competed with other participants until one player had achieved five wins. A group of three men of differing abilities engaged in a round-robin tournament, and a group of six men with comparable abilities also engaged in a round-robin tournament. Heart rate time series were calculated from the ECGs as indices of autonomic nerve activity, and the cross-correlation function (CCF) was calculated from two sets of time-series data obtained from a fighting pair. The results showed that the heart rate increased greatly when the participant played against an actual person, compared with that when the participant was playing the game alone. This indicates that a fight against other participants increases the heart rate.The results for a pair with different abilities showed that the CCF and the change in heart rate of a strong player was smaller than for other pairs, indicating that only the weaker player exhibited the fight-or-flight response. On the other hand, the results for a pair with comparable abilities exhibited a high CCF, indicating that they both exhibited the fight-or-flight response with a similar temporal pattern. These results suggest that the appearance of the fight-or-flight response is related to one's opponent's ability.

Disclosures: K. Watanabe: None. **N. Saijo:** None. **M. Kashino:** None.

Poster

770. Cardiovascular Regulation II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 770.01/R9

Topic: F.07. Autonomic Regulation

Support: SNF grant 31003A_160325

Title: The parvalbumin-positive PV2-nucleus of the midbrain PAG

Authors: S. LEHMANN[1], A. BABALIAN[1], F. GIRARD[1,2], F. DAVIS[2], *M. R. CELIO[1];
[1]Sci. and Med., Univ. of Fribourg, Fribourg, Switzerland; [2]Howard Hughes Med. Inst., Janelia Farm, Ashburn, VA

Abstract: The periaqueductal gray (PAG), is known to play a key role in the integration and modulation of autonomic responses. It harbors two of the main terminal fields of the hypothalamic parvafox-nucleus, namely the Su3- and PV2-nuclei. This latter nucleus was yet unknown, leading us to perform diverse studies to characterize its extent, connections, gene expression and function. The PV2-nucleus is an elongated cluster composed of ~500 parvalbumin-expressing neurons, located in the ventromedial region of the distal PAG. Using anterograde-tracing methods, the main projections of the PV2-nucleus were found to innervate the Su3-nucleus of the PAG, the parvafox-nucleus of the lateral hypothalamus, the gemini nuclei of the posterior hypothalamus, the septal region and the diagonal band of the forebrain, as well as various nuclei within the reticular formation in the midbrain and brainstem. The parvafox-nucleus and the lateral orbital cortex also target several of the mentioned regions. Within the brainstem, projections of the PV2-nucleus were discrete, but involved areas implicated in autonomic control. The PV2-nucleus expressed various peptides and receptors, including the receptor for Adcyap, a peptide secreted by one of its main afferences, the parvafox-nucleus. Expression of VGat-1 in a subpopulation of PV2-neurons indicate a partly inhibitory nature of this nucleus. Experiments to determine the possible function of the PV2-nucleus in a circuitry involving the orbitofrontal cortex, the parvafox and the Su3-nucleus are being conducted. These preliminary results suggest an involvement of the PV2-nucleus in the control of the respiratory and the cardiovascular system.

Disclosures: S. Lehmann: None. **A. Babalian:** None. **F. Girard:** None. **F. Davis:** None. **M.R. Celio:** None.

Poster

770. Cardiovascular Regulation II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 770.02/R10

Topic: F.07. Autonomic Regulation

Support: AHA 16SDG26590000
UT Health SA Start-Up
R25 IMSD Trainee Grant

Title: Two roads diverged: Cardiac vagal motor neurons and their role in high fat diet-induced cardiovascular disease pathophysiology

Authors: *L. ESPINOZA, C. R. BOYCHUK;
Univ. of Texas Hlth. San Antonio, San Antonio, TX

Abstract: Cardiovascular disease (CVD) is the leading cause of death world-wide, accounting for 31% of global deaths each year. Obesity can arise from an unhealthy fatty diet, and is an independent risk factor for the development of various forms of CVD including hypertension. One potential conduit to hypertension is tachycardia, and the vagus nerve—one of the primary components of the parasympathetic branch of the autonomic nervous system—regulates heart rate, thereby highlighting vagal motor drive as a promising candidate for novel CVD therapeutics. Cardiac-related vagal innervation originates from two primary neuronal populations: the nucleus ambiguous (NA) and dorsal motor nucleus of the vagus (DMV). Studies have illustrated the therapeutic potential of DMV optogenetic activation in models of CVD. However, little is known about the electrophysiological properties of cardiac-projecting DMV neurons, or how these are altered by high fat diet (HFD) exposure. Our limited understanding comes from recent studies in unlabeled DMV neurons, which have shown that HFD leads to decreased neuronal excitability. However, the mechanism of this inhibited activity remains elusive. Therefore, we hypothesized that HFD-mediated increases in inhibitory current to cardiac-related vagal neurons leads to a decrease in cardiac vagal drive, and ultimately, CVD. In this study, we characterized the differences in the electrophysiological signaling properties and contribution to heart rate modulation between retrogradely labeled NA and DMV neurons, both under control and HFD conditions. Our approach employed retrograde tracing to identify cardiac-related vagal neuron populations; *in vitro* whole-cell patch-clamp electrophysiology to assess their signaling properties; and *in vivo* heart rate telemetry to monitor HFD-induced alterations in heart rate modulation. Tracing studies confirmed that the NA contains significantly more retrogradely labeled neurons from the SA node than the DMV. Whole-cell patch clamp data demonstrate that labeled neurons in the DMV have distinct electrophysiological properties compared to those in the NA. Heart rate telemetry found that mice challenged with HFD for a two-week period had increased heart rate and decreased indices of parasympathetic activity as early as two days following HFD exposure. These changes occurred in the absence of significant changes in fed-state blood glucose levels, food intake, or body weight. Our findings suggest that increasing parasympathetic drive prior and during HFD exposure may be a promising therapeutic target for obesity-induced CVD.

Disclosures: L. Espinoza: None. **C.R. Boychuk:** None.

Poster

770. Cardiovascular Regulation II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 770.03/R11

Topic: F.07. Autonomic Regulation

Support: NIH Grant RO1-HL-141560

Title: Vagus nerve stimulation activates supramedullary pathways to potentiate activity of nucleus of solitary tract (NTS) neurons

Authors: C. M. COOPER[1], M. C. ANDRESEN[2], R. P. CAMPBELL[3], *E. BEAUMONT[1]; [1]Biomed. Sci., East Tennessee State Univ., Johnson City, TN; [2]Physiol. and Pharmacol., Oregon Hlth. & Sci. Univ., Portland, OR; [3]Emory & Henry Col., Emory, VA

Abstract: **Background:** Vagus nerve stimulation (VNS) is currently used to treat patients with drug resistant epilepsy, depression and, more recently, heart failure. The mild intensities used in chronic VNS suggest activation of a subset of myelinated primary visceral afferents connected directly to NTS neurons. Here we monitored the activity of 2nd and higher order NTS neurons in response to peripheral vagal activation using therapeutic VNS criteria.
Methods: NTS neuronal spike activity was recorded in chloralose anesthetized rats. Controls (n=12) were compared to rats after a mid-collicular knife cut (n=8). The cut severed connections between the brainstem including NTS and supramedullary regions. A bipolar coil electrode was implanted around the left cervical vagus nerve. Single tungsten electrodes were stereotaxically placed in the left caudal medial NTS. Threshold intensity, single or paired shocks established vagal afferent activation of single NTS neurons to determine conduction velocity as well as synaptic order (2nd vs higher). Once vagal connectivity was established, VNS condition stimuli followed clinically styled guidelines using a current intensity that induced a 5% bradycardia.
Results: Our chief findings indicate that a mid-collicular knife cut significantly reduced basal spontaneous activity of 2nd order NTS neurons receiving myelinated vagal input (from 13 ± 1.5 Hz to 2.1 ± 0.31 Hz, $p<0.01$). In these particular NTS neurons, the activity increases associated with acute VNS were similar between control and knife cut animals. Finally, the knife cut eliminated activity increases associated with acute VNS in higher order NTS neurons and also in 2nd order neurons receiving unmyelinated vagal input ($p<0.05$).
Conclusions: Interestingly, higher order NTS neurons and 2nd order NTS neurons receiving unmyelinated vagal input are activated in response to myelinated vagal afferent activation during VNS and this activation is interrupted by the knife cut. Concurrently, the knife cut decreased spontaneous activity in NTS receiving myelinated input, but preserved increased activation with VNS, most likely because VNS directly activated their myelinated axons. Supramedullary descending projections to NTS, in which a proportion of them are coming from the paraventricular nucleus of the hypothalamus (PVN), are needed to amplify the peripheral neuronal signal from VNS. The present study begins to define the pathways activated during VNS and will help to better identify the central nervous system contributions to the therapeutic benefits of VNS therapy.

Disclosures: C.M. Cooper: None. **M.C. Andresen:** None. **R.P. Campbell:** None. **E. Beaumont:** 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.; NIH RO1-HL-141560.

Poster

770. Cardiovascular Regulation II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 770.04/R12

Topic: F.07. Autonomic Regulation

Support: Intra mural

Title: Intra and extraneural activity in the vagus nerve recorded by platinized graphene fiber electrodes

Authors: *M. A. GONZÁLEZ-GONZÁLEZ[1], R. A. JALLILI[2], G. WALLACE[3], M. I. ROMERO-ORTEGA[1];
[1]Bioengineering, The Univ. of Texas at Dallas, Dallas, TX; [2]RMIT Univ., Melbourne, Australia; [3]Univ. of Wollongong, Wollongong, Australia

Abstract: Neurmodulation of the vagus nerve (VN) is clinically used for the treatment of intractable epilepsy and depression, and currently investigated for the use in morbid obesity, tinnitus and stroke. The VN is the largest autonomic nerve, it connects the periphery organs with different integrative areas in the brain to maintain homeostasis. It has a heterogeneous anatomical composition (~80% afferents and ~20% efferent fibers), resulting in complex functional electrophysiology that responds in a unique way to different physiological stimulus. The requirement of low impedance electrodes with high signal-to-noise ratio (SNR) to allow for sensitive recordings are imperative to understand the VN activity in response to specific physiological stimulus. Conventional electrodes are fabricated with platinum or platinum iridium and have limited sensitivity and low charge injection capacity (Qinj, ~0.05-0.26 mC/cm2), whereas intraneural electrodes fabricated with carbon nanotubes have shown promise (CSC ~372 mC/cm2, 12.5 kΩ). Here we report the use of platinized graphene fiber electrodes for the recording of intra and extra-neural activity in VN. We recently reported the fabrication of high performance platinized graphene fibers (40 µm diameter) obtained form liquid crystalline dispersions of graphene oxide, with excellent electrochemical characteristics (CSC and Qinj ~947 and ~46 mC/cm2 respectively). In this study nine adult male Sprague Dawley rats, were used to record the vagus nerve activity during: i) systemic reduction in Oxygen tension, ii) decreased mean arterial pressure induced by intravenous nitroprusside treatment, and iii) evoked activity in response to proximal vagus nerve stimulation using a platinum hook electrode. In each condition, specific activity waveforms and activity patterns were correlated to the treatments over baseline conditions with high signal to noise ratios (SNR~4.3). The data support the use of these electrodes as autonomic neural interfaces to decode the VN electrical activity. This technology find application in the design of new therapies directed to specific health dysfunctions and for the design of peripheral prosthesis.

Disclosures: **M.A. González-González:** None. **R.A. Jallili:** None. **G. Wallace:** None. **M.I. Romero-Ortega:** None.

Poster

770. Cardiovascular Regulation II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 770.05/R13

Topic: F.07. Autonomic Regulation

Support: United Therapeutics

Title: Directional biasing of vagal fiber activation using anodal block waveforms

Authors: ***U. AHMED**, Y.-C. CHANG, M. CRACCHIOLO, J. N. TOMAIO, M. F. LOPEZ, L. RIETH, T. ZANOS, S. ZANOS;
Inst. of Bioelectronic Med., Feinstein Inst. For Med. Res., Manhasset, NY

Abstract: One of the challenges in the clinical application of vagus nerve stimulation (VNS) is selection of fiber activation in order to maximize the desired and minimize undesired physiological effects of VNS. In cases where only afferent effects of VNS are sought, efferent effects need to be suppressed, and vice-versa. Anodal block, the suppression of conduction of stimulus-evoked volleys along a hyperpolarized patch of membrane (anode) has been tested in peripheral nerves to achieve directional activation, with varying success. In this study, we tested whether anodal block, with appropriate electrode and stimulus characteristics, can be attained in the context of cervical VNS. In male Sprague-Dawley rats anesthetized with isoflurane, two custom-made, flexible bipolar electrodes (1mm distance between the 2 poles) were placed on left or right vagus, 5mm apart: one electrode was used for stimulation, the other for recording of evoked compound nerve potentials (CNAPs). Stimulation consisted of short trains of rectangular pulses with different polarities, amplitudes and pulse widths. Stimulus-elicited changes in breathing rate and heart rate were used as physiological indices of afferent and efferent fiber activation, respectively. CNAPs and physiological responses to stimuli of different polarities suggested activation of both afferent and efferent fibers, in different proportions. For stimulation pulse waveforms of intermediate intensities and longer pulse widths, cathode caudad polarity was associated with predominantly efferent fiber activation, whereas cathode-cephalad polarity with predominantly afferent fiber activation. The fact that differences in the physiological and CNAP responses to different rectangular waveform polarities can be seen with even short stimulus trains suggests that stimulation polarity can be used to bias current and future VNS-based therapies towards afferent or efferent effects.

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Poster

770. Cardiovascular Regulation II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 770.06/R14

Topic: F.07. Autonomic Regulation

Support: NIH R01DC006213

Title: Breathing across emotionally-salient states in mice

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Abstract: Emotional states are associated with distinct autonomic respiration patterns in humans; this observation generated a theory that breathing likely serves as a strong physiological predictor of emotional state. For instance, in panic disorder, breathing abnormalities not only manifest as a result of a panic attack, but cardiorespiratory variability is thought to precede and even trigger the attacks themselves. Thus, understanding the neural mechanisms that drive emotionally-relevant breathing may give insight into dysregulated circuits that exist in some mental disorders. In rodent models, investigation focuses on central pattern generators in the brainstem that control the basic motor output necessary for breathing. However, which neural regions provide top down regulation to these respiratory centers during emotional states remains unknown. While a few studies demonstrate that rodents slow their breathing during freezing, a stereotypical motor response to fear, the relationship between breathing and emotion during frequently used assays is little explored. To address the relationship between breathing and emotional states in mice, we implanted an intranasal cannula into the nasal cavity and used a pressure sensor to monitor breathing in awake, behaving animals. The mice were exposed, in a randomized order, to a range of emotionally-salient stimuli including: an attractive odor, a predator odor, tail suspension test, restraint stress, and fear conditioning. We then used a MATLAB toolbox, BreathMetrics, to rigorously analyze respiration during specific behavioral bouts from these assays such as freezing, sniffing, struggling, or immobility. This analysis revealed that breathing changes reflect specific states such as freezing post fear conditioning or predator odor as well as struggling and immobility in the tail suspension test. These data suggest that respiration patterns may effectively distinguish emotionally-salient states in rodents.

Disclosures: E.C. Janke: None. **M. Ma:** None. **A.H. Moberly:** None.

Poster

770. Cardiovascular Regulation II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 770.07/R15

Topic: F.07. Autonomic Regulation

Support: NIH grant HL142489

Title: Piezoelectric sensors for noninvasive breath rate tracking in a cage setting

Authors: R. L. BERNAT[1,2], A.-H. LIN[3], A. AGARWAL[1], K. D. DONOHUE[4,1], ***B. F. O'HARA**[2,1];
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Abstract: The ability to track respiratory output in rodents provides physiological information relevant to disease states. Noninvasive methods enable longitudinal breath tracking related to disease progression, response to drug treatment, and more rigorous testing of adverse respiratory effects of drugs, such as opioids. Whole body plethysmography is the gold standard for noninvasive monitoring of breathing, and provides accurate measures of rate and tidal volume. However, this method confines the animal to a small space during data collection, requires a period of acclimation, and limits data collection to a few hours. A method to collect breathing data from a home-cage setting would greatly simplify research procedures, and reduce stress to research animals. Piezoelectric sensors are pressure sensors that produce voltage in direct proportion to the pressure applied, and are used in the PiezoSleep system (Signal Solutions LLC) to noninvasively monitor sleep and wake. While the signal resulting from respiration during low activity is used as a feature in the sleep/wake decision statistic for sleep scoring, breathing itself has not been formally investigated. Breath signals are recorded from piezo sensors on the cage floor when animals are sleeping or during periods of low activity. For most research purposes, breath parameters during sleep are highly relevant, when involuntary central respiratory drive is required to maintain breathing. Therefore, a method to continuously monitor breathing during sleep would provide a simpler option. We investigated the accuracy of piezo sensing to track respiratory information in mice of different ages, strains, sex and weight by simultaneously collecting respiratory output by plethysmography and piezo sensors. A plethysmography chamber was fitted with a piezo sensor, and plethysmograph and piezo respiratory output was recorded, along with video. Breath rates are estimated from both the plethysmography and piezo signals over short time intervals using an autocorrelation-based method. All valid estimates are then combined over larger intervals to compute a more robust mean or median breath rate. Graphical representations of raw signals were also overlaid for visual observation, to examine areas of disagreement, and to compare video. During sleep and quiet rest, the two signals

matched well. Areas of disagreement showed brief arousals, twitching, yawning, and repositioning. Initial analysis show a 10% (or .25 Hz) root mean square disagreement between the modalities (90% agreement). Analysis is ongoing for data collected in different strains, sex, ages and weights of mice, along with independent studies in rats.

Disclosures: **R.L. Bernat:** A. Employment/Salary (full or part-time):; Signal Solutions LLC. **A. Lin:** None. **A. Agarwal:** A. Employment/Salary (full or part-time):; Signal Solutions LLC. **K.D. Donohue:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Signal Solutions LLC. **B.F. O'Hara:** 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.; Signal Solutions LLC. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Signal Solutions LLC, GISMO Therapeutics. F. Consulting Fees (e.g., advisory boards); GISMO Therapeutics.

Poster

770. Cardiovascular Regulation II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 770.08/R16

Topic: F.07. Autonomic Regulation

Support: NIH Grant HL13671002

Title: Hypoventilation in infant rats following orexin receptor blockade

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Abstract: Orexinergic neurons in the lateral and perifornical hypothalamus project widely to respiratory and regions of the brainstem. Orexin neurons are most active in wakefulness and are mostly silent in sleep. In adult animals, chronic orexin deficiency reduces the respiratory response to CO_2 but has no apparent effect on resting ventilation. The acute effects of orexin on breathing have not been described, either in adult or infant animals. A better understanding of orexin's effects on breathing is important because there is evidence of sleep apnea in narcoleptic patients that have reduced orexin signaling. There is also pathological evidence of orexinergic dysfunction in the Sudden Infant Death Syndrome (SIDS), which occurs in sleep and is associated with reduced ventilation. We hypothesized that orexin receptor blockade would lead to acute hypoventilation in a vigilance state-dependent manner. To test this hypothesis we used whole-body plethysmography to monitor breathing of infant and adult rats treated with

suvorexant, a selective orexin 1 and 2 receptor antagonist. In pups, we determined vigilance state using standard behavioral criteria, confirmed by video. In adults, vigilance state was determined with EEG and EMG. Pups were studied during the light period, and adults were tested at the transition from the dark to light period, when orexin levels peak. Rats cycled through wakefulness (W), quiet sleep (QS, or NREM in adults) and active sleep (AS, or REM in adults) for 1 hr at which point suvorexant (5mg/kg for pups; 20 mg/kg for adults, in 50% DMSO; n=8 pups, n=3 adults) or vehicle alone (n=8 pups) was injected via an intra-abdominal cannula. Rats were monitored for another 1 hr. We analyzed the effects of suvorexant on respiratory frequency (f), tidal volume (V_T), and the ventilatory equivalent (V_E/VO_2) in W, QS/NREM and AS/REM. Significant effects of drug treatment were determined with 2 factor repeated measures ANOVA, and Sidak post-hoc analysis (pups), or paired t-tests (adults). Suvorexant significantly reduced the f of pups, by 18% in W and QS (data were combined; p=0.0003), and by 9% in AS (p=0.02), with no effect on V_T in any state. Due to its effect on f, suvorexant decreased V_E/VO_2 by ~23% in W and QS (p=0.03), with no effect in AS. Vehicle alone had no significant effects on any respiratory variables (treatment x time: $p<0.01$ for both variables). In adults, suvorexant tended to reduce f in W (by 9%; p=0.24). These data suggest that in infant rats, acute orexin blockade reduces respiratory frequency leading to hypoventilation, especially in W and QS.

Disclosures: R. Spinieli: None. **K.J. Cummings:** None.

Poster

770. Cardiovascular Regulation II

Location: Hall A

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Program #/Poster #: 770.09/R17

Topic: F.07. Autonomic Regulation

Support: NIH Grant DK099598
NIH Grant HL122829

Title: Trpv1 dependent modulation of synaptic inputs and activity of presympathetic neurons in the rostral ventrolateral medulla

Authors: H. GAO[1], A. ZSOMBOK[2], *A. DERBENEV[3];
[1]Physiol., Dept. of Physiol., New Orleans, LA; [2]Dept Physiol, [3]Tulane Univ., New Orleans, LA

Abstract: Presympathetic neurons in the rostral ventrolateral medulla (RVLM) are best known for determining the level of sympathetic vasomotor tone, and thus blood pressure. Chronic activation of RVLM neurons increases sympathetic output and vasomotor tone. The activity of neurons depends on their intrinsic properties and the balance of inhibitory and excitatory synaptic inputs. Transient receptor potential vanilloid type 1 (TRPV1) channels, non-selective cation channels widely expressed in the central and peripheral nervous system have potent

effects on autonomic motor neurons. TRPV1 was shown to be expressed in the RVLM; therefore, we hypothesized that activation of TRPV1 receptors enhances the excitability of presympathetic RVLM neurons. Whole-cell patch-clamp recordings in brainstem slices were used to determine TRPV1-dependent regulation of presympathetic RVLM neurons identified with the trans-synaptic retrograde viral vector PRV-152. Application of a TRPV1 receptor agonist, capsaicin (1 μM) significantly increased the frequency of miniature inhibitory postsynaptic currents (mIPSCs) from 1.3±0.3 Hz to 3.0±0.6 Hz ($p<0.05$) without changes in amplitude in 6 out of 19 presympathetic RVLM neurons. On the other hand, capsaicin increased the frequency of miniature excitatory postsynaptic currents (mEPSCs) from 2.3±0.9 Hz to 14.8±4.8 Hz ($p<0.05$) without changes in amplitude of mEPSCs in 5 out of 11 presympathetic RVLM neurons. In the presence of tetrodotoxin (TTX), capsaicin application resulted in depolarization (5 out of 16) or hyperpolarization (5 out of 16) of RVLM neurons. In the presence of synaptic blockers (strychnine, gabazine, kynurenic acid, and TTX) the TRPV1-dependent modulation of presympathetic RVLM neurons was lacking. In summary, our data demonstrate that a population of presympathetic neurons receives excitatory or inhibitory TRPV1-expressing inputs and activation of these inputs alter the excitability of presympathetic neurons in the RVLM. These findings suggest that modulation of RVLM neurons by TRPV1 represents a potential means of modulating sympathetic vasomotor tone and control of blood pressure.

Disclosures: H. Gao: None. **A. Zsombok:** None. **A. Derbenev:** None.

Poster

770. Cardiovascular Regulation II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 770.10/R18

Topic: F.07. Autonomic Regulation

Support: Heart and Stroke Foundation of Ontario

Title: Paraventricular nucleus of the hypothalamus mediates the cardioinhibitory responses to activation of the paraventricular nucleus of the thalamus

Authors: *M. PUIGBONET[1], Z. LI[2], J. CIRIELLO[3];
[1]Health, Wellness and Sci., Georgian Col., Barrie, ON, Canada; [2]Dept. Physiol. and Pharmacol., Univ. of Western Ontario, London, ON, Canada; [3]Dept. Physiol. and Pharmacol., Univ. Western Ontario, London, ON, Canada

Abstract: The paraventricular nucleus of the thalamus **(**PVT) is known to function as a site of integration of afferent information from brainstem, limbic and cortical structures involved in visceral and homeostatic regulation, and affective behaviors. We have shown that the sympathoinhibitory effects on arterial pressure (AP), but not heart rate (HR), elicited by PVT are

mediated in part by a pathway involving the central nucleus of the amygdala (ACe). This study investigated whether the HR responses to PVT activation involved a relay within the hypothalamus. In the first series of experiments, cardiovascular responsive sites were identified in the anterior PVT using L-glutamate (Glu; 10 nL, 0.25 M) microinjections in chloralose-anesthetized Wistar rats. Glu elicited decreases in mean AP (MAP, -20 ± 3 mmHg) and HR (-15 ± 5 bpm). In the second series, iontophoretic injections of the anterograde tract tracer PHA-L (2.5%) were made at the cardioinhibitory sites in the anterior PVT in the Wistar rats. Within the hypothalamus, PHA-L labelled fibers and presumptive terminals were found bilaterally in and around the anterior, dorsolateral and the medial parvocellular components of the paraventricular nucleus of the hypothalamus (PVH). A few scattered PHA-L labelled fibers were also observed within the posterior magnocellular component of PVH and the supraoptic nucleus. PHA-L labelling was also found within the lateral and dorsomedial hypothalamic areas, and the area of the tuber cinereum. As PVH is known to play a pivotal role in autonomic regulation, in the final series, bilateral microinjection (100 nL) of either the synaptic blocker $CoCl_2$, the non-specific Glu antagonist kynurenic acid or the selective NMDA receptor antagonists 2-amino-5-phosphonovalerate were made into PVH in chloralose-anesthetized Wistar rats. Although injections of these compounds did not significantly alter the resting level of AP or HR, all compounds attenuated the MAP responses (grouped data; -15 ± 5 mmHg; $p<0.01$) and blocked the HR responses (grouped data, -3 ± 5 bpm; $p<0.01$) to PVT activation (MAP, -25 ± 3 mmHg; HR, -19 ± 7). These data, taken together with our previous findings, suggest that PVT functions to alter cardiac sympathoinhibitory responses associated with arousal, stress, and affective behaviors through a glutamatergic pathway relaying in PVH, while the PVT associated MAP depressor responses are mediated predominantly through a sympathoinhibitory neuronal circuit involving the ACe.

Disclosures: **M. Puigbonet:** None. **Z. Li:** None. **J. Ciriello:** None.

Poster

770. Cardiovascular Regulation II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 770.11/R19

Topic: F.07. Autonomic Regulation

Support: NIH (SPARC) grant #: 3 U18 EB021759

Title: Chronic recording of rat vagal tone with carbon nanotube yarn electrodes

Authors: *J. MARMERSTEIN[1], D. M. DURAND[2];
[1]Biomed. Engin., Case Western Reserve Univ., Cleveland, OH; [2]Dept Biomed. Eng, Case Western Res. Univ., Cleveland, OH

Abstract: The autonomic nervous system governs subconscious control and sensing of visceral organ activity. It has recently become a focus for novel therapeutic technologies, termed “bioelectronic medicine”. The vagus nerve is the largest autonomic nerve, innervating nearly every organ in the body; “vagal tone” is a clinical measure presumed to indicate overall levels of vagal activity. Low vagal tone has been associated with many severe conditions such as diabetes, heart failure and hypertension, yet has so far only been measured indirectly through the heart rate variability (HRV). We have now developed a methodology to directly measure vagal activity in chronic animals, allowing for the first time, true measures of vagal tone. Using microwire electrodes made of carbon nanotube (CNT) yarns implanted inside the vagus nerves of rats, we have recorded vagal tone directly for the first time with simultaneous ECG for measurement of HRV. While the name vagal tone implies a tonic level of baseline activity in the vagus nerve, our results show that baseline neural activity does not correlate with changes in common HRV metrics used for vagal tone, including root mean square of successive differences (RMSSD) and high frequency component of RR-interval (respiratory frequency, 0.5-2.0Hz). It has been hypothesized that HRV may be driven by phasic vagal activity related to respiration. Using changes in RR-interval, we measured average vagal activity during heart rate decreases (presumed expiration) and heart rate increases (presumed inspiration). As expected, vagal activity is *increased* during expiration and decreased during inspiration. The magnitude difference between vagal activity during expiration and inspiration, termed respiratory vagal difference (RVD) was found to have a significant negative correlation with both RMSSD and HF component.
For the first time, we have been able to record vagal tone from the vagus nerve directly, allowing for better understanding of how HRV relates to changes in vagus activity. Unexpectedly, changes in RVD correlated negatively with HRV, suggesting that this metric may not be a direct measure of efferent vagal control of HRV, although this still supports a relationship between HRV and changes in activity in the vagus nerve.

Disclosures: J. Marmerstein: None. **D.M. Durand:** None.

Poster

770. Cardiovascular Regulation II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 770.12/R20

Topic: F.07. Autonomic Regulation

Support: MOST 107-2635-B-320-001

Title: Activation of metabotropic glutamate receptor subtype 5 and protein kinase c pathways in the rostral ventrolateral medulla as a central mechanism for methamphetamine-induced pressor effect in rats

Authors: *H.-H. LIN[1,2], C.-C. LAI[3], C. FANG[2], C.-Y. KUO[2], Y.-W. WU[2];
[1]Dept. of Physiol., [2]Master Program in Med. Physiol., [3]Dept. of Pharmacol., Tzu Chi Univ., Hualien, Taiwan

Abstract: The acute hypertensive effect produced by methamphetamine (MA) has been well known mainly by catecholamines release from peripheral sympathetic terminals. However, the central mechanism of the BBB-penetrating molecule in the pressor effect remains unclear. Since the rostral ventrolateral medulla (RVLM) is the major regulating center of sympathetic and cardiovascular activity in the central nervous system, we hypothesized the RVLM might serve as a central target of MA-induced pressor effect. We monitored the pressor effect on conscious free-moving rats and anesthetized rats by i.p. (2 and 10 mg/kg) or i.c.v. (50, 150 and 500 nmol) injection of MA, respectively. Meanwhile, we evaluated the expression of FOS protein and the phosphorylation state of NMDA receptor subunit GluN1, an index of NMDA receptor activation, in the RVLM. Our data showed that both i.p. and i.c.v. MA induced dose-dependent pressor effects. Besides, MA increased FOS expression, PKC activity, and phosphorylated GluN1-ser 896 (pGluN1-ser 896) in the RVLM. Unilateral microinjection of a potent PKC inhibitor and a specific mGluR5 antagonist into the RVLM dose-dependently attenuated the i.c.v. MA-induced increase in the mean arterial pressure (MAP) and pGluN1-ser 896 in the RVLM. However, we found direct microinjection of MA (2 or 20 nmol) into the RVLM did not change the MAP. By using microdialysis and HPLC, we collected and analyzed dialysate from the RVLM after i.c.v. injection of MA 150 nmol. We found that the concentration of glutamate in the RVLM was significantly increased at first 10 min period after i.c.v. injection of MA. The paraventricular nucleus of the hypothalamus (PVN) has been recognized one of the major origins of glutamatergic innervation to the RVLM, which lead us to reason that the PVN is a logical neural substrate for MA action. Microinjection of MA (2 and 20 nmol) into the unilateral PVN increased the MAP in a dose-dependent manner in anesthetized rats. Administration of MA into the PVN also increased PKC activity, pGluN1-ser 896, and glutamate concentration in the RVLM. We conclude that MA may act on PVN leading to glutamate release in the RVLM further to activation of mGluR5-PKC pathways which will serve as a central mechanism for MA-induced pressor effect in rats.

Disclosures: H. Lin: None. **C. Lai:** None. **C. Fang:** None. **C. Kuo:** None. **Y. Wu:** None.

Poster

770. Cardiovascular Regulation II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 770.13/S1

Topic: F.07. Autonomic Regulation

Support: Conacyt Mexico Grant 252702

Title: Chronic administration of sodium hydrosulfide and l cysteine restores the cardiovascular changes induced by high fat diet in rats

Authors: *C. B. GOMEZ, S. HUERTA DE LA CRUZ, G. J. MEDINA-TEROL, J. H. BELTRÁN-ORNELAS, A. SÁNCHEZ-LÓPEZ, D. L. SILVA-VELASCO, D. CENTURIÓN; Pharmacobiology, Cinvestav, Mexico City, Mexico

Abstract: Hydrogen sulfide plays an important role in the regulation of the cardiovascular system, insulin secretion, and glucose homeostasis. The aim of the present study was to examine the effects of chronic administration of sodium hydrosulfide (NaHS), L-Cysteine (L-Cys) and DL-Propargylglycine (DL-PAG) on the changes induced by a high-fat diet (HFD) in zoometric and metabolic variables as well as cardiovascular changes such as hypertension and sympathetic hyperactivity. For this purpose, 200-220 g male Wistar rats were fed a normal fat diet (NFD, n=6) or HFD (n=30) for 12 weeks. Next, the HFD rats were randomly divided into 5 subgroups (n=6 each) which received daily i.p. injections during 4 weeks of: (1) nothing (Control); (2) vehicle (PBS; 1 ml/kg); (3) NaHS (5.6 mg/kg); (4) L-Cys (300 mg/kg); or (5) DL-PAG (1 mg/kg). Then, an oral glucose tolerance test, hormone plasma levels and blood pressure were determined. The cardiovascular responses to stimulation of the vasopressor sympathetic tone or i.v. administration of the agonists noradrenaline ($\alpha_{1/2}$-adrenoceptors), methoxamine (α_1-adrenoceptors) and UK 14,304 (α_2-adrenoceptors) were determined in pithed rats. Then, heart, liver and adipose tissue were obtained and weighted. We found that HFD significantly increased: (1) zoometric variables, which were decreased by NaHS and L-Cys; (2) metabolic variables, ameliorated by DL-PAG; (3) haemodynamic variables, which were totally reversed by NaHS and L-Cys; and (4) the vasopressor responses induced by sympathetic stimulation, which were diminished by NaHS and L-Cys. In conclusion, chronic treatments with NaHS and L-Cys are effective in reducing adipose tissue and ameliorating the cardiovascular changes induced by obesity; meanwhile, DL-PAG ameliorates metabolic variables. These effects could involve a reduction of the sympathetic tone, inviting us to explore deeper into the mechanism underlying this long-term effect.

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Poster

770. Cardiovascular Regulation II

Location: Hall A

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Program #/Poster #: 770.14/S2

Topic: F.07. Autonomic Regulation

Support: American Heart Association (19POST34430205 to GMPRS)

NIH (HL 28785 to PGG)

Title: C1 neuron activation maintains blood pressure during mild hemorrhage

Authors: *G. M. SOUZA, R. L. STORNETTA, D. S. STORNETTA, S. B. ABBOTT, P. G. GUYENET;
Univ. of Virginia, Charlottesville, VA

Abstract: Background: During hemorrhage, BP is initially maintained near normal (compensated phase) by an increase in sympathetic nerve activity (SNA). However, further blood loss (>20-25% blood volume) causes an abrupt and severe BP drop (late or "decompensated" phase) associated with a paradoxical and unexplained reduction of SNA. Under several circumstances (e.g. hypoxia, anesthesia) SNA and BP are largely determined by the level of activity of catecholaminergic presympathetic neurons (C1 neurons) located within the rostral ventrolateral medulla (RVLM). **Goals:** In this study we sought to determine the contribution of the C1 neurons to BP and heart rate during the early and decompensated phases of hemorrhage in non-anesthetized rats. **Methods:** We determined the contribution of the C1 cells to BP by measuring how much this variable drops when the C1 neurons are selectively, briefly (10s) and bilaterally silenced using optogenetics. We transduced the C1 neurons with the inhibitory proton pump Archaerhodopsin by microinjecting AAV2-DIO-ArchT3.0-eYFP bilaterally into the RVLM of adult TH-Cre rats. Four weeks later, C1 neurons were inhibited at regular intervals by delivering green light (532 nm, continuous pulse for 10 s) while the rats (unanesthetized) were subjected to a controlled hypotensive hemorrhage (18 ml/kg of blood withdrawal over 20 minutes). Data were analyzed using one-way ANOVA and results were considered significant when $p<0.05$. **Results:** C1 inhibition produced a much larger BP drop during the early compensated phase of hemorrhage than before hemorrhage (-25 ± 4 vs. -6 ± 2 mmHg, n=4). By contrast, the BP drop elicited by C1 cell inhibition during the decompensated phase of hemorrhage (-3 ± 3 mmHg) was no different from the drop at rest. Before hemorrhage, C1 inhibition caused a slight tachycardia ($+7 \pm 2$ bpm) at rest whereas HR was reduced by C1 inhibition during the early phase of hemorrhage (-20 ± 10 bpm). **Conclusions:** C1 neuron activation contributes to BP stability during the compensated phase of hemorrhage. C1 neurons may be inactive during the decompensated phase and thus may contribute to the paradoxical BP decrease.

Disclosures: G.M. Souza: None. **R.L. Stornetta:** None. **D.S. Stornetta:** None. **S.B. Abbott:** None. **P.G. Guyenet:** None.

Poster

770. Cardiovascular Regulation II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 770.15/S3

Topic: F.07. Autonomic Regulation

Support: NIH Grant HL-72125

Title: Moxibustion reduces blood pressure and heart rate in conscious hypertensive rats

Authors: *Y. GONG, S. MALIK, Z.-L. GUO, L.-W. FU, S. C. TJEN-A-LOOI;
Susan Samueli Integrative Hlth. Inst., Univ. of California, Irvine, Irvine, CA

Abstract: Electroacupuncture (EA) with bilateral stimulation of the acupoints ST36-37 stimulating the deep peroneal nerves attenuates sympathetic outflow and change of blood pressure in reflex hypertension. EA also decreases the elevated blood pressure, but not the heart rate, in cold-induced hypertension through the rostral ventral lateral medulla (rVLM). Moxibustion stimulating the thermosensitive transient receptor potential vanilloid type-1(TRPV1) receptors at ST36 acupoint similarly modulates sympathoexcitatory blood pressure reflexes through the opioid system in the hypothalamus. However, it remains unclear if moxibustion influences hemodynamic parameters including blood pressure and heart rate, in spontaneously hypertensive conscious rats. We hypothesize that moxibustion decreases the elevated blood pressure and heart rate in spontaneous hypertensive rats (SHR). Rats randomly allocated into three groups: moxibustion at ST36, control point G39 twice per week for five weeks, or third group without moxibustion. Another two groups of SHR rats received a 5-week twice a week EA at ST36-37 or sham-EA ST36-37 (no electrical input) treatment. Blood pressure and heart rate were measured in all of the 5 groups of rats. To determine the moxibustion-induced activation of neurons in the medulla, rats subjected to 30 min moxibustion were examined for c-Fos expression in the rVLM and the nucleus tractus solitaries (NTS), a site participating in the regulation of heart rate. We observed that moxibustion in contrast to EA could not display the long-lasting blood pressure lowering effect over the course of 5-week treatment. On the other hand, we observed that the blood pressure accompanied with heart rate were reduced for at least 24 hours and recovered by 48 hours. Heart rate change was not observed in the EA-treated rats. Immunohistochemical staining for c-Fos expression was observed in the rVLM and the NTS implying that moxibustion may include both sympathetic and parasympathetic systems during modification of elevated blood pressure.

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Poster

770. Cardiovascular Regulation II

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Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 770.16/S4

Topic: F.07. Autonomic Regulation

Support: CONACyT Grant 252702

Title: Role of potassium channels on the vasopressor sympathetic outflow inhibitioninduced by hydrogen sulfide

Authors: *S. HUERTA DE LA CRUZ, G. J. MEDINA-TEROL, J. H. BELTRÁN-ORNELAS, S. K. MONTIEL-GÓMEZ, C. B. GOMEZ, A. SANCHEZ-LOPEZ, D. CENTURIÓN; Pharmacobiology, Cinvestav Sede Sur, Mexico City, Mexico

Abstract: It is well known that hydrogen sulfide is a novel gasotransmitter with important cardiovascular effects. Indeed, it has been recently demonstrated that a continuous infusion of a H_2S donor, NaHS, is capable to inhibit the sympathetic outflow although the mechanisms remain elusive. This study evaluated the involvement of several potassium channels on the H_2S-induced sympatho-inhibition by using several selective blockers. For this purpose, male Wistar rats were anaesthetized, pithed and cannulated. The left carotid was connected to a pressure transducer to record blood pressure and heart rate meanwhile the right femoral vein was cannulated for gallamine and potassium channels blocker administration and the left femoral vein was cannulated for NaHS i.v. continuous infusion. After that, animals received selective electrical stimulation of the vasopressor sympathetic outflow (T_7-T_9). Animals were divided into 2 main groups. The first one was subdivided into 6 sets to evaluate de effect of K^+ channels blocker on NaHS-induced sympatho-inhibition. Thus, prior to 310 μg/kg min NaHS i.v. continuous infusion animals received: (1) bidistilled water (tetraethylammonium, 4-aminopyridine and barium chloride vehicle; 1 ml/kg); (2) tetraethylammonium (non-selective K^+ channels, 16.5 mg/kg); (3) 4-aminopyridine (non-selective voltage-dependent K^+ channels; 5 mg/kg); (4) $BaCl_2$ (inward rectifier K^+ channels; 65 μg/kg); (5) DMF 5%, glucose 10% and NaOH 0.1N (glibenclamide vehicle; 1 ml/kg); and (6) glibenclamide (ATP-dependent K^+ channels; 10 mg/kg). The second group was divided into 4 subgroups that received: (1) tetraethylammonium (16.5 mg/kg); (2) 4-aminopyridine (5 mg/kg); (3) $BaCl_2$ (65 μg/kg); (4) glibenclamide (10 mg/kg) and did not receive NaHS i.v. continuous infusion in order to evaluate the per se effect of K^+ channels blocker on the vasopressor responses induced by selective electrical stimulation. The NaHS-induced sympatho-inhibition was: (1) unaffected by vehicles; (2) slightly reversed by $BaCl_2$; and (3) abolished by tetraethylammonium, 4-aminopyridine and glibenclamide, meanwhile vasopressor responses induced by selective electrical stimulation remained unaffected by (1) tetraethylammonium; (2) $BaCl_2$; (3) glibenclamide and (4) significantly increased by 4-aminopyridine. Taken together, our results suggest that NaHS-induced sympatho-inhibition is mainly mediated by activation of voltage and ATP-dependent K^+ channels and, to a lesser extent, by inward rectifier K^+ channels.

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Poster

770. Cardiovascular Regulation II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 770.17/S5

Topic: F.07. Autonomic Regulation

Support: Deputy Vice-Chancellor Partnership Fund, University of Kent
NIH Grant
The Physiological Society UK, Travel Grant

Title: Afferent bone marrow drive to periaqueductal gray in modulation of blood pressure in the spontaneously hypertensive rat

Authors: *S. KOUTSIKOU[1], D. M. BAEKEY[2], L. F. HAYWARD[3], J. ZUBCEVIC[2]; [1]Medway Sch. of Pharm., Univ. of Kent, Chatham Maritime, United Kingdom; [2]Dept. of Physiological Sci., [3]Dept Physiol Sci., Univ. of Florida, Gainesville, FL

Abstract: Introduction: A range of pathophysiological conditions are characterized by dysfunctional immune and autonomic nervous system (ANS), including cardiovascular, pain, mental and autoimmune disorders. Here, we present new data from a hypertensive rodent model characterized by dysfunctional immune system and ANS suggesting an altered afferent communication between the bone marrow (BM), the main hematopoietic organ, and brainstem autonomic regions. **Methods**: Male adult spontaneously hypertensive rats (SHR) and their normotensive control Wistar-Kyoto (WKY) rats were used in this study. Rats were anesthetized with isoflurane (1.5%), and mean arterial pressure (MAP) and heart rate (HR) were monitored in real time via a femoral arterial catheter and ECG leads. A hole was drilled in the femoral BM of all rats for delivery of electrical impulses (100 square pulses at 20Hz; 5mA, 500us), before and after a unilateral bicuculline (BIC) injection (100nl, 0.4mM) in the dorsolateral, lateral, or ventrolateral periaqueductal gray (PAG). **Results:** Electrical BM stimulation produced an immediate and similar stimulation intensity-dependent drop in MAP and HR in both WKY and SHR. However, the MAP and HR responses to electrical stimulation were significantly enhanced in the SHR following an injection of BIC in PAG regions. **Conclusion:** We propose that an enhanced BM afferent input to the PAG, possibly due to elevated inflammatory events in the SHR BM, will in turn modulate the ANS. This BM-brainstem neuronal circuitry may be important in maintenance of cardiovascular, pain and immune homeostasis.

Disclosures: S. Koutsikou: None. **D.M. Baekey:** None. **L.F. Hayward:** None. **J. Zubcevic:** None.

Poster

771. Biological Rhythms: Entrainment and Phase Shifts

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 771.01/S6

Topic: F.08. Biological Rhythms and Sleep

Support: CB Department Funding

Title: Impacts of dim light at night and phthalate exposure on circadian locomotor and feeding behaviors and hypothalamic gene expression

Authors: *K. HATCHER[1], Y. PATEL[2], M. M. MAHONEY[3];
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Abstract: The circadian system synchronizes physiology and behavior with the environment. This timing system is regulated by exogenous and endogenous cues, such as light and hormones, respectively. Neuroendocrine signaling in the hypothalamus controls circadian behaviors such as locomotion and feeding. Phthalates, including di-(2-ethylhexyl) phthalate (DEHP), are ubiquitous endocrine disruptors capable of modifying the endocrine system and its outputs, including metabolism. Further, dim light at night (dLAN, i.e. urban light pollution), alters feeding behavior and metabolism. Despite our knowledge of the impact of DEHP and dLAN on other endocrine systems, the effects of dLAN and phthalate exposure on circadian behaviors, as well as underlying neuroendocrine control of these behaviors, have remained largely unexplored. Here, we tested the hypothesis that dLAN, DEHP, or combined dLAN and DEHP exposure disrupts locomotor activity and feeding behaviors, as well as underlying neuroendocrine regulators of these behaviors. Adult CD-1 male and female intact mice were individually housed with running wheels to measure daily locomotor behavior. Mice (8/sex/group) were treated for 30 days with one of the following: 12h:12h light:dark and corn oil (Control); 12h:12h light:dLAN with 5 lux light during the dark phase and corn oil control (dLAN); 12h:12h light:dark with 50µg/kg/day DEHP (DEHP); or 12:h12:h light:dLAN with 5 lux light during the dark phase and 50µg/kg/day DEHP (DEHP-dLAN). DEHP or corn oil control were administered orally by gently pipetting into the cheek every morning at lights on. Light phase and dark phase food consumption was measured every 12hrs by weighing food in each cage. Males were less active than females, regardless of treatment. DEHP males had significantly reduced total activity compared to control males. Females exhibited reduced nocturnal activity compared to males, and each female treatment group resulting in reduced nocturnal activity compared to control females. Females from all treatment groups were more active during the early part of their light cycle compared to controls, indicating increased diurnal behavior. Although females ate less food overall, no treatment affected food consumption in either males or females. We also aimed to

investigate the effect of DEHP and dLAN on neuropeptide and neuropeptide receptor expression in the arcuate nucleus (ARC) and dorsomedial hypothalamus (DMH). Preliminary data indicates that there was no effect of treatment on gene expression of *Pacap* or its receptor *Pac1r* in the ARC/DMH. Together, these data provide some of the first evidence indicating that dLAN and DEHP result in maladaptive behaviors.

Disclosures: K. Hatcher: None. **Y. Patel:** None. **M.M. Mahoney:** None.

Poster

771. Biological Rhythms: Entrainment and Phase Shifts

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 771.02/S7

Topic: F.08. Biological Rhythms and Sleep

Title: Circadian resonance and entrainment in three spiders (Frontinella communis, Metazygia wittfeldae, and Cyclosa turbinata)

Authors: *R. RAGSDALE, C. SHONE, M. K. MILLER, T. C. JONES, D. MOORE;
Biol. Sci., East Tennessee State Univ., Johnson City, TN

Abstract: Circadian rhythms, endogenous rhythms which typically cycle with a period of approximately 24 hours, are widespread among eukaryotes and organize many internal functions as well as behaviors such as locomotor activity. Previous research indicates these rhythms are advantageous to organisms' survival when they closely match the period of their environment (i.e., exhibit circadian resonance). Desynchrony between internal and environmental periods causes a number of pathological outcomes, including reduced longevity. Additionally, organisms are generally unable to synchronize their internal rhythms with external periods which are very different from their own, suggesting the presence of physiological limits to this system. As some species of spiders exhibit internal periods very different from 24 hours, the question addressed here is if this concept of circadian resonance applies to these spiders as well. The present study compares survivorship within three species of spider (n=166, 135, and 118, respectively, all female) with varying internal periods (*Frontinella communis:* τ=29.05±0.62 hours, *Metazygia wittfeldae*: τ=22.74±0.24h, and *Cyclosa turbinata*: τ=18.54±0.28h) among three light:dark (L:D) cycles with different periods: 19h (9.5h light:9.5h dark), 24h (12:12), or 29h (14.5:14.5). If circadian resonance is relevant to spiders, we expect that spiders in non-resonant L:D cycles should exhibit reduced longevity. Instead, no spider species suffered reduced longevity in non-resonant light cycles. Because non-resonant light cycles have been shown to have little to no effect on the longevity of organisms that are unable to entrain to environmental time cues, a second experiment was designed to evaluate whether these spiders were able to entrain to each L:D cycle. 10-11 spiders of each species were placed into locomotor activity monitors and exposed to one of the three light cycles for 14 days and then transferred to complete darkness for

13 days. These data show that all spider species were able to entrain to all L:D cycles. These results indicate a previously undescribed level of plasticity in spider circadian rhythms and suggest that they are released from selective pressure to maintain a near 24-hour internal period among these species.

Disclosures: **R. Ragsdale:** None. **C. Shone:** None. **M.K. Miller:** None. **T.C. Jones:** None. **D. Moore:** None.

Poster

771. Biological Rhythms: Entrainment and Phase Shifts

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 771.03/S8

Topic: F.08. Biological Rhythms and Sleep

Support: BBSRC BB/M009122/1
Eli Lilly & Co.

Title: Age-related changes in corticosterone circadian rhythm and stress-reactivity

Authors: ***M. G. JACKSON**[1], H. MARSTON[3], S. L. LIGHTMAN[2], E. S. J. ROBINSON[1]; [1]Physiology, Pharmacol. and Neurosci., [2]Dorothy Hodgkin Building, Univ. of Bristol, Bristol, United Kingdom; [3]Eli Lilly and Co., Basingstoke, United Kingdom

Abstract: Aging is associated with many physiological changes, including changes to the circadian clock. This includes significant changes in behaviour, temperature regulation and hormone release. Changes in cortisol (CORT) are of interest as CORT is a key downstream regulator of peripheral clock genes and has a profound effect on behaviour. Previous research in humans has demonstrated age-related changes in the pattern of cortisol including a reduction in circadian amplitude. The use of aged rodents could provide a valuable way to study the underlying neurobiology and behavioral impact of disrupted biological rhythms. The aim of the present study was to (1) assess changes in CORT circadian rhythm in aged rodents and (2) assess stress reactivity using CORT response to a noise stressor. 8 male Sprague-Dawley aged rats (23 mo) and 8 younger sex and strain-matched controls (7 mo) were kindly provided by Eli Lilly & Co. Free-running rats underwent automated blood sampling. Briefly, following intravenous cannulation of the right jugular vein a blood sample was drawn automatically every 10 mins for 28 h. At 26 h a 100 db noise stressor was played. CORT concentration was measured using an in-house radioimmunoassay. A CORT profile of n = 7 younger rats and n = 6 aged rats was obtained. Values for peak and nadir CORT were calculated using area under the curve analysis (AUC). RM two-way ANOVA analysis of plasma CORT in aged and young rats over 26 h show a significant interaction between circadian time and age group, $F(1,11) = 5.263$, $p = 0.042$. Bonferroni post hoc analysis revealed younger rats have a higher peak and nadir CORT than

aged rats (p = 0.027 and 0.011 respectively). There was no difference in CORT peak vs nadir in aged rats (p = 0.261) but there was a difference in CORT peak vs nadir in the younger rats (p = 0.001). AUC analysis of the stress response showed younger rats have a larger CORT response to noise stress compared to aged rats (t(6.761) = 4.993, p = 0.002, unpaired t-test). Overall, this indicates that aged rats have a blunted CORT circadian rhythm and a blunted stress response. Further work will elucidate the molecular underpinnings of this disruption, and how this change may result in changes in behaviour.

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Poster

771. Biological Rhythms: Entrainment and Phase Shifts

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 771.04/S9

Topic: F.08. Biological Rhythms and Sleep

Title: Lights clock action circadian rhythms of locomotor activity in larinioides cornutus indicate extreme flexibility in photo-entrainment

Authors: *M. K. MILLER[1], T. C. JONES[2], D. MOORE[2];
[1]Biomed. Sci., [2]Biol. Sci., East Tennessee State Univ., Johnson City, TN

Abstract: Circadian clocks are responsible for scheduling behavioral and physiological processes at the most appropriate times of day. The resulting daily rhythms synchronize (entrain) to external environmental cues (zeitgebers). This phenomenon of entrainment enables organisms to anticipate daily changes in environmental conditions such as sunrise/sunset, temperature variations, availability of prey, etc. Given the critical nature of entrainment to survival, it is no surprise that the mechanism is conserved across taxa. The misalignment of the intrinsic clock with the external environment results in a plethora of negative consequences, made apparent by studies involving shift work and jet lag. The focus of the present study is to investigate the chronobiology of female *Larinioides cornutus* (Araneidae), a nocturnal orb-weaving spider, with an emphasis on entrainment to light:dark (LD) cycles. Locomotor activity of adult female spiders was monitored via infrared sensor as a measure of circadian output. We found that both lights-off and lights-on are influential zeitgeber cues for both activity onset and offset (advance assay n=28, delay assay n=32). Phase shifting experiments reveal that these spiders (n=16) can re-entrain within 2 days to LD phase-shifts of 6 hours, and within 3 days when shifted by 12 hours. These re-entrainment rates are vastly accelerated compared to mammals, which adjust at a rate of around 1 day/ 1 hour of phase shift. In other words, spiders have minimal jet-lag responses, suggesting an increased level of plasticity in the spider circadian clock rarely observed in other organisms. Typical of circadian rhythms in nearly all organisms, activity persisted (free-runs)

under constant conditions. However, in constant darkness (DD), a drastic change in periodicity was revealed in 66% of individuals (n=48), from 23.4 to 25.2 hours, likely indicating the interaction of multiple oscillators. Evidence favoring this interpretation is the consistency in endogenous periods before and after the period shifts among all of the spiders. In contrast, under constant light (LL) conditions, 65% of spiders (n=28) were arrhythmic, suggesting high sensitivity to light. If present, the periods in LL were normally distributed over an unusually broad range, from 16.7 to 34.9 hours. Spiders have received scarce attention with respect to their chronobiology, but due to the atypical rates of re-entrainment to LD phase-shifts, spontaneous changes in free-running period under DD, and arrhythmicity in LL, we propose that spiders provide a valuable comparative model system for elucidating fundamental mechanisms of circadian clocks.

Disclosures: **M.K. Miller:** None. **T.C. Jones:** None. **D. Moore:** None.

Poster

771. Biological Rhythms: Entrainment and Phase Shifts

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 771.05/S10

Topic: F.08. Biological Rhythms and Sleep

Support: Department of Navy, Office of Naval Research Multidisciplinary University Research Initiative (MURI) Award, Award number N00014-15-1-2809.

Title: Dietary prebiotics alter gut microbial ecology and facilitate clock/sleep re-entrainment to chronic circadian disruption

Authors: *R. S. THOMPSON[1,2], M. GAFFNEY[1], A. GONZALEZ[3], S. HOPKINS[1], T. KELLEY[1], M. VITATERNA[5], F. W. TUREK[5], C. A. LOWRY[1,2], P. C. DORRESTEIN[4,6], K. P. WRIGHT, Jr.[1], R. KNIGHT[3], M. FLESHNER[1,2];
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Abstract: Chronic circadian disruption (CDR) is one challenge known to produce negative health consequences, including disrupted sleep and circadian misalignment. Prebiotic nutrients produce favorable changes in gut microbial ecology that can impact physiology and reduce the negative health impacts of challenge. This study tested the hypotheses that ingestion of dietary prebiotics increase the abundance of health-promoting microbes and reduce the negative impacts of CDR on host physiological variables like sleep and core body temperature. Prebiotic-enriched

or caloric-nutrient matched control diets were fed ad libitum to male, Sprague Dawley rats (n = 20-23/group) throughout 8 weeks of CDR (weekly, 12h light/dark reversal). Sleep EEG and core body temperature were recorded via biotelemetry (F40-EET; DSI) in freely moving rats. In order to investigate species level changes, shotgun metagenomics revealed that rats eating prebiotic diet had higher levels of two specific gut microbial species. In order to examine these diet induced gut microbial changes across time we successfully classified these species between the shotgun DNA and 16S rRNA data analyses. The 16S rRNA fecal analysis showed that rats eating prebiotic diet had little change in beta/alpha diversity after 2 days on diet, but after 5 weeks on diet had altered beta/alpha diversity and increases in two specific gut microbial species/genus. CDR had a small effect on evenness of alpha diversity. During exposure to 8 weeks of CDR rats eating prebiotic diet had facilitated re-alignment of the bathyphase of diurnal core body temperature (ClockLab; Actimetrics) scored by an observer blind to treatment of each animal. Rats eating prebiotic diet also returned to normal diurnal NREM sleep faster than those eating control diet at 6 and 8 weeks of CDR. Finally, gut microbial changes were correlated with average number of days to re-entrain at 4 weeks CDR exposure and the time spent in NREM sleep after both 6 and 8 weeks of CDR. These data suggest that prebiotic diet induced alterations in gut microbial ecology are significantly related to improved host outcomes in physiological variables (i.e. core body temperature and the sleep/wake cycle) in rats with a history of CDR. All procedures were approved by the University of Colorado IACUC.

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Poster

771. Biological Rhythms: Entrainment and Phase Shifts

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 771.06/S11

Topic: F.08. Biological Rhythms and Sleep

Support: Aging Brain Initiative

Title: Extended gamma sensory stimulation in cognitively normal individuals

Authors: *B. JACKSON[1,2], D. CHAN[1,3], H.-J. SUK[2], S. BEACH[1], D. STARK[1], V. FERNANDEZ[1], N. MILMAN[1], C. STEARNS[1], E. BOYDEN[2], E. BROWN[1], L.-H. TSAI[1]; [1]Picower Inst. of Learning and Memory, Massachusetts Inst. of Technol., Cambridge, MA; [2]McGovern Inst. for Brain Research, Massachusetts Inst. of Technol., Cambridge, MA; [3]Dept. of Neurology, Massachusetts Gen. Hosp., Boston, MA

Abstract: Recent research into using non-invasive stimulation to alter functional brain frequencies has led to exciting results in both healthy and cognitively impaired individuals. Transcranial alternating current stimulation has been shown to be capable of increasing theta-gamma frequency coupling in the temporal areas of cognitively normal individuals. This stimulation led to increased working memory performance in older adults. Cortex-wide gamma frequency synchronization has been associated with both attention and long-term memory encoding; disruption of this synchronization may also be relevant to Alzheimer's disease. Previous unpublished work in our group has found that we are able to produce robust gamma frequency entrainment in healthy older adults using only external light and sound stimulation. Due to its relevance in cognitive ability, we exposed healthy older individuals to two weeks of one-hour daily, gamma frequency (40 Hz) light and sound and investigated changes in electroencephalography (EEG), functional MRI, and cognitive function using a battery of tests. Both the initial and post-treatment EEG sessions showed significant entrainment at 40 Hz across the cortex; indicating robust, global entrainment with our device. After two weeks of stimulation, we found significant changes in fMRI activation of the hippocampal, parahippocampal, and visual association regions during a face-name association task, which may indicate improvements in associative memory formation during the presentation of novel stimuli. Finally, early results indicate increases in a variety of cognitive abilities quantified through a battery of cognitive tests delivered pre and post intervention. Overall, these results indicate that repeated exposure to gamma sensory stimulation may be cognitively beneficial to healthy older individuals.

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Poster

771. Biological Rhythms: Entrainment and Phase Shifts

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 771.07/S12

Topic: F.08. Biological Rhythms and Sleep

Support: Aging Brain Initiative
R25 NS065743
NIH NIA

Title: Bimodal stimulation in cognitively healthy individuals prompts widespread 40 Hz entrainment and global synchronization: A preliminary study of non-invasive stimulation for treating Alzheimer's disease

Authors: *N. E. P. MILMAN[1], D. CHAN[1,3], H. J. SUK[2,1], B. L. JACKSON[2,1], S. BEACH[1], D. STARK[1], V. FERNANDEZ[1], C. STEARNS[1], E. N. BOYDEN[2], E. S. BROWN[1], L. H. TSAI[1]; [1]Picower Inst. for Learning and Memory, [2]McGovern Inst. for Brain Res., MIT, Cambridge, MA; [3]Neurol., Massachusetts Gen. Hosp., Boston, MA

Abstract: Gamma frequency (25 to 100 Hz) neural oscillations play a vital role in various higher order cognitive functions (Fries, *Ann Rev of Neuroscience*, 2009) and are disrupted in many cognitive diseases, namely Alzheimer's Disease (AD). Previous research in our lab demonstrated that visual and auditory stimulation at 40 Hz could entrain the primary sensory cortices and attenuate AD-related pathology in AD mouse models, showing removal of amyloid-beta, microglia clustering as well as improved cognitive outcomes (Iaccarino et al., *Nature*, 2016; Martorell et al., *Cell, 2019).* With this in mind, we investigated whether non-invasive sensory stimulation could induce 40 Hz entrainment and increase gamma-band synchronization in human subjects, as a preclinical study for using this strategy to treat AD. We developed a device that can concurrently deliver light and sound at 40 Hz, which was used to stimulate cognitively normal subjects (23 males, 23 females; age-range 22-75) over acute and hour-long sessions. Electroencephalogram (EEG) recordings showed that our sensory stimulations could safely entrain the human brain at 40 Hz, with the bimodal stimulation (i.e., concurrent visual and auditory stimulation) inducing the strongest and most widespread entrainment as well as synchronization at 40 Hz. We also found that hour-long bimodal stimulation led to steady entrainment and synchronization throughout the stimulation period without adverse effects. These findings suggest that our sensory stimulation strategy is a safe and effective way of inducing 40 Hz entrainment and synchronization in humans, which may have therapeutic benefits in people suffering from AD.

Disclosures: N.E.P. Milman: None. **D. Chan:** None. **H.J. Suk:** None. **B.L. Jackson:** None. **S. Beach:** None. **D. Stark:** None. **V. Fernandez:** None. **C. Stearns:** None. **E.N. Boyden:** F. Consulting Fees (e.g., advisory boards); Cognito Therapeutics. **E.S. Brown:** F. Consulting Fees (e.g., advisory boards); Cognito Therapeutics. **L.H. Tsai:** F. Consulting Fees (e.g., advisory boards); Cognito Therapeutics.

Poster

771. Biological Rhythms: Entrainment and Phase Shifts

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 771.08/S13

Topic: F.08. Biological Rhythms and Sleep

Support: NSERC

Title: Investigating the effect of chronic photoperiod shifts on hippocampal-dependent and independent tasks

Authors: *T. T. S. CASSELL[1], J. M. CLEARY[2], M. L. HOUSE-DENINE[1], S. HIGDON[1], S. H. DEIBEL[4], C. M. THORPE[3];
[1]Psychology, Mem. Univ. of Newfoundland, St. Johns, NL, Canada; [2]Mem. Univ. of Newfoundland, Corner Brook, NL, Canada; [3]Psychology, Mem. Univ. of Newfoundland, St John's, NL, Canada; [4]Canadian Ctr. for Behavioural Neuroscience, Neurosci., Univ. of Lethbridge, Lethbridge, AB, Canada

Abstract: The light-dark cycle is the most potent environmental cue in the development of circadian rhythms. Previously it has been shown that rats exposed to a chronic light manipulation (i.e., 64 days) experienced deficits in the acquisition of a hippocampal-dependent (HD) task. The purpose of the current study was to assess whether a 30-day light manipulation was salient enough to result in a deficit in the acquisition of a HD task. First, 32 male Long Evans rats were entrained to a 12:12 light-dark cycle (i.e., 7:00am-7:00pm). Then, 16 of the rats were exposed to a 30-day light manipulation (i.e., LM group). Next, rats were trained on both the hippocampal-independent (HI) and HD tasks. The HD task consisted of a rapid acquisition, massed training, and competition phase of the Morris Water Maze task, each followed by a no-platform probe. There was a significant difference in the rapid acquisition phase of the HD task, with the LM rats taking longer to learn the task than control rats. However, this deficit was not present in the other phases of the HD task or the probes. Additionally, there were no significant differences in performance on the HI task. To conclude, using less than half of the chronic light manipulation resulted in the impairment of the rapid acquisition of the HD task. This implies that 30 days of circadian misalignment can result in detrimental effects in the acquisition of a HD task.

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Poster

771. Biological Rhythms: Entrainment and Phase Shifts

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 771.09/S14

Topic: F.08. Biological Rhythms and Sleep

Support: CIHR MOP142458

Title: Analysis of circadian behaviour and clock-gene expression after prenatal administration of valproic acid: Implication for autism spectrum disorders

Authors: *S. FERRARO, N. DE ZAVALIA, S. DOBRIC, M. ALONSO-MAYOR, S. AMIR; Concordia Univ., Montreal, QC, Canada

Abstract: Autism Spectrum Disorder (ASD) is a pervasive developmental disorder characterized by restrictive patterns of behaviour and alterations in social interaction and communication. Accompanied by co-morbid disorders, 44-80% ASD patients exhibit sleep-wake cycle disturbances, potentially implicating alterations within the circadian system. Administration of the anti-epileptic drug, valproic acid (VPA), on day 12.5 of gestation results in rodent pups with ASD-like phenotypes. Research has shown that irregular sleep-wake cycles exacerbate ASD symptomology and further impair social performance. While altered sleep-wake cycles have been identified in ASD individuals, little has been done to assess the contribution of the circadian system to these findings. The objective of this study is to characterize circadian behaviour and clock-gene expression in a VPA-induced animal model of autism to highlight perturbations potentially contributing to sleep-wake cycle disturbances. Male offspring introduced to running-wheel apparatuses underwent various circadian challenges, including baseline light-dark cycles, constant dark/light and phase advance/delay protocols. Baseline analysis revealed a significant increase in light phase activity bouts (defined as one count of activity/minute for ten consecutive minutes) in VPA-treated animals (control: 1.1 ± 0.1795, VPA: 1.917 ± 0.2865 $p < 0.05$). Moreover, VPA-treated animals show greater distribution of wheel-running behaviour across light-dark phases, while controls show greater activity confinement to the dark phase (light activity/total activity; control: 0.07550 ± 0.01609, VPA: 0.1724 ± 0.01506. $p < 0.0001$). Further investigation reveals a later running-activity offset in VPA-animals ($p < 0.0005$). Constant light analysis reveals greater running activity in VPA animals ($p < 0.05$), and an increase in the number of days to reach arrhythmicity (control: 12.89 ± 0.5638, VPA: 23.93 ± 2.069. $p < 0.0005$). A 1-hour light pulse (150 lux) at CT 15 after six days of constant dark was used to assess the phase-shifting capacity of the SCN. VPA-treated animals demonstrated a lesser phase-shift when compared to controls (total hours shifted; control: 2.238 ± 0.1688, VPA: 1.495 ± 0.1549 $p<0.005$). Together, these results suggest alterations in photic-entrainment capacity in VPA-treated animals.

Disclosures: S. Ferraro: None. **N. de Zavalia:** None. **S. Dobric:** None. **M. Alonso-Mayor:** None. **S. Amir:** None.

Poster

771. Biological Rhythms: Entrainment and Phase Shifts

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 771.10/S15

Topic: F.08. Biological Rhythms and Sleep

Support: ERC Consolidator Grants 2015

Title: Examining the optimal timing for closed loop auditory stimulation of slow wave sleep in young and older adults

Authors: *M. NAVARRETE[1], J. SCHNEIDER[2], H.-V. V. NGO[3], M. VALDERRAMA[4], A. J. CASSON[2], P. A. LEWIS[1];
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Abstract: Slow wave sleep (SWS) is typified by the presence of cortical slow oscillations (SO, < 1Hz), and closed loop auditory stimulation (CLAS) is a method for enhancing SWS. CLAS presents auditory clicks synchronous with the SO, boosting the SO amplitude and phase-locked spindle power (12-15Hz). Still, the optimal timing for click delivery remains unclear. In this study, we took advantage of the inherent variability of click delivery of CLAS to examine the best timing for maximal enhancement of both SO amplitude and spindle likelihood during SWS. Moreover, we evaluated the main factors for sleep spindle odds in an acoustic stimulation condition. For this, we analysed the dynamic reactivity of post-stimuli SO and spindles in young (N = 21, 25.7±4.7 years, 14 females) and older adults (N =17, 55 ±5 years, 9 females) as a function of the phase of stimulation on the ongoing SO (φ_{SO}).
Comparison of CLAS between sham and stimulation conditions revealed that clicks applied anywhere on the positive SO wave increased wave amplitudes and spindle likelihood, although this interval of opportunity was shorter in older people (Welch's t-test $t(35.6) = 3.6$, $P < .001$). However, within condition analysis revealed that for both populations the optimal timing for click delivery is close to the SO peak phase ($\varphi_{SO} = 87.2°$ in young and $\varphi_{SO} = 83.6°$ in older subjects, where 90° is the peak phase of the SO wave and 0° its negative to positive zero crossing). Our work also indicates that spindle likelihood after stimulation is modulated by the phase of the SO in young subjects but not in the older population. A binary logistic regression analysis showed that the main factor determining spindle likelihood in young subjects were SO phase components ($\chi^2 = 24.8$, $P < .001$; *Sin(φ_{SO}), t*(3.12) P = .002; *Cos(φ_{SO}), t*(2.19) P =.028; *Lag, t*(0.48) P > .05), while for older subjects the main factor for spindle odds was the temporal lag since the last spindle ($\chi^2 = 14.3$, $P = .012$; *Lag, t*(-2.35) P = .019; *Sin(φ_{SO}), t*(1.86) P > .05; *Cos(φ_{SO}), t*(0.26) P > .05). Maximal spindle chance occurred after clicks applied on the rising slope of the positive SO half-wave in young adults.
Our data suggest that CLAS can boost SOs and spindles based on the fluctuation of sensory inputs modulated by the thalamocortical networks during the SO. Finally, we speculate that the optimal timing of CLAS is defined within wake-like intervals in which peripheral networks can recruit larger thalamocortical populations.

Disclosures: **M. Navarrete:** None. **J. Schneider:** None. **H.V. Ngo:** None. **M. Valderrama:** None. **A.J. Casson:** None. **P.A. Lewis:** None.

Poster

771. Biological Rhythms: Entrainment and Phase Shifts

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 771.11/S16

Topic: F.08. Biological Rhythms and Sleep

Support: SERB EMR/2017/001237
NIMHANS

Title: Short photoperiod exposure reverses ventral subicular lesion-induced affective and cognitive deficits in Wistar rats

Authors: *S. DUTTA GUPTA[1], B. N. SRIKUMAR[1], B. SHANKARANARAYANA RAO[2], B. M. KUTTY[3];
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Abstract: Photoperiod has enduring effects on physiological and behavioral phenotypes such as metabolism, cognition, and affective behavior. Phototherapy has emerged as a safe and effective chronotherapeutic in neurodegenerative conditions such as Alzheimer's and Parkinson's disease, though the underlying mechanism remain elusive. Subiculum, a crucial output structure of the hippocampal formation, mediates a wide range of neurocognitive functions such as learning and memory, motivation, and adaptive behavior. The present study demonstrates the impact of selective bilateral lesioning of the ventral subiculum on behavioral phenotypes such as anxiety, depression and cognitive functions like empathy and sociality, attention and spatial navigation. Ventral subicular lesion (VSL) resulted in heightened anxiety, anhedonia, increased behavioral despair, and decreased self-care. The VSL rats exhibited a considerable degree of impaired social cognition, in terms of altered social preference, social novelty and empathy with altered ultrasonic vocalization. Also, the VSL rats displayed an attentional deficit when tested in a 3 and 5-objects based attention task. We observed a 2-fold increase in plasma corticosterone level in the VSL rats indicating its involvement in the hypothalamo-pituitary-adrenal axis dysfunction. Interestingly, the anxiety- and depressive-like phenotypes were completely ameliorated when VSL rats were exposed to a short photoperiod regime (SPR, 6/18h light-dark cycle) for 21 days. However, exposure to SPR resulted in the recovery of pro-social behavior and social novelty but not the overall sociability of the VSL rats. There was a significant recovery in spatial navigational functions, but SPR could not restore the attentional deficits in the VSL rats. We further observed a decrease in plasma corticosterone level at ZT6 time-point, which might be associated with the behavioral and cognitive recovery. The underlying mechanism is currently been investigated using assessment of adult neurogenesis and glucocorticoid receptors

expression. In summary, the study highlights the efficacy of photoperiod manipulation as a novel, non-pharmacological approach in mitigating the affective and cognitive deficits associated with central nervous system insult.

Disclosures: S. Dutta Gupta: None. **B.N. Srikumar:** None. **B. Shankaranarayana Rao:** None. **B.M. Kutty:** None.

Poster

771. Biological Rhythms: Entrainment and Phase Shifts

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 771.12/S17

Topic: F.08. Biological Rhythms and Sleep

Support: NIH Grant GM117650

Title: Dna methylation modulates period aftereffects of circadian entrainment without affecting transient phase shifts

Authors: *S. KIM[1], D. G. MCMAHON[2];
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Abstract: The suprachiasmatic nucleus (SCN) is a brain region where photic and non-photic inputs reflecting environmental regularities converge onto peptidergic neurons that serve as a central pacemaker of circadian rhythms in the rest of the body. Light inputs can acutely induce a phase shift of circadian rhythms in the SCN and elicit a lasting change in the circadian period that is otherwise genetically determined. Recently, it was reported that DNA methylation mediates circadian period changes in mice entrained to non-24hr light cycles inducing SCN-specific changes in transcription. This suggests that long-term circadian clock plasticity involves epigenetic modifications. However, the mechanism remains largely unknown. To test whether DNA methylation is a mechanism underlying light-induced circadian aftereffects, we investigated the role of DNA methylation in aftereffects of the photoperiod entrainment. Pharmacological inhibition of DNA methyltransferases *in vivo* during entrainment suppressed the circadian period aftereffect and a rhythm amplitude aftereffect, suggesting that DNA methylation is a fundamental mechanism of circadian aftereffects. Since circadian aftereffects are thought to stem from acute changes in a circadian rhythm, we tested whether epigenetic changes in the SCN also play a role in short-term circadian clock plasticity, or acute circadian phase shifts. Pharmacological inhibition of DNA methyltransferases followed by light pulses at night *in vivo* suppressed the period change in the locomotor activity rhythm without affecting an acute phase shift. To confirm that circadian phase shifts take place at the core clock level in the SCN independent of DNA methylation, we performed a Period2::luciferase assay with vasoactive intestinal peptide (VIP), an endogenous neuropeptide mediating light signaling in the

SCN. Consistent with the behavioral experiment, VIP application in the SCN at circadian night produced a comparable phase shift even in the presence of a DNA methylation inhibitor. This shows that transient changes in SCN circadian rhythms do not require DNA methylation. Taken together, our findings suggest that DNA methylation takes part in modulating circadian aftereffect expression of acute circadian phase shifts.

Disclosures: S. Kim: None. **D.G. McMahon:** None.

Poster

771. Biological Rhythms: Entrainment and Phase Shifts

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 771.13/S18

Topic: F.08. Biological Rhythms and Sleep

Support: CAPES/STINT
American Tinnitus Association

Title: OLM neurons phase lock with type 2 theta in anxiogenic environments

Authors: *J. WINNE[1], R. N. LEAO[3], G. NASCIMENTO[2], K. KULLANDER[4];
[1]Brain Inst., [2]Biomed. Engin. Dept., Federal Univ. of Rio Grande do Norte, Natal, Brazil; [3]Brain Inst., UFRN, Natal, Brazil; [4]Uppsala Univ., Uppsala, Sweden

Abstract: Our group has previously shown that stimulation of oriens-lacunosum moleculare (OLM) neurons in CA1 of the ventral hippocampus increase risk-taking behavior and induce type 2 theta oscillations (theta2). We have also shown that anxiety-like behavior induced by acute tinnitus (salicylate treatment) generates theta2 in the open field test. In this work, we have imaged OLM cell activity using GCamp6F and microendoscopic fluorescente imaging in freely moving mice (Chrna2-cre line) and local field potential recordings in the open-field test. In order to induce anxiety and theta2, animals were pre-treated with salicylate (that induces tinnitus-related anxiety). We found that OLM cells phase-lock to theta2 and show highly coherent activity. In another set of experiments, we tested the hypothesis that OLM cell stimulation prevents anxiety-like behavior in tinnitus. For that purpose, we expressed ChR2 in OLM cells (using a cre-dependent viral vector). We found that OLM stimulation prevented anxiety-like behavior similarly to anxiolytic drugs. These results further demonstrate that OLM neurons are key to circuits that control anxiety and these neurons can be target for the development of anxiolytic therapies. Moreover, OLM cells may also be a target for treatment of mood disorders associated to tinnitus.

Disclosures: J. Winne: None. **R.N. Leao:** None. **G. Nascimento:** None. **K. Kullander:** None.

Poster

771. Biological Rhythms: Entrainment and Phase Shifts

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 771.14/T1

Topic: F.08. Biological Rhythms and Sleep

Support: CIHR Foundation Grant FDN-143337
CIHR Frederick Banting and Charles Best Canada Graduate Scholarships Doctoral Awards (CGS-D)

Title: A neural circuit for non-photic phase shifting of circadian rhythms by an acute salt load

Authors: *C. GIZOWSKI[1], C. W. BOURQUE[2];
[1]McGill Univ. Hlth. Ctr., Montreal, QC, Canada; [2]McGill Univ., Montreal, QC, Canada

Abstract: While clock time is normally adjusted by daylight onset, it can also be regulated by non-photic stimuli through unknown mechanisms. In this project, we examined if an acute salt load can acutely regulate clock time. The organum vasculosum lamina terminalis (OVLT) is a preoptic nucleus that contains neurons capable of detecting hypernatremia. We therefore examined if OVLT neurons can modulate SCN clock neurons. Histological and tracing experiments showed that salt-sensitive OVLT neurons project to the SCN. Interestingly, SCN VP neurons primarily receive GABAergic synaptic events. Further tracing experiments indicated that sodium-sensitive GABA OVLT neurons project to the SCN. Preliminary results suggest GABA excites SCN VP neurons during wake time, when SCN electrical activity is low. Electrophysiological analysis in slices further revealed that a salt load delivered to the OVLT significantly increases the frequency of spontaneous GABA synaptic currents and triggers an anticipatory shift in the onset of electrical activity in SCN clock neurons. Furthermore, systemic salt load injections during the dark period significantly phase advances circadian locomotor activity in mice. These data show that the SCN not only drives circadian rhythms, but also receives important physiological signals that can mediate non-photic adjustments in clock time and possibly adapt organisms to dynamic environments.

Disclosures: C. Gizowski: None. **C.W. Bourque:** None.

Poster

771. Biological Rhythms: Entrainment and Phase Shifts

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 771.15/T2

Topic: F.08. Biological Rhythms and Sleep

Title: Analysis of learning management system logins identifies interactions between social jetlag, gender, and academic performance

Authors: *A. E. SCHIRMER[1], B. L. SMARR[2], A. ISHAMI[1], M. VUJNOVICH[1];
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Abstract: Misalignments between endogenous circadian rhythms and the built environment (i.e., social jet lag, SJL) result in learning and attention deficits. Currently, there is no way to assess the impact of SJL on learning outcomes of large populations as a response to schedule choices, let alone to assess which individuals are most negatively impacted by these choices. A standard part of most university course work now involves logging into a centralized Learning Management System (LMS) to register for classes, check schedules, turn in homework, and join discussion boards, for example. We hypothesized that these login events would reflect information about the biological rhythms of the students, and could therefore be mined to quantify effects of circadian stability, gender, and social jetlag on academic performance in the real world, covering a large population at the level of the individual. Login data from over 14,000 students were collected from the Northeastern Illinois University learning management system Desire 2 Learn (D2L) and interactions between gender, SJL, and academic performances were explored. The activity profiles revealed that the majority of students experience more than 30 minutes of SJL on average, with greater amplitudes correlating strongly with a significant decrease in academic performance, especially in people with later apparent chronotypes. In addition, login patterns in female students were found to be less variable across the semester and decreased variability correlated with increased academic performance. Understanding these interactions at the individual- and population-level will help guide schedule choice and reduce SJL. This would serve to maximize academic performance to the benefit of individual students and the universities they attend.

Disclosures: A.E. Schirmer: None. **B.L. Smarr:** None. **A. Ishami:** None. **M. Vujnovich:** None.

Poster

771. Biological Rhythms: Entrainment and Phase Shifts

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 771.16/T3

Topic: F.08. Biological Rhythms and Sleep

Title: Reinforcement of the circadian clock restores alcohol tolerance and decreases toxicity in aged *Drosophila*

Authors: *A. K. DE NOBREGA, L. C. LYONS;
Biol. Science, Program in Neurosci., Florida State Univ., Tallahassee, FL

Abstract: Alcohol consumption and abuse in middle-aged and older adults has become a significant economic and health issue, with more than 75% of the alcohol-induced poisoning deaths occurring in these age groups. Surprisingly, little progress has been made in identifying the cellular mechanisms that underlie alcohol sensitivity and toxicity in middle and old age. One of the factors potentially underlying age-related pathologies is the weakening of the circadian system with age. Previously, we found that the circadian clock modulates alcohol sensitivity and toxicity and that circadian dysfunction significantly increases alcohol sensitivity and mortality. Moreover, we found that age-related increases in alcohol toxicity first occur during early middle age and correlate with a weakening of the circadian system. We hypothesize that age-related weakening of the circadian system can exacerbate alcohol pathologies and increase mortality following alcohol exposure. The similarity in alcohol-induced behaviors across species combined with its comparatively short lifespan and the availability of precise tools to manipulate neuronal gene expression make *Drosophila* a practical model for studies of aging and alcohol neurobiology. In the current studies, we investigated whether strengthening the circadian system in aged flies ameliorates the age-related increases in alcohol sensitivity and mortality. As the *Drosophila* circadian system can be entrained by temperature cycles, we used temperature cycles (25°C:18°C) coupled to the light-dark (12h:12h) cycle to strongly reinforce the circadian system. Circadian reinforcement through the dual entrainment paradigm did not alter mortality in young flies but significantly reduced mortality following repeated alcohol exposures in middle-aged and older flies. We found that temperature reinforcement of clock function significantly decreased the sensitivity to alcohol in young and middle-aged flies (10d and 20d) and restored the development of long-term tolerance (24 h) in middle-aged flies. In older flies under temperature and light entrainment, tolerance was restored only when a longer pre-exposure to alcohol was used. Temperature entrainment alone was sufficient to partially restore functional tolerance in middle-aged flies, although the flies were more sensitive to alcohol than flies entrained by light and temperature cycles. Overall, our results suggest that signaling in the light-entrainment pathway may be disturbed in middle-aged and older flies and that ensuring robust clock function ameliorates age-related changes in alcohol sensitivity.

Disclosures: **A.K. De Nobrega:** None. **L.C. Lyons:** None.

Poster

771. Biological Rhythms: Entrainment and Phase Shifts

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 771.17/T4

Topic: F.08. Biological Rhythms and Sleep

Support: NIH Grant AI-67406

Title: Wavelet analyses of behavioral ultradian rhythms in male and female C57BL/6 mice

Authors: *J. P. RIGGLE[1], K. G. ONISHI[1], B. L. SMARR[3], L. M. KAY[1,2], B. J. PRENDERGAST[1,2];
[1]Psychology, Inst. of Mind and Biol., [2]Committee on Neurobio., Univ. of Chicago, Chicago, IL; [3]Psychology, UC Berkeley, Berkeley, CA

Abstract: Behavioral ultradian rhythms (URs) are biological rhythms in the 1-6 h range. URs play a role in sleep, food intake, metabolism, and hormone pulsatility, and are understudied relative to circadian rhythms. Challenges to the analysis of URs include circadian harmonic contamination, intrinsic non-stationarity, and defeciencies in traditional chronobiological time series analysis methods in dealing with these problems. Recently, wavelet analysis has emerged as a method for overcoming these issues. Here we used the continuous wavelet transform to examine the roles of sex, gonadal hormones and seasonal changes in day length on the period and power of ultradian rhythms of locomotor activity in C57BL/6 mice. The results identify sex differences in ultradian rhythms and a marked effect of seasonal changes in day length on ultradian period and on the distribution of ultradian power in mice.

Disclosures: **J.P. Riggle:** None. **K.G. Onishi:** None. **B.L. Smarr:** None. **L.M. Kay:** None. **B.J. Prendergast:** None.

Poster

771. Biological Rhythms: Entrainment and Phase Shifts

Location: Hall A

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Program #/Poster #: 771.18/T5

Topic: F.08. Biological Rhythms and Sleep

Support: Jacob E. Nyenhuis Grant for Faculty-Student Collaboration at Hope College
Towsley Research Scholars Award at Hope College

Title: Revealing functional brain activity following excitotoxic injury to retinal ganglion cells in a diurnal rodent model

Authors: N. KRAUSE[1], C. BRENNAN[1], J. DYKE[1], G. FOGO[3], *A. J. GALL[2];
[2]Psychology, [1]Hope Col., Holland, MI; [3]Univ. of Michigan, Ann Arbor, MI

Abstract: Intrinsically photosensitive retinal ganglion cells (ipRGCs) transmit light signals to the brain and contribute to non-image forming vision, such as synchronizing circadian rhythms to the light-dark cycle. Our lab recently showed that ipRGCs are resistant to excitotoxic damage and remain functional following N-methyl-D-aspartic acid (NMDA) administration to the retina, in a diurnal rodent, the Nile grass rat (Arvicanthis niloticus). Importantly, whereas non-image forming vision remained functional due to the survivability of ipRGCs, image-forming vision was significantly impaired due to damage to traditional retinal ganglion cells (RGCs). Specifically, RGC damage led to behavioral deficits in the Morris Water Maze, a test that requires rodents to use visual cues in order to find a hidden platform. We hypothesized that brain areas that are critical for image-forming vision in NMDA-treated grass rats would have significantly less neuronal activity than controls. To test this hypothesis, we used cFos, a marker for neuronal cell activation, to visualize neuronal activity in the brains of NMDA-treated grass rats and controls. We predicted that the primary visual cortex (V1), a brain region that is involved in image-forming vision, would exhibit significantly less cFos in NMDA-treated grass rats vs. controls. In contrast, we predicted that the suprachiasmatic nucleus (SCN), intergeniculate leaflet (IGL), and olivary pretectal nucleus (OPT), brain areas that are involved in non-image forming vision, would exhibit no difference in the amount of cFos in NMDA-treated grass rats vs. controls. We found that brain regions that receive projections from ipRGCs and are critically involved in non-image forming vision, such as the SCN, IGL and OPT, did not exhibit a significant change in cFos cells in NMDA-treated grass rats vs. controls. In contrast, V1 expressed significantly less cFos in NMDA-treated grass rats, suggesting that image-forming vision was impaired. Altogether, the present study aims to reveal the functionality of retinorecipient brain regions that are involved in visual functions following excitotoxic injury to RGCs in a diurnal rodent model, the Nile grass rat.

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Poster

771. Biological Rhythms: Entrainment and Phase Shifts

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Program #/Poster #: 771.19/T6

Topic: F.08. Biological Rhythms and Sleep

Support: NSF Grant IOS1456706
NIH Grant MH15947

Title: Per1 and c-Fos expression in infralimbic prefrontal cortex (IL) of adult male rats following activation of IL-projecting serotonergic Raphe nucleus neurons at ZT1 or ZT13

Authors: *H. K. STRNAD[1], J. R. RAVENEL[2], S. P. SHARMA[1], M. J. HARTSOCK[3], R. L. SPENCER[1];
[1]Psychology and Neurosci., Univ. of Colorado at Boulder, Boulder, CO; [2]Dept. of Psychology and Neurosci., Univ. of Colorado, Boulder, CO; [3]Univ. of Colorado Boulder, Boulder, CO

Abstract: Circadian rhythms are oscillations in physiology and behavior that optimize organismal function throughout the 24-hour day. Information about daily fluctuations in environmental ambient light is relayed to the suprachiasmatic nucleus (SCN) of the hypothalamus through the retinohypothalamic tract. The SCN aligns its activity to this photic entrainment signal and communicates daily timing information to the rest of the brain and body. However, given a paucity of direct projections from the SCN to extra-hypothalamic brain regions, it is yet unknown how the SCN communicates time of day information to other brain regions. Although glucocorticoid hormone secretion appears to play some role, it is not alone sufficient to drive extra-SCN circadian gene expression independent of SCN activity. Serotonergic neurons from the raphe nucleus (RN) have been shown to be necessary for non-photic entrainment of circadian rhythms, possibly via direct innervation of the SCN. RN neurons project extensively throughout the brain, and serotonin receptor sub-types are localized on a variety of neural cell types (e.g. both pyramidal cells and interneurons). Our lab has previously demonstrated that there is rhythmic clock gene expression in the infralimbic prefrontal cortex (IL), and disruption of IL clock gene expression alters IL-dependent function (conditioned fear extinction learning) (Chun et al, JBR 30:417, 2015; Woodruff et al, eNeuro.0455-18). The current project used Cre-dependent excitatory Designer Receptors Exclusively Activated by Designer Drugs (DREADD) in adult male rats to selectively drive activity of IL-projecting serotonergic neurons of the RN to test whether these inputs contribute time of day information to an extra-SCN brain region. The DREADD activator clozapine-*N*-oxide (5 mg/kg) or vehicle was administered at ZT13 (n = 6-8), approximately one hour before daily peaks in hippocampal and peripheral serotonin levels, or ZT1 (n = 4-7), 12 hours later. Tissue was then extracted and analyzed for changes in *c-Fos* and *Per1* mRNA in the IL via fluorescent and radioactive (S^{35}) *in situ* hybridization.

Disclosures: H.K. Strnad: None. **J.R. Ravenel:** None. **S.P. Sharma:** None. **M.J. Hartsock:** None. **R.L. Spencer:** None.

Poster

771. Biological Rhythms: Entrainment and Phase Shifts

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 771.20/T7

Topic: F.03. Neuroendocrine Processes

Support: NIH/NIGMS grants R01GM083913
NIH/NIGMS grants R01GM100893
NIH/NINDS grant R01NS094211
Wayne E. Crill Endowed Professorship

Title: Indoleamines related to melatonin are secreted from the pineal gland at night and act on melatonin receptors

Authors: *B. LEE[1], D.-S. KOH[1], I. BUSSI[2], H. O. DE LA IGLESIA[2], C. HAGUE[3], B. HILLE[1]; [1]Physiol. and Biophysics, [2]Biol., [3]Pharmacol., Univ. of Washington, Seattle, WA

Abstract: In darkness, melatonin is produced by the pineal gland, a neuroendocrine organ in the brain. Night signals from the retina pass through the suprachiasmatic nucleus (SCN), the master biological clock, and eventually to the superior cervical ganglia, which send postganglionic sympathetic fibers to the pineal that release norepinephrine (NE). Sympathetic NE upregulates the rate-limiting pineal enzyme arylalkylamine N-acetyltransferase (AANAT), which synthesizes N-acetylserotonin (NAS) from serotonin. This precursor is converted to melatonin in one more step. AANAT also converts tryptamine to N-acetyltryptamine (NAT), a structural analog of melatonin. The literature suggests that NAT and NAS are secreted from the pineal gland at night together with melatonin. Do NAT and NAS have similar roles as melatonin? To answer this question, we first tested whether NAT and NAS activate melatonin receptors 1 (MT_1) and 2 (MT_2) using dynamic mass redistribution (DMR), a real-time optical assay. The receptors overexpressed in HEK293 cells were activated by melatonin, NAT, and NAS, but melatonin was more potent than NAT and NAS for both receptors. All effects were blocked by melatonin receptor antagonists. Thus, NAT and NAS are weak partial agonists. We next investigated secretion of the three agonist indoleamines from isolated rat pineal glands with ultra performance liquid chromatography-mass spectrometry (UPLC/MS). NE treatment for 6 hours increased pineal secretion of melatonin, NAT, and NAS by 12, 38, and 41 fold, respectively. Finally, we measured serum levels of the three agonist indoleamines to examine whether NAT and NAS are also night hormones. Serum melatonin increased 32 fold at night, an increase completely abolished after pinealectomy. For NAT and NAS, the basal serum concentrations were already elevated and showed no or weaker circadian rhythms, respectively. The night serum levels of NAT and NAS were several orders of magnitude lower than the EC_{50} for melatonin receptor activation. Taken together, three agonist indoleamines secreted by the pineal gland can activate

melatonin receptors, but in circulating blood only the melatonin concentration is high enough to activate peripheral melatonin receptors. NAT and NAS may still act in a circadian paracrine manner on receptors in or near the pineal gland where they are at higher concentration, or there may be other more sensitive peripheral receptors for them.

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Poster

772. Fear and Aversive Learning and Memory: Modulatory Factors

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 772.01/T8

Topic: G.01. Appetitive and Aversive Learning

Support: NIH Grant MH113053

Title: Roles for dorsal raphe/periaqueductal gray and retrorubral field dopamine in adaptive fear

Authors: *K. M. WRIGHT, E. LEE, M. A. MCDANNALD;
Dept. of Psychology, Boston Col., Chestnut Hill, MA

Abstract: Fear in the face of certain threat is healthy and adaptive. However, equivalent levels of fear to uncertain threat and certain safety is maladaptive. Disruptions to brain regions underlying successful discrimination of danger and safety may have clinical implications in disordered fear. While considerable research has identified brain regions essential to acquiring fear to certain threats; neural circuits for adaptive fear across a range of uncertain threats are less understood. Dopamine (DA) is widely studied neuromodulator with distinct populations scattered throughout the midbrain. The ventral tegmental area and substantia nigra are canonical sources of midbrain dopamine. Yet many more dopamine populations exist. Here we investigated roles for noncanonical dorsal raphe/ventrolateral periaqueductal gray (vlPAG) and retrorubral field (RRF) dopamine in fear modulation. Male, Long Evans rats were given bilateral 6-hydroxydopamine (6-OHDA) depletions or sham procedures. Following recovery, rats received fear discrimination in which three auditory cues predicted unique foot shock probabilities: danger ($p = 1.00$), uncertainty ($p = 0.25$) and safety ($p = 0.00$). Control rats with DA intact demonstrated excellent discrimination to each of the three cues: high fear to danger, intermediate to uncertainty and low to safety. Depleting vlPAG DA disrupted overall fear discrimination while depleting A8 DA disrupted the temporal emergence of discrimination over cue presentation. The results reveal distinct, but essential roles for vlPAG and RRF DA in adaptive fear.

Disclosures: K.M. Wright: None. **E. Lee:** None. **M.A. McDannald:** None.

Poster

772. Fear and Aversive Learning and Memory: Modulatory Factors

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 772.02/T9

Topic: G.01. Appetitive and Aversive Learning

Support: NIMH Grant MH117791
Grant DA034010

Title: Dorsal raphe 5-HT updates fear via negative prediction error

Authors: *R. A. WALKER, R. L. SUTHARD, T. PERISON, N. M. SHEEHAN, E. K. ENABULELE, M. H. RAY, A. DILEO, M. A. MCDANNALD;
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Abstract: The dorsal raphe nucleus (DRN) contains the largest population of serotonergic neurons in the central nervous system. Serotonin is a widely functioning neuromodulator, but previous research has suggested a possible role for serotonin in fear learning. Here we sought to investigate whether DRN serotonin could be involved in fear updating via prediction error signaling. Using TPH2-cre rats bred on the background of Long-Evans, serotonergic neurons in the DRN were selectively deleted via cre-caspase or labeled with a cre-YFP control fluorophore in experiment 1. Rats underwent 16 sessions of fear discrimination training during which three cues were associated with different probabilities of foot shock: safety p=0.00, uncertainty p=0.375, and danger p=1.00. This task was designed such that it requires the use of prediction errors to demonstrate appropriate fear, specifically for the uncertainty cue. After fear discrimination, rats underwent 8 sessions of selective extinction, during which the uncertainty cue was no longer paired with shock. Results indicated that DRN serotonin is needed to accurately decrease fear to uncertainty during extinction, as rats with serotonin depletion were slower to extinguish fear to the uncertainty cue and did not extinguish to the same extent as YFP controls. In experiment 2, we sought to causally implicate DRN serotonin in prediction error signaling via optogenetics. Again using TPH2-cre rats, cre-dependent halorhodopsin or a cre-YFP control fluorophore was infused into the DRN, and optical ferrules were bilaterally implanted to allow for delivery of 532 nm light. Inhibition of serotonergic neurons was achieved by delivering light at the time of shock omission to the uncertainty cue during selective extinction in order to target the time of negative prediction error. Fear to the uncertainty cue in the halorhodopsin group remained high during the optogenetic manipulation, whereas fear in the control group extinguished normally. Fear to any cue did not change due to light delivery during omission on safety cue trials or during positive prediction error periods for either group, indicating the effects were specific to negative prediction error signaling. Together, experiments

1 and 2 demonstrate a role for DRN serotonergic neurons in fear updating, particularly via negative prediction error signaling.

Disclosures: **R.A. Walker:** None. **R.L. Suthard:** None. **T. Perison:** None. **N.M. Sheehan:** None. **E.K. Enabulele:** None. **M.H. Ray:** None. **A. DiLeo:** None. **M.A. McDannald:** None.

Poster

772. Fear and Aversive Learning and Memory: Modulatory Factors

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 772.03/T10

Topic: G.01. Appetitive and Aversive Learning

Support: BRAIN U01 MH109104

Title: Cholinergic modulation of learned and innate threat processing

Authors: *P. RAJEBHOSALE[1], L. W. ROLE[2], D. A. TALMAGE[3];
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Abstract: Threat response behaviors are found virtually in all animal species, and circuits that encode these behaviors in the mammalian brain are evolutionarily conserved. The amygdala, a key region in these circuits, is highly interconnected to various critical nodes in the processing of threat and generation of defensive responses.
The basolateral portion of the amygdala (BLA) is densely innervated by cholinergic axons originating from cholinergic nuclei in the basal forebrain. Neurons in the nucleus basalis/substantia innominata posterior (NBM/SIp) and the ventral pallidum/substantia innominata anterior (VP/SIa) form the major cholinergic input to the BLA, suggesting a potential role for these basal forebrain cholinergic neurons (BFCNs) in the modulation of associative threat processing. In support of this hypothesis we present a few key findings:
We found that in associative threat conditioning, activity of BLA-projecting BFCNs was necessary during both threat acquisition, and retrieval to obtain the typical conditioned response (CR), freezing, as well as activation-induced fos expression in the amygdala. Inhibiting BFCNs of the NBM/SIp only during retrieval was sufficient to ablate the CR, whereas inhibiting VP/SIa BFCNs had no effect on the CR.
NBM/SIp BFCNs were activated during threat memory acquisition and the same neurons were reactivated during memory retrieval. During threat memory retrieval, high responding mice showed greater reactivation of the acquisition-activated pool of cholinergic neurons compared to low responding mice who underwent the same training conditions, or to mice who were not shocked on training day. Thus, the degree of reactivation of these neurons is specific to aversive conditioning and corresponds to the extent of the conditioned response. Based on these

observations we suggest the recruitment of a cholinergic modulatory engram in associative threat memory.
In contrast, during innate threat processing (predator odor exposure), we found that NBM/SIp BFCNs were not activated; however, we observed robust activation of VP/SIa BFCNs, particularly BLA-projecting VP/SIa BFCNs. Inhibition of BLA-projecting BFCNs produced a switch favoring active rather than passive avoidance behaviors.
These results demonstrate the presence of a population of associative threat learning-engraphed cholinergic neurons in the NBM/SI and separate populations in the VP/SI involved in modulating non-associative (innate) threat processing.

Disclosures: P. Rajebhosale: None. **L.W. Role:** None. **D.A. Talmage:** None.

Poster

772. Fear and Aversive Learning and Memory: Modulatory Factors

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 772.04/T11

Topic: G.01. Appetitive and Aversive Learning

Support: NIH Grant DA034010

Title: A role for the nucleus accumbens core in adaptive fear scaling

Authors: *M. H. RAY[1], A. N. RUSS[1], R. A. WALKER[1], M. A. MCDANNALD[2];
[1]Psychology, [2]Dept. of Psychology, Boston Col., Chestnut Hill, MA

Abstract: Environmental threats exist on a continuum from unlikely to certain. Adaptive behavior requires fear to scale to the level of threat. In two experiments, we determined the role of the nucleus accumbens core (NAcc) in adaptive fear scaling. In experiment 1, male Long Evans rats received bilateral neurotoxic NAcc lesions, permanently ablating NAcc neurons, or sham surgery, leaving NAcc neurons intact. In experiment 2, male Long Evans rats received bilateral NAcc viral infusions of either halorhodopsin (Halo; AAV-hSyn-eNpHR3.0-EYFP) or a control fluorophore (YFP; AAV-hSyn-EYFP) and optical ferrules dorsal to the NAcc. Following recovery, rats were trained to nose poke for food pellets then underwent Pavlovian fear discrimination in which three auditory cues were associated with unique foot shock probabilities: danger ($p = 1.00$), uncertainty ($p = 0.25$), and safety ($p = 0.00$). Fear was measured using suppression of rewarded nose poking. In experiment 1, rats underwent sixteen sessions of Pavlovian fear discrimination. Sham rats acquired excellent fear discrimination, showing high fear to danger, intermediate fear to uncertainty, and low fear to safety. NAcc lesioned rats failed to show the same degree of discrimination, exhibiting decreased fear to danger and increased fear to safety. This pattern was most evident when assessing fear in the first 2-s of cue onset. While shams showed evidence of discrimination in ~600-ms, such discrimination was not

observed in NAcc rats until nearly 2-s. In experiment 2, YFP and Halo rats underwent 10 sessions of Pavlovian fear discrimination, two sessions of cable habituation, and eight sessions of laser illumination. The final eight sessions consisted of alternating two session blocks of cue illumination or ITI illumination (12.5mW – 532 nm light). During habituation and ITI illumination, YFP and Halo rats showed rapid, adaptive discrimination to the three cues. During cue illumination, only YFP rats achieved adaptive fear scaling. NAcc inhibition during cue presentation resulted in increased fear to safety and an inability to discriminate between safety and uncertainty only in Halo rats. Congruent with experiment 1, this pattern was specific to the first 2-s of cue onset. The results demonstrate an integral role for the NAcc in acquisition and expression adaptive fear scaling.

Disclosures: M.H. Ray: None. **A.N. Russ:** None. **M.A. McDannald:** None. **R.A. Walker:** None.

Poster

772. Fear and Aversive Learning and Memory: Modulatory Factors

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 772.05/T12

Topic: G.01. Appetitive and Aversive Learning

Support: Agence Nationale de la Recherche
Labex Memolife
Fondation Pierre Deniker
CNRS
INSERM
Collège de France

Title: Emotional memory encoding in medial prefrontal cortex: Single unit activity during fear acquisition, extinction, renewal, and sleep

Authors: *M. N. POMPILI[1,2], R. TODOROVA[1], G. MAKDAH[1], E. M. LEROUX[1], T. M. JAY[2], B. P. GODSIL[2], S. I. WIENER[1];
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Abstract: A growing literature shows that the medial prefrontal cortex (mPFC) controls fear behavior and modulates emotional memory during fear conditioning and extinction learning. Its sub-regions play distinctive roles, with the dorsal part (dmPFC) implicated in fear expression while the ventral part (vmPFC) modulates fear inhibition and extinction. mPFC immediate early gene expression and synaptic plasticity change in conditioning and extinction learning, suggesting that emotional memory trace storage is controlled there. Recent studies recorded mPFC neurons to characterize the neurophysiological mechanisms underpinning the control of

fear behavior, but the precise neural code to store, retrieve, consolidate, and modulate emotional memory remain obscure. One hypothesis is that the mPFC is a key link in a network forming associations about risky and safe stimuli and contexts. New experiences may modify representations of such emotional valences, and the dorsal and ventral mPFC may have different encoding mechanisms supporting their respective roles in this. However, there is a lack of consensus on these subjects. Moreover, it is unknown whether and how mPFC adapts its coding strategies to support between-days extinction learning and memory consolidation. To answer these questions, we recorded 7866 single units in mPFC in five rats undergoing a 8-15 consecutive days protocol composed of habituation, discriminative auditory fear conditioning, extinction, and within-subject renewal test (ABA scheme) as well as during sleep preceding and following each session (6-8 hours of recording per day). Of these units, 947 were in the anterior cingulate, 702 in medial orbital, 2833 in prelimbic, 1219 in infralimbic, and 465 in dorsal peduncular mPFC sub-regions (up to 257 units recorded simultaneously). Fearful behavior was monitored and quantified with head mounted inertial sensors and multiple cameras. After conditioning, rats increased freezing to both shock-coupled (CS+) and uncoupled (CS-) stimuli and startle reflexes were potentiated. These reactions decreased with extinction training. The analyses characterize the evolution of responses to CS+ and CS- during conditioning, extinction, and renewal in the various regions of mPFC and the differences between rats discriminating and those generalizing their responses to the two stimuli. Moreover, we test whether the reactivation of these units during sleep correlates with memory consolidation. These results will permit a better understanding of mPFC neural coding strategies that support emotional memory.

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Poster

772. Fear and Aversive Learning and Memory: Modulatory Factors

Location: Hall A

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Title: Somatostatin neurons in the bed nucleus of stria terminalis enhance auditory fear memory formation

Authors: ***B. BRUZSIK**[1], L. BIRO[1], H. SZEBIK[1], K. R. SAROSDI[1], H. ORSOLYA[1], E. SIPOS[2], D. ZELENA[2], V. CSILLAG[3], I. FARKAS[3], E. MIKICS[1], M. TOTH[1];

[1]Translational Behavioural Neuroscience, Inst. of Exptl. Medicine, HAS, Budapest, Hungary; [2]Behavioral and Stress Studies, Inst. of Exptl. Medicine, HAS, Budapest, Hungary; [3]Endocrine Neurobiology, Inst. of Exptl. Medicine, HAS, Budapest, Hungary

Abstract: The bed nucleus of stria terminalis (BNST) mediates defensive behaviors to various threats and accordingly hyperactivation of this region is a common phenomenon of anxiety disorders. The involvement of BNST in learned fear responses is less clear, although its anatomical connectivity suggests a potential role in conditioned fear responses. BNST consists of mainly GABAergic neurons (vGAT+) expressing different neuropeptides such as corticotropin-releasing factor (CRF+) and somatostatin (SOM+). These neurons project to various brain regions involved in Pavlovian fear conditioning and anxiety, but it is still unknown how these cells modulate conditioned fear responses. Here, we used chemogenetics to modulate neuronal activity in the BNST during fear memory consolidation. Stimulation of BNST neurons in male vGAT-cre mice selectively impaired fear extinction in conjunction with increased fear recall in safe context (generalization) without affecting freezing in the shock context. Modulation of vGAT neurons in the open field test and predator odor avoidance also confirmed their anxiogenic properties. Activation of SOM+ neurons during fear memory consolidation similarly enhanced cue-dependent fear recall in the safe context. Intriguingly, chemogenetic modulation of CRF+ neurons had no effect on fear recall and anxiety-related behavior. Chemogenetic modulation of the above mentioned cell populations during extinction training had limited effect on freezing response. Our data underlines the importance of anxiety circuits in maladaptive fear memory formation, indicating elevated BNST activity as a potential vulnerability factor to trauma related anxiety disorders.

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Poster

772. Fear and Aversive Learning and Memory: Modulatory Factors

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 772.07/T14

Topic: G.01. Appetitive and Aversive Learning

Support: Natural Sciences and Engineering Council (NSERC)

Title: The fearless paradox

Authors: *T. D. LAPOINTE, M. WOLTER, F. LERI;
Univ. of Guelph, Guelph, ON, Canada

Abstract: Negative reinforcement is said to occur when a response is maintained by the avoidance of an aversive event (unconditioned stimulus such as pain; US). An avoidance response is typically activated by a warning signal (conditioned stimulus; CS) that subjects respond to in order to avoid an aversive stress state. However, observations of subjects trained on two-way signaled active avoidance (SigAA) have indicated that the negative stress reaction produced by the CS dissipates during training. So then, what maintains avoidance behaviour? The goal of the current research was to explore this so called "fearless paradox." Separate groups of male Sprague-Dawley rats were trained for 6 days on SigAA using different foot-shock intensities (0, 0.2, 0.4 and 0.8 mA, n=9 each) and tested for stress-induced analgesia immediately after SigAA sessions. After a 3-day pause, avoidance was re-tested for two consecutive days (7 & 8), and on day 9, the session occurred in the absence of foot-shock. It was found that learning to avoid foot-shock was associated with reduced hot-plate latencies. As well, exposure to the CS in the absence of foot-shock produced significant stress-induced analgesia only in animals that did not acquire the avoidance response. Overall, this study confirms that once learned, avoidance behaviour is not dependent on stress reduction.

Disclosures: T.D. Lapointe: None. **F. Leri:** None.

Poster

772. Fear and Aversive Learning and Memory: Modulatory Factors

Location: Hall A

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Program #/Poster #: 772.08/T15

Topic: G.01. Appetitive and Aversive Learning

Support: Sub award of NIH Grant P20GM103449.

Title: NinaA: A novel mediator of pain memory in *drosophila melanogaster*

Authors: *A. CROCKER, G. PIL, K. SARIKAYA, J. MARRIOTT, E. VINTON, K. TABER; Middlebury Col., Middlebury, VT

Abstract: The detection, learning, and recall of pain is crucial to all animals' survival. Dysregulation of these functions can contribute to a number of anxiety disorders. Here we characterize the role of the *NinaA* gene which appears to play a part in painful memory formation and stress behavior in the fly. *NinaA* is known to be important for trafficking Rhodopsin 1 (Rh1) out of the ER in the eye. *Rh1* is also involved in temperature preference. However, our data suggests that the actions of NinaA are independent of *Rh1*. Previously we found that the *NinaA* gene is down-regulated following memory formation. Flies carrying a mutation in the *NinaA* gene fail to form longterm, aversive odor memories. Our preliminary data suggest that these flies fail to centrally integrate the aversive nature of electric shock. This deficit is also seen when trained with noxious heat. Our data suggests that *NinaA* animals generate a stress response to

noxious stimuli, as measured by an increase in wall following behavior, but once that noxious stimuli is removed, the heightened stress response ends. This is in contrast to wild type flies who show enhanced stress responses for at least 10 minutes following painful stimuli exposure. We hypothesize that this failure to maintain a normal stress response to painful stimuli reduces their capacity to maintain long-term memories. We also hypothesize that this is mediated through the DAL neuron. The DAL neuron is important for stress behavior in the fly. Further characterization of both the *NinaA* gene and the DAL neuron will shed light on the role ancient stress pathways play in memory formation in the fly.

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Poster

772. Fear and Aversive Learning and Memory: Modulatory Factors

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Topic: G.01. Appetitive and Aversive Learning

Support: NIH 5R01MH101440
KU

Title: Deletion of the prion like domain of CPEB2 in mice impairs long-term memory of one-trial inhibitory avoidance

Authors: *M. L. HUFF[1], B. A. EBNER[2], K. SI[3];
[1]Stowers Inst. For Med. Res., Kansas City, MO; [2]Univ. of Kansas Med. Ctr., Kansas City, KS; [3]Stowers Inst. for Med. Res., Kansas City, MO

Abstract: Memories can last for hours or even years in humans, yet the molecular basis of this memory persistence is still not fully understood. Previous work revealed the specific isoform of neuronal RNA binding protein cytoplasmic polyadenylation element binding protein (CPEB) is required specifically for the persistence of memory in Drosophila. This memory stabilization relies on CPEB's self-sustaining amyloidogenic (prion-like) properties. In mouse and in human two CPEB variants, CPEB3 and CPEB2, have similar properties to Drosophila CPEB. Here we report the consequence of removal of CEPB2 prion-like domain in long-term memory consolidation and stabilization in mice. Wildtype (B6/J) and homozygous prion-like domain deletion ($PD^{-/-}$) littermates were trained on one-trial inhibitory avoidance. On training day, mice received a single, inescapable footshock (0.5mA, 1s) upon fully stepping through from the illuminated to the darkened compartment. Retention was tested days or weeks later and latency to cross from the illuminated to darkened "shock" compartment was recorded. Separate groups of animals were tested at 30 min and 3 h post-footshock to assess short-term memory. Long-term

memory was also tested using an object location task (retention tested at 24 h) and classical fear conditioning (single 1.5mA, 2s footshock; test at 24h). Anxiety was measured in an elevated plus maze. Sessions were recorded and analyzed using EthoVision software. During inhibitory avoidance testing, $PD^{-/-}$ animals show reduced retention latencies compared to matched wildtypes when trained at 1, 3, or 6 months of age. This impairment persisted when retention was repeatedly tested up to 2 months after training. Retention latencies of $PD^{-/-}$ animals at 30 min or 3 h post-training were also decreased compared to wildtype littermates. There was no significant difference in freezing between wildtype and $PD^{-/-}$ animals in classical fear conditioning and no significant difference in the object location task. $PD^{-/-}$ mice enter the open arms more often and spend cumulative time in the open arms of the EPM suggesting reduced basal anxiety. Together, these findings suggest that lack of the CPEB2 prion-like domain disrupts learning and memory. Future studies will examine the temporal nature of CPEB2 effects on learning and memory using conditional $PD^{-/-}$ animals.

Disclosures: M.L. Huff: None. **B.A. Ebner:** None. **K. Si:** None.

Poster

772. Fear and Aversive Learning and Memory: Modulatory Factors

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 772.10/T17

Topic: G.01. Appetitive and Aversive Learning

Support: NIH R01MH110425

Title: Effects of the partial NMDAR agonist D-cycloserine on the acquisition of discriminative safety learning and fear extinction

Authors: *A. ESCOBEDO[1], C. H. L. LEE[2], E. M. SOWINSKI[2], R. HERAKOVICH[2], S. SANGHA[1];
[1]Psychological Sciences, Purdue Inst. for Integrative Neurosci., [2]Psychological Sci., Purdue Univ., West Lafayette, IN

Abstract: Individuals suffering from posttraumatic stress disorder (PTSD) have difficulty maintaining reduced fear levels after extinction-based therapies, as well as reducing fear levels in response to explicit safety cues. Prior research has shown that the partial NMDA receptor agonist, D-Cycloserine (DCS), can facilitate the acquisition and consolidation of fear extinction in humans and rodents. However, it is unclear if this facilitation is limited to non-discriminative fear paradigms, where the subject first learns to fear a cue which is then later extinguished, or if it can also facilitate discrimination between a fear cue and a safety cue. The present study examined the effects of DCS in adult male Long Evans rats during a fear, safety, and reward cue discrimination conditioning task, as well as its effect on subsequent fear extinction. We

hypothesized that DCS would facilitate discrimination learning between a fear cue paired with shock and a combined fear+safety cue presented without a footshock, and this facilitated discrimination would then facilitate subsequent fear extinction. DCS (30.0 mg/kg i.p) was administered during each discrimination learning session, which resulted in marginally greater fear inhibition during the fear+safety cue versus the fear cue; however, this improved discrimination did not facilitate subsequent drug-free fear extinction. In a separate group we tested the hypothesis that DCS would facilitate the acquisition and consolidation of fear extinction in non-discriminative fear learning based on prior research. After fear conditioning to a single fear cue, DCS was administered either directly before fear extinction or directly after, to assess its effect on acquisition versus consolidation. In neither case did we see improved extinction retention one day later. Together, our data indicate that DCS provides mild improvement on inhibiting fear in the presence of a safety cue, but that it does not facilitate the acquisition or consolidation of non-discriminative fear extinction.

Disclosures: A. Escobedo: None. **C.H.L. Lee:** None. **E.M. Sowinski:** None. **R. Herakovich:** None. **S. Sangha:** None.

Poster

772. Fear and Aversive Learning and Memory: Modulatory Factors

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 772.11/T18

Topic: G.01. Appetitive and Aversive Learning

Title: Sex dependent influence of gut dysbiosis on defensive behaviors and basolateral amygdala dendritic morphology

Authors: V. WILK, C. GEARY, K. BARTON, P. JEFFERSON, S. ROZENTAL, ***A. L. MOUSLEY**, C. BAKER, D. ESTEBAN, H. BERGSTROM;
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Abstract: It is now well understood that imbalances in the gut microbiome influence brain function and behavior. Less studied are sex-dependent effects of gut microbiome dysbiosis on defensive behaviors. To determine whether antimicrobial (ATM)-induced gut dysbiosis modulates anxiety-like behaviors and auditory cued fear conditioning, male and female adult (PN70+) C57BL/6N mice voluntarily consumed a non-absorbable ATM cocktail (1.2 mg/mL neomycin, 2 mg/mL bacitracin, and 1.2 µg/mL pimaricin) or tap water control over a 10-day period. Open field behavior, auditory cued fear conditioning, contextual recall and cued recall were tested on days 5-10 of the ATM treatment. Results revealed a significant ATM-induced decrease in anxiety-like behavior in the open field of male (n=20/treatment group), but not female (n=20/treatment group) mice. While there were no effects of ATM treatment on fear conditioning or context fear recall, cued fear memory recall was impaired in female, but not male

mice. Together these data suggest the gut microbiota exerts a sex-dependent influence on anxiety-like behavior and the consolidation of auditory cued fear memory. Considering the essential role for the basolateral amygdala (BLA) in cued fear memory consolidation, studies are underway examining the structure of BLA principal neuron dendritic morphology following ATM-induced gut microbiome dysbiosis in male and female mice. We are also exploring the effects of microbiome dysbiosis on microbiome diversity. DNA extractions will be sequenced for taxonomic identification and relative quantification of bacteria.

Disclosures: **A.L. Mousley:** None. **V. Wilk:** None. **K. Barton:** None. **P. Jefferson:** None. **S. Rozental:** None. **C. Baker:** None. **D. Esteban:** None. **H. Bergstrom:** None. **C. Geary:** None.

Poster

772. Fear and Aversive Learning and Memory: Modulatory Factors

Location: Hall A

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Program #/Poster #: 772.12/T19

Topic: G.01. Appetitive and Aversive Learning

Title: Binge alcohol consumption impairs fear extinction retrieval in adolescent C57BL/6N mice

Authors: M. SCARLATA, K. LAWSON, J. BEZEK, A. MOUSLEY, L. LICHTY, C. CHO, C. MANGAN, ***H. C. BERGSTROM**;
Psychological Sci., Vassar Col., Poughkeepsie, NY

Abstract: Deficits in fear extinction recall are thought to contribute to the development of post-traumatic stress disorder (PTSD). Those with PTSD often drink alcohol and drinking tends to increase after trauma exposure. Despite the high co-occurrence of PTSD and alcohol use, the neurobehavioral impact of alcohol on the retrieval of established fear extinction memory is understudied. We recently showed that alcohol impaired extinction retrieval in adult male C57BL/6N mice (Scarlata et al., 2019). An outstanding question is the impact of alcohol on fear extinction retrieval in adolescent and female mice. The primary objective of this research is to study the age- and sex-related neurobehavioral impact of voluntary EtOH exposure on fear extinction memory retrieval. Male and female C57BL/6N mice underwent auditory cued fear conditioning and extinction between postnatal (PN) days 36-40 (mid-adolescent) and PN70+ (adult). Thirty-six hours later, mice were placed in a social “Drinking-in-the-Dark” (sDID) paradigm for 5 consecutive days. In this novel DID procedure, pair housed mice are permitted olfactory, auditory, visual and tactile interactions through perforated dividers while presented with a two-hour exposure to EtOH (20% v/v solution) or tap water three-hours into the natural dark cycle. Seventy-two hours following EtOH or water exposure, mice were tested for fear memory extinction retrieval, contextual renewal, and spontaneous recovery (30 days following extinction training). In adolescent mice, there was greater freezing in the EtOH group relative to controls, indicating impaired extinction retrieval. There were no differences in contextual

renewal, confirming previous findings. Work is currently underway characterizing the adult group. EtOH-induced neuroadaptations following fear extinction retrieval will be identified by mapping neuronal activity across a corticolimbic network using Arc/arg3.1 immunohistochemistry.

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Poster

772. Fear and Aversive Learning and Memory: Modulatory Factors

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 772.13/T20

Topic: G.01. Appetitive and Aversive Learning

Title: The role of the inflammatory response on the aversive learning

Authors: *G. F. ANTUNES, F. VENETUCCI, M. A. KUROKI, C. C. DE OLIVEIRA, L. C. T. DOS SANTOS, M. D. D. SENO, A. P. CAMPOS, R. D. PAGANO, R. C. R. MARTINEZ; Inst. Sirio Libanês De Ensino E Pesquisa, São Paulo, Brazil

Abstract: Impairments in learning, memory and cognitive functions have been suggested to be mediated by inflammatory response, which could be mostly attributed to glial cells. In the two way active avoidance test, two distinct subpopulations are identified based on the number of avoidance responses, the good and poor performers. The goal of our project was to investigate the correlation between glial activation, cytokine release and avoidance response. For that, we evaluated the inflammatory profile of good and poor performers in the prefrontal cortex, hypocampus and amygdala. Our data showed that in the prefrontal cortex, there was a reduction in the levels of IL-1 beta ($F_{(2.45)}$=3.58; P<0.05, followed by Newman-Keuls post hoc test), TNF-alfa ($F_{(2.45)}$=26.48; P<0.001, followed by Newman-Keuls post hoc test) and CINC-1 ($F_{(2.45)}$=17.48; P<0.0010, followed by Newman-Keuls post hoc test) in the good and poor performers in comparison with control animals. The good performers showed higher levels of IL-6 ($F_{(2.45)}$=17.86; P<0.001, followed by Newman-Keuls post hoc test), in comparation with the other groups. The poor performers showed reduction in levels of IL-10 ($F_{(2.45)}$=8.89; P<0.001, followed by Newman-Keuls post hoc test) in comparison with the other groups. The good performers showed higher levels of IL-17 in comparation with poor performers ($F_{(2.45)}$=3.90; P<0.05, followed by Newman-Keuls post hoc test).
In the hippocampus, there was no statistical difference among the groups considering the levels of IL-1 beta ($F_{(2.45)}$=3.23; P>0.05); TNF-alfa ($F_{(2.45)}$=2.39; P>0.05); CINC ($F_{(2.45)}$=1.04; P>0.05); IL-6 ($F_{(2.45)}$=1.06; P>0.05); IL-10 ($F_{(2.45)}$=1.88; P>0.05) and IL-17 ($F_{(2.45)}$=2.55; P>0.05). In the amygdala, good performers showed higher levels of IL-1beta ($F_{(2.45)}$=14.99; P<0.05, followed by Newman-Keuls post hoc test); TNF- alfa ($F_{(2.45)}$=14.00; P<0.05, followed by Newman-Keuls

post hoc test) in comparison with poor performers group. There was no statistical differences considering the levels of CINC-1 ($F_{(2.45)}$=1.63; P>0.05); IL- 6 ($F_{(2.45)}$=0.74; P>0.05); IL-10 $F_{(2.45)}$=0.16; P>0.05) and IL-17 ($F_{(2.45)}$=3.04; P>0.05). The main contributions of our work is to better understand the role of glial cells in the aversive learning and contribute to the development of other therapeutic approaches for cognitive dysfunction.

Disclosures: G.F. Antunes: None. **F. Venetucci:** None. **M.A. Kuroki:** None. **C.C. de Oliveira:** None. **L.C.T. dos Santos:** None. **M.D.D. Seno:** None. **A.P. Campos:** None. **R.D. Pagano:** None. **R.C.R. Martinez:** None.

Poster

772. Fear and Aversive Learning and Memory: Modulatory Factors

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 772.14/U1

Topic: G.01. Appetitive and Aversive Learning

Support: NIH Grant P50MH103222
Dartmouth College Scholarly Innovation Grant

Title: Stress-induced impairments in fear learning are causally related to increased kynurenic acid formation in the prefrontal cortex

Authors: *A. D. KLAUSING[1], D. J. BUCCI[2], R. SCHWARCZ[1];
[1]Dept. of Psychiatry, MPRC, Univ. of Maryland Sch. of Med., Baltimore, MD; [2]Dept. of Psychological and Brain Sci., Dartmouth Col., Hanover, NH

Abstract: Severe and/or prolonged stress has many detrimental effects and often causes cognitive impairments. Experimental manipulation of kynurenic acid (KYNA) affects learning and memory in animals. However, the link between a stress-induced change in KYNA and a change in cognitive function has yet to be explored. Here we examined whether acute stress increases KYNA levels in the brain and, specifically, if a stress-induced increase in KYNA is causally related to impairments in fear learning. Adult male Sprague-Dawley rats (250-300 g) were tested using three different acute stress models (restraint, exposure to fox urine, or inescapable shocks). Extracellular KYNA levels were determined in the prefrontal cortex by *in vivo* microdialysis (n = 6/group). In rats that received inescapable shocks, extracellular KYNA levels were increased by ~85%. The other two stressors were much less effective (<25% change in KYNA levels compared to baseline). Another cohort of rats (n = 8/group) underwent a fear discrimination procedure immediately after the termination of stress. During training, rats were exposed to two different auditory tones - one paired with a foot shock (CS+) and the other unpaired (CS-). One week later, rats were tested for freezing behavior during re-exposure to both auditory stimuli in a novel context without any shocks delivered. Only rats receiving inescapable

shocks were unable to discriminate between CS+ and CS-. All other groups exhibited greater freezing to CS+ than to CS-. To further examine the impact of KYNA manipulation on behavior, a separate group of animals received a s.c. injection of the irreversible KYNA synthesis (kynurenine aminotransferase II) inhibitor PF-04859989 1 h before initiation of the stress challenge. Application of the KYNA synthesis inhibitor blocked the stress-induced KYNA increase (n = 6-7/group) and normalized the impairment in fear discrimination (n = 12-17/group) in rats that received inescapable shocks. Taken together, these findings indicate a causal relationship between a stress-induced KYNA increase and fear learning impairments. Pharmacological inhibition of KYNA synthesis may therefore be a therapeutic option for treating cognitive dysfunctions in stress-related disorders. (see also Cochran et al., this meeting)

Disclosures: A.D. Klausing: None. **D.J. Bucci:** None. **R. Schwarcz:** None.

Poster

772. Fear and Aversive Learning and Memory: Modulatory Factors

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 772.15/U2

Topic: G.01. Appetitive and Aversive Learning

Support: NIH Grant MH112337

Title: Elevation of kynurenic acid levels impairs the renewal of conditioned fear

Authors: K. B. COCHRAN, M. C. EDDY, M. P. SATURNO, *D. J. BUCCI;
Psychological and Brain Sci., Dartmouth Col., Hanover, NH

Abstract: Kynurenic Acid (KYNA), a product of tryptophan degradation by astroglia, is an antagonist of both NMDA glutamate and alpha-7 nicotinic acetylcholine receptors, both of which are critically involved in fear learning and memory. Recently, we have shown that stress can increase the concentration of KYNA in the prefrontal cortex of rats, causing the generalization of fear to otherwise innocuous stimuli (see Klausing et al, this meeting). The present study extends this work by testing the effects of increased KYNA concentration on the extinction and renewal of conditioned fear. Twenty-four rats received a single session of fear conditioning during which a tone was paired with foot shock in a standard conditioning chamber (Context A). Rats were then divided into three groups (8/group) matched for the levels of freezing behavior observed during the conditioning session. During the next four daily sessions, fear to the tone was extinguished by presenting the tone without foot shock in a different chamber (Context B). Two hours before each of the extinction sessions, the Control and L-KYN REN groups were injected with a vehicle solution and the third group, L-KYN EXT/REN, received an injection of 100mg/kg L-KYN, the precursor of KYNA, to elevate KYNA concentration. Finally, fear to the tone was tested by re-exposing rats to the tone in Contexts A and B. The Control group again

received vehicle treatment before the test sessions, and groups L-KYN REN and L-KYN EXT/REN received L-KYN two hours before the test sessions. As is typically observed, rats in the control group exhibited significantly less fear to the tone in Context B compared to Context A, reflecting the canonical 'renewal' of fear when the extinguished cue is encountered in a context other than the extinction context. Rats in the L-KYN EXT/REN and L-KYN REN groups exhibited a diminished renewal effect. In a prior study, we found that injections of L-KYN during extinction alone also decreased renewal. A subsequent context fear reacquisition session showed that this was not simply due to a KYNA-induced inability to distinguish between the two contexts. Together with the present findings, these data suggest that elevated KYNA levels impair the ability to use contextual information to guide appropriate behavior to fear-conditioned cues. This may have implications for understanding altered fear renewal that is observed in persons with anxiety-related disorders such as PTSD.

Disclosures: K.B. Cochran: None. **M.C. Eddy:** None. **M.P. Saturno:** None. **D.J. Bucci:** None.

Poster

772. Fear and Aversive Learning and Memory: Modulatory Factors

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 772.16/U3

Topic: G.01. Appetitive and Aversive Learning

Title: Parametric modulators of active conditioned fear responding

Authors: S. S. WASIELEWSKI, M. FANIKOS, E. GOLDEN, *R. M. S. SHANSKY; Northeastern Univ., Boston, MA

Abstract: Post-traumatic stress disorder is twice as likely to develop in women than in men. However, the neurobiological mechanisms underlying this difference are mostly unknown, as conditioned fear responses have traditionally been studied in only male subjects. We have previously shown that darting behavior, an active conditioned fear response, is preferentially utilized by female subjects, but we do not know how the experimental parameters of a fear conditioning protocol influence the prevalence of darting. One possible explanation for this sex difference is that the larger size of males prevents them from engaging active responding in standard testing chambers, so in the first experiment, we examined darting as a factor of space by performing a conditioned fear memory retrieval test in an open field arena. Female and male Sprague Dawley rats underwent a 2-day auditory fear conditioning paradigm. Day 1 presented 5 habituation CS and 7 CS-US pairs inside a typical fear conditioning chamber. On day 2, the subjects were placed in either a large open field arena or a smaller open field insert that was the size of the day 1 fear conditioning chamber. The subjects were then presented with 7 CSs. Darting, freezing, rearing, and grooming were quantified using a combination of automated and

experimenter-observed scoring. We then performed immunohistochemistry for c-fos expression in the prefrontal cortex, periaqueductal gray, basolateral amygdala, and ventral hippocampus. Animals in the open field exhibited more darting than in the smaller space, but females exhibited darting at a 3-fold rate compared to males, suggesting that even with ample room in which to engage escape behavior, darting is still a predominantly female response. In experiment 2, we examined darting as a factor of shock intensity. Male and female rats underwent auditory fear conditioning using either 0.3 or 0.5 mA shock USs. Regardless of shock intensity, darting was observed in approximately 3-4 times as many females as males. In addition, we observed an escalation in response to the shock itself in females but not males, suggesting that shock perception may underlie sex differences in associated fear processing.

Disclosures: R.M.S. Shansky: None. **S.S. Wasielewski:** None. **E. Golden:** None. **M. Fanikos:** None.

Poster

772. Fear and Aversive Learning and Memory: Modulatory Factors

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 772.17/U4

Topic: G.01. Appetitive and Aversive Learning

Support: NIMH R56 MH11493

Title: Sex specific reversal of context generalization in cued fear conditioning by TRPV1 antagonist

Authors: *M. MEJDELL[1], A. WINTER[1], J. COLOM-LAPETINA[3], M. MORENA[4], A. S. NASTASE[4], M. N. HILL[5], R. SHANSKY[2];
[2]Behavioral Neurosci., [1]Northeastern Univ., Boston, MA; [3]Brown Univ., Providence, RI; [5]Hotchkiss Brain Inst., [4]Univ. of Calgary, Calgary, AB, Canada

Abstract: Experiencing a traumatic event is twice as likely to cause post-traumatic stress disorder in women as it is in men. Despite this imbalance, the majority of the literature on neural mechanisms that underlie PTSD comes from research in male model animals. The endocannabinoid (eCB) system, which is involved in modulating the stress response, is just beginning to be understood as potentially sexually dimorphic system. A better understanding of sex differences in these processes is critical to progress in developing more personalized therapies for PTSD patients of both sexes. To explore the influence of eCB interactions on fear learning and memory processes, male and female rats were tested in a standard cued fear conditioning and extinction paradigm, after systemic administration of either CB1 receptor antagonist AM251, coupled AM251 with a TRPV1 antagonist Capsazepine, or vehicle. We measured baseline and cue-elicited freezing in all animals, finding that AM251 during fear

conditioning elicited enhanced context generalization the following day and impaired extinction in females only. Capsazepine caused a reversal of this generalization effect and improved extinction in females with no effect in males. Using mass spectrometry, we evaluated anandamide levels immediately post-fear conditioning in the hippocampus, prefrontal cortex, and amygdala in a separate cohort of male and female rats, and found a female-specific increase in hippocampal anandamide. These results demonstrate sex differences in the neural mechanisms related to memory processes and associative learning, and point to a specific role for the endocannabinoid system in modulating context processing in the female brain.

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Poster

772. Fear and Aversive Learning and Memory: Modulatory Factors

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 772.18/U5

Topic: G.01. Appetitive and Aversive Learning

Support: NIMH Grant R01 MH062122
Staglin Center for Brain and Behavioral Health

Title: Sex differences in contextual fear learning and generalization

Authors: *J. M. TROTT, R. ADISON, M. S. FANSELOW;
Psychology, UCLA, Los Angeles, CA

Abstract: Contextual fear learning can be used to study the acquisition and generalization of a fear memory. Therefore, it is a useful model to study learning processes relevant to healthy functioning and mental illness, particularly those related to anxiety disorders. Contextual fear generalization is especially relevant to anxiety disorders, which are often defined by expressing fear and/or anxiety in safe contexts. Anxiety disorders are sexually dimorphic with regard to occurrence and severity of episodes such that females tend to experience more frequent and more severe episodes. Presented here are a series of experiments examining contextual fear learning in male and female rats, with a focus on generalization. With some variation, these experiments use a 3-day procedure in which Day 1 consists of pre-exposure to the to-be-shocked context, Day 2 consists of a single context-shock pairing, and Day 3 consists of testing in either the same or a novel environment. Increasing the amount of pre-exposure on Day 1 or time before shock (placement-to-shock-interval; PSI) on Day 2 both lead to enhanced conditioning. It is unknown if these periods use the same process such that they are simply additive or if there are different processes underlying the learning during each period. Historically, male rats tend to show greater contextual fear than females at low PSI's, and this effect can be abolished by a sufficiently long

pre-exposure session. Thus, for these experiments, relatively short pre-exposure and PSI's are used to determine any sex differences in fear learning. With longer pre-exposure periods, female rats show greater contextual fear and more evidence of discrimination. With shorter pre-exposure periods, male rats show more contextual fear and evidence of discrimination, consistent with previous literature. Pre-exposure to a non-shocked safe context prior to conditioning abolished these effects, but did result in increased variability, consistent with the BACON model. The BACON model is a conceptual and computational model of hippocampal contextual learning. One of the major suggestions of the model is that the hippocampus can have two functional modes, one for building a contextual representation (which would mostly happen during pre-exposure) and one for retrieving that representation, prior to shock for example (which would happen during Day 2's PSI). It was found that pre-exposure timing and PSI timing were not equivalent to each other. Animals with 120s of pre-exposure and a 30s PSI show a differential level and time-course of fear expression than animals who received 30s of pre-exposure and a 120s PSI, and this further depended on sex and strain of the rat.

Disclosures: J.M. Trott: None. **R. Adison:** None. **M.S. Fanselow:** Other; founding board member and Director of Research for Neurovation Labs, Inc., which is developing diagnostic and treatment tools for Post-Traumatic Stress Disorder.

Poster

772. Fear and Aversive Learning and Memory: Modulatory Factors

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 772.19/U6

Topic: G.01. Appetitive and Aversive Learning

Support: NIH-NIAAA Grant R01AA026530
NSF DGE-1650604
Staglin Center for Brain and Behavioral Health

Title: Influences of stress severity and sex on changes in fear learning, anxiety and alcohol consumption following stress exposure

Authors: *S. T. GONZALEZ[1], V. MARTY[2], S. LELE[2], R. VO[2], I. YENOKIAN[2], C. Q. YANG[1], K. AHMED[1], I. SPIGELMAN[2], M. S. FANSELOW[1];
[1]Psychology, [2]Div. of Oral Biology, Sch. of Dent., Univ. of California Los Angeles, Los Angeles, CA

Abstract: Post-traumatic stress disorder (PTSD) develops after exposure to traumatic events and can involve an exaggerated fear response to stimuli that are reminiscent of the original stressor. In addition, PTSD is frequently co-morbid with other disorders including substance abuse. However, not all individuals who experience trauma develop PTSD and the factors that promote

susceptibility versus resilience to the effects of stress are poorly understood, although the disorder occurs more commonly in women than in men. To understand these aspects of the disorder our laboratory has developed a model of stress exposure termed stress-enhanced fear learning (SEFL) that captures many of these features. In this model, exposure to a traumatic stressor (either 4 or 15 unsignalled footshocks) in one context sensitizes fear learning to a mild stressor (1 unsignalled footshock) in a second context. In this study we investigated the extent to which the SEFL model captures the heterogeneity of PTSD and identified potential predictors of susceptibility versus resilience to the effects of stress. In this study both male and female rats received assessments of anxiety and alcohol consumption prior to traumatic stress exposure, and a battery of fear learning, anxiety and alcohol consumption tests following stress exposure. We found that while males and females did not differ on most measures of fear learning following stress, males showed elevated anxiety relative to females. In addition, we found evidence of distinct "susceptible" and "resilient" populations that showed a constellation of behavioral changes relating to fear learning, anxiety and fear extinction. Lastly, we found that baseline levels of anxiety were uniquely predictive of susceptibility to the effects of stress in females, but not in males. These results indicate that the SEFL model is a powerful tool for probing the behavioral and biological factors that promote susceptibility versus resilience to the effects of stress.

Disclosures: S.T. Gonzalez: None. **V. Marty:** None. **S. Lele:** None. **R. Vo:** None. **I. Yenokian:** None. **C.Q. Yang:** None. **K. Ahmed:** None. **I. Spigelman:** None. **M.S. Fanselow:** Other; Director of research at Neurovation labs.

Poster

772. Fear and Aversive Learning and Memory: Modulatory Factors

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 772.20/U7

Topic: G.01. Appetitive and Aversive Learning

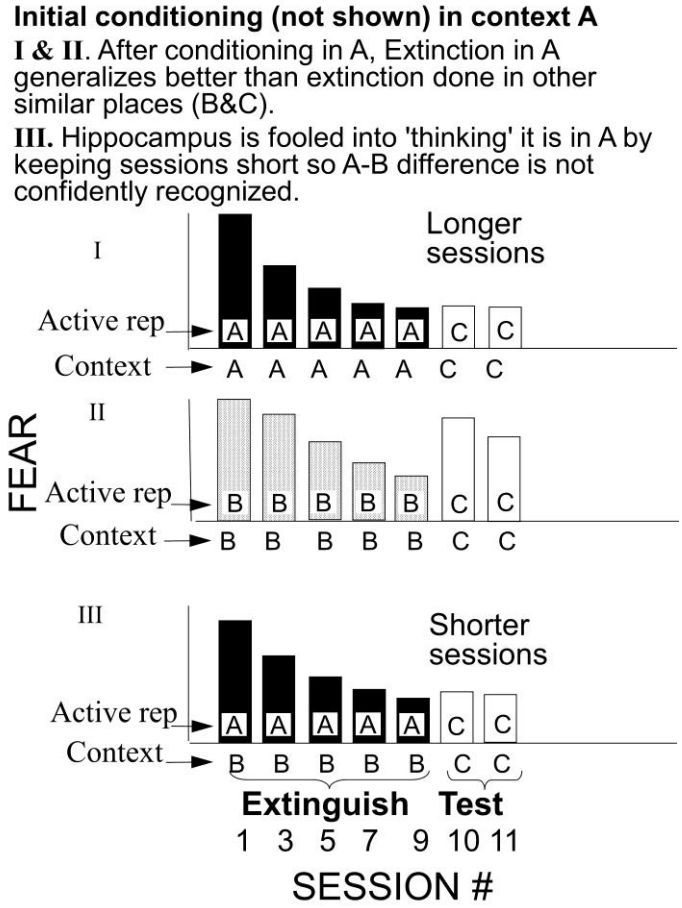
Support: NIH Grant RO1 MH062122

Title: Extinction in a Bayesian model of context fear conditioning, with possible implications for exposure therapy

Authors: *F. B. KRASNE, M. S. FANSELOW;
Dept Psychol, UCLA, Los Angeles, CA

Abstract: BACON (Krasne et al, 2015), is a neuro-computational model of context fear conditioning in which contextual representations are formed in the hippocampus and association of fear to them occurs in the amygdala. Representation creation and updating (association of additional contextual attributes on future occasions), as well as fear conditionability and

expression in amygdala, are controlled by degree of confidence that a currently active representation really is that of the current context. Confidence is assessed by the Bayesian Weight of Evidence of representation validity (Brep), computed by comparing currently observed with recalled attributes. The model provides plausible explanations for aspects of context fear conditioning such as the immediate shock deficit, slow onset of conditioned fear, and false conditioning, and also rationalizes seemingly discrepant findings on the role of dentate in recall (Bernier et al, 2017). Here we add extinction to the model (BaconX) by assuming that non-reinforced fear causes inhibition to be conditioned to the same representations that evoke fear. Extinction consolidates only if BaconX is confident that a non-reinforced place is actually where conditioning occurred. These assumptions lead to several interesting design features and predictions; among them: (1) Extinction-causing inhibition must be applied downstream of the conditioning locus (cf. Herry et al 2008, Extinction neurons). (2) Extinction carried out in the conditioning context generalizes better than extinction in a different ("surrogate") context (as done in exposure therapy) (see Fig, I & II). (3) In a novel surrogate context (eg. a virtual reality simulator), the representation of the conditioning context itself will always be activated if sessions are kept too short for a representation of the surrogate context to be created. Therefore extinction will generalize much better than if established in long exposure therapy sessions where a representation of the therapy context would get created.



Disclosures: **F.B. Krasne:** None. **M.S. Fanselow:** None.

Poster

772. Fear and Aversive Learning and Memory: Modulatory Factors

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

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Topic: G.01. Appetitive and Aversive Learning

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ANR-10-LABX-54 MEMO LIFE
ANR-11- IDEX-0001-02 PSL* Research University

Title: Dissociation of fear initiation and maintenance by breathing-driven prefrontal oscillations

Authors: *S. BAGUR[1], J. M. LEFORT[1], M. M. LACROIX[1], G. DE LAVILLÉON[1], C. HERRY[2], M. CHOUVAEFF[1], C. BILLAND[1], H. GEOFFROY[1], K. BENCHENANE[1]; [1]MOBs Team, Lab. Plasticité du Cerveau, ESPCI, PSL Univ., Paris, France; [2]Neurocentre Magendie, Circuits Neuronaux des Apprentissages Associatifs, Bordeaux, France

Abstract: During emotional states, the body undergoes multiple changes which have been suggested to feedback to the brain to influence neural processing. Herewe report that in mice very regular 4Hz breathing mediates such a bodily feedback during fear-related freezing behavior. Both surgical ablation and optogenetic perturbation of the olfactory bulb, the key relay structure for the respiratory related 4Hz oscillation, decrease time spent freezing. More importantly, using probabilistic modelling of behaviour, we show that the two manipulations specifically reduce freezing maintenance without impacting its initiation, dissociating these two phenomena. Finally we show that this oscillation is transmitted to the prefrontal cortex where it organizes neural firing and optogenetic probing of the circuit demonstrates frequency-specific tuning that maximizes prefrontal cortex responsivity at 4Hz, the breathing frequency during freezing. These results point to a brain-body-brain loop in which the initiation of emotional behavior engenders somatic changes which then feedback to the cortex to directly participate in sustaining emotional states.

Disclosures: S. Bagur: None. **J.M. Lefort:** None. **M.M. Lacroix:** None. **G. de Lavilléon:** None. **C. Herry:** None. **M. Chouvaeff:** None. **C. Billand:** None. **H. Geoffroy:** None. **K. Benchenane:** None.

Poster

773. Dopamine, Reward, and Reinforcement

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 773.01/U9

Topic: G.02. Motivation

Support: NIH Grant NS100050
NIH Grant DA042739
NIH Grant DA005010
NSF NeuroNex Award 1707408

Title: Temporally specific dopaminergic control of reward-conditioned movements

Authors: *K. LEE[1], L. D. CLAAR[2], K. I. BAKHURIN[3], A. HACHISUKA[1], S. C. MASMANIDIS[1];
[1]Neurobio., UCLA, Los Angeles, CA; [2]Allen Inst. for Brain Sci., Seattle, WA; [3]Duke Univ., Durham, NC

Abstract: Midbrain dopamine (DA) neurons encode both reward and movement-related events, and are implicated in disorders of reward processing as well as movement. However, disentangling the contribution of DA neurons in reinforcing versus generating movements is challenging and has led to lasting controversy. We dissociated these functions in mice trained on a Pavlovian trace conditioning task, in which presentation of an olfactory cue frequently elicited a conditioned response in the form of anticipatory licking that began prior to reward delivery. In this task, movement generation and reinforcement signals occur at distinct time periods (pre- and post-reward, respectively), and can thus be disentangled with temporally precise optogenetic manipulations. To test the contribution of DA neurons to these processes we virally expressed eNpHR3.0 in lateral ventral tegmental area (VTA) DA neurons (n = 14 eNpHR3.0 and 14 YFP DAT-Cre mice, including medial regions of substantia nigra pars compacta, SNc). We examined behavioral performance across multiple test sessions representing different time periods of optogenetic stimulation. Each session was comprised of three blocks of 40 trials, with the laser activated in the second block. Continuously inhibiting DA neurons for 2 s immediately after reward delivery significantly reduced the probability of anticipatory licking, and this deficit was reversed when the optical stimulation was removed. However, inhibiting neurons for 4 s prior to reward (i.e., in the time period coinciding with cue presentation and the onset of anticipatory licking) had a comparatively smaller effect on licking. A similar bias toward the post-reward period was found for DA neurons in the lateral SNc (n = 9 eNpHR3.0 DAT-Cre mice). In contrast, inhibiting the secondary motor cortex (n = 9 eNpHR3.0 mice) produced a significantly greater effect on behavior in the pre-reward as opposed to the post-reward period. To further deconstruct the behavioral role of post-reward DA signals, we parametrically delayed the timing

(0, 0.25, 0.5, 1 s) of inhibitory optical stimuli relative to the reward (n = 10 eNpHR3.0 and 11 YFP mice). Additionally we performed optogenetic activation of DA neurons during an extinction test (n = 10 Chrimson and 8 YFP DAT-Cre mice). We found that DA activity within about one second of the expected reward time is both necessary and sufficient to sustain conditioned responses on future trials. Together, the results indicate a temporally restricted role of DA neurons primarily related to reinforcing stimulus-reward associations, and suggest that directly generating movements is a comparatively less important function.

Disclosures: K. Lee: None. **L.D. Claar:** None. **K.I. Bakhurin:** None. **A. Hachisuka:** None. **S.C. Masmanidis:** None.

Poster

773. Dopamine, Reward, and Reinforcement

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 773.02/U10

Topic: G.02. Motivation

Support: KAKEN 18K07401
KAKEN 16K16648
KAKEN 16H05135
KAKEN 15K01837
KAKEN 26460328

Title: Does baldness of attractive male decrease his external and internal power to fascinate female in mice?

Authors: *Y. N. OHNISHI, Y. KAWAHARA, Y. H. OHNISHI, A. NISHI;
Dept. of Pharmacol., Kurume Univ. Sch. of Med., Kurume, Japan

Abstract: Baldness is one of fearful aging phenomenon for men. Complete baldness sometimes enhances masculinity, but partial baldness is believed to decrease sexual attractiveness in most cases. We have previously presented that attractiveness of male mice to female mice is dependent on their appearance and self-confidence, not smell nor voice (SfN 2017, SfN 2018). In those experiments, we used behavior-based measurement with video camera tracking system for female movement in big white box, in which four littermate male mice were placed in four jail transparent boxes set on the corner one by one. The female mouse was allowed to move freely in the big box for 20 minutes. We summed up the total time around each male box for the last ten minutes as preference behavior. Surprisingly, attractive and/or un-attractive male mice were existed despite the same genetic background, suggesting that female mice have a common preference for male attractiveness. This trend of preference disappeared by hiding male mice with four-layered air-permeable filter. Furthermore, genetically blind female mice showed

completely different trend of preference against the same male mice set, indicating that appearance may be one of major factors of male attractiveness. In this report, we focus on the importance of hair appearance. We examined whether hair-cut and whisker trimming of attractive male mouse can affect his attractiveness to female mice. Additionally, we will perform in vivo microdialysis analyses under the experimental conditions, because dopamine levels in the nucleus accumbens of female mice responded to attractive male mice, but not to un-attractive male mice. As internal factor, self-confidence for male attractiveness also seemed to be important as well as external factor like appearance. Because we detected that harem situation of un-attractive male mouse didn't enhance his attractiveness, but isolated situation of attractive male mouse with watching the harem condition of un-attractive male mouse overnight decreased his attractiveness, we will try to examine the effect of the combination of above isolated situation and hair-cut with whisker trimming on his attractiveness. These experiments will reveal preference nature and mesolimbic dopamine reaction of female mice against male attractiveness, and the importance of self-confidence of male mice for male attractiveness.

Disclosures: **Y.N. Ohnishi:** None. **Y. Kawahara:** None. **Y.H. Ohnishi:** None. **A. Nishi:** None.

Poster

773. Dopamine, Reward, and Reinforcement

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 773.03/U11

Topic: G.02. Motivation

Support: NIH-RO1MH091119.

Title: Stress transforms lateral habenula reward responses into punishment signals

Authors: *S. SHABEL[1], C. WANG[2], B. MONK[3], S. ARONSON[3], R. MALINOW[4];
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Abstract: Neuronal activity in the lateral habenula (LHb), a brain region implicated in depression [Proulx CD, Hikosaka O, & Malinow R (2014) Nat Neurosci 17(9):1146-1152], decreases during reward and increases during punishment or reward omission [Matsumoto M & Hikosaka O (2007) Nature 447(7148):1111-1115]. While stress is a major risk factor for depression and strongly impacts the LHb, its effect on LHb reward signals is unknown. Here we image LHb neuronal activity in behaving mice and find that acute stress transforms LHb reward responses into punishment-like neural signals; punishment-like responses to reward omission also increase. These neural changes matched the onset of anhedonic behavior and were specific to LHb neurons that distinguished reward and its omission. Thus, stress distorts LHb responsivity to positive and negative feedback, which could bias individuals towards negative

expectations, a key aspect of the proposed pathogenesis of depression [Beck AT (1967) Depression: clinical, experimental, and theoretical aspects. (Harper & Row, New York) 6th Ed].

Disclosures: S. Shabel: None. **C. Wang:** None. **B. Monk:** None. **S. Aronson:** None. **R. Malinow:** None.

Poster

773. Dopamine, Reward, and Reinforcement

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 773.04/U12

Topic: G.02. Motivation

Support: NIH grant DA025634

Title: Central exendin-4 selectively suppresses cue-evoked phasic dopamine spikes and resultant behavior

Authors: *V. R. KONANUR, T. M. HSU, M. F. ROITMAN;
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Abstract: Cues predictive of food reward evoke both phasic increases in mesolimbic dopamine activity and appetitive and consummatory behaviors. We showed previously that the magnitude of cue-evoked dopamine activity scales with hunger or central activation of its hormone mimetics (e.g. ghrelin). Activation of central receptors for glucagon-like peptide 1 (GLP-1) via long-acting analogues (e.g. exendin-4) suppresses food intake but its effects on cue-evoked phasic mesolimbic signaling, a signal critical for reinforcement and goal-directed action, remain unknown. Here, a 1s tone preceded the availability (20s) of a sipper that delivered 0.3M sucrose followed by a randomly selected inter-trial interval (30-60s) for 30 trials. On each trial, the latency to begin licking and the number of licks were measured in food restricted rats that expressed cre-recombinase under the control of the tyrosine hydroxylase promotor (n=5 male and 5 female TH-cre+). After 10 days of training, rats received a virally-mediated vector to express a genetically encoded calcium indicator (GCaMP6f; proxy for neural activity) and a fiber optic implant targeting dopamine neurons of the ventral tegmental area (VTA). Upon recovery, fluorescent calcium transients were measured in dopamine neurons during cue -> sipper sessions. 45 minutes prior to the session, rats received a central infusion of the GLP-1 receptor agonist exendin-4 (0, 0.05 or 0.1μg). Consistent with previous work, exendin-4 suppressed measures of appetitive and consummatory behavior – with stronger suppression observed in females. Exendin-4 had no effect on spontaneous phasic dopamine signaling throughout the session. However, it did selectively and dose-dependently suppress the magnitude of cue-evoked dopamine responses, independent of sex (0.39±0.06, 0.27±0.06, 0.04±0.05 ΔF/F for 0, 0.05 and 0.1μg, respectively; $p<0.05$). We performed linear regression and found, when controlling for

sex and drug dose, an indirect relationship between cue-evoked dopamine activity and latency to begin licking and a direct relationship with number of licks/trial. As cue-evoked dopamine promotes approach behavior, exendin-4 may be of therapeutic value for its ability to suppress neural substrates involved in cognitive and reinforcement related overeating.

Disclosures: V.R. Konanur: None. **T.M. Hsu:** None. **M.F. Roitman:** None.

Poster

773. Dopamine, Reward, and Reinforcement

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 773.05/U13

Topic: G.02. Motivation

Support: NIH Grant DA025634

Title: The subfornical organ recruits phasic dopamine signaling to water availability via multi-order pathways

Authors: *T. M. HSU, V. R. KONANUR, P. BAZZINO, M. F. ROITMAN;
Psychology, Univ. of Illinois at Chicago, Chicago, IL

Abstract: Changes in physiological state, including hunger, satiety, and body fluid homeostasis, can strongly modulate phasic dopamine signalling and goal-directed behaviors. Here we examine the novel hypothesis that the subfornical organ (SFO), a key central thirst detector, relays need state information to mesolimbic dopamine pathways to regulate thirst-motivated behaviors. To capture phasic dopamine dynamics, we utilized in vivo fiber photometry in rats that express protein-based fluorescent sensors to measure ventral tegmental area (VTA) dopamine neuron activity (Cre-dependent gCaMP6f in TH-Cre+ rats) or dopamine release (dLight1.2) in the nucleus accumbens shell (NAc shell). In water-restricted rats allowed intermittent, cued sipper access, we first demonstrated that VTA dopamine neuron activity and NAc shell dopamine release develop to cues associated with water. After training under water-restriction, we find a lack of cue-evoked VTA and NAc phasic dopamine activity when rats are water-sated. SFO glutamatergic neurons (SFO^{glu}) are engaged during thirsty states and selective activation of SFO^{glu} neurons engages robust water intake in water-sated animals. We found that DREADDs mediated activation of SFO^{glu} neurons mimics thirst in recruiting phasic dopamine activity, as SFO^{glu} activation increases water-cue evoked VTA dopamine responses. To identify potential relay nodes, we find that activation of SFO^{glu} increases c-fos expression not only in the VTA and NAc, but also the lateral hypothalamus (LH). Given previous work demonstrating that activation of a subset of LH neurons that produce neurotensin stimulates thirst, we found that intra-VTA administration of neurotensin dose-dependently increases cue-evoked VTA phasic dopamine activity in water-sated animals - data that suggests LH neurotensin to VTA dopamine neuron

communication mediates thirst-motivated behaviors. Overall, our findings reveal that thirst powerfully influences phasic dopamine signalling and that this occurs via multi-order SFO to VTA pathways.

Disclosures: T.M. Hsu: None. **V.R. Konanur:** None. **P. Bazzino:** None. **M.F. Roitman:** None.

Poster

773. Dopamine, Reward, and Reinforcement

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 773.06/U14

Topic: G.02. Motivation

Title: Distinct subregions of nucleus accumbens shell D2 neurons projections to ventral pallidum drive different movement,valence and reward motivation

Authors: *Y. YAO;
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Abstract: Nucleus accumbens(NAc) plays an important role in emotion and motivation. Most of the NAc neurons are medium spiny neurons (MSNs), divided into dopamine-expressing receptor 1(D1) neurons and dopamine-expressing receptor 2(D2) neurons. D1 neurons are widely accepted to be associated with positive reinforcement and reward, while the role of D2 neurons are more evasive. D2 neurons transmit messages indirectly via VP and are traditionally associated with negative reinforcement and aversion. However, some reports have attributed movement inhibition or even positive motivational roles to them. Here, we combine optogenetics, Fluorescence in situ hybridization(FISH) and whole-brain mapping of inputs and outputs to demonstrate the anatomical and functional heterogeneity of the NAc shell D2 neurons. D2 neurons in ventral medial nucleus accumbens shell increase movement speed and those in the lateral nucleus accumbens shell decrease movement speeds, while the dorsal medial nucleus accumbens shell has no effect on movement speed. Furthermore, D2 neurons in the dorsomedial zone drive positive preference and increase reward motivation while D2 neurons in the ventromedial and ventrolateral zones are aversive and decrease reward motivation. D2 neurons in different subregions of nucleus accumbens project to overlapping zones in VP but downstream cell targets are of different cell types. Therefore, the finding the heterogeneity in function by anatomical location clears up much of the controversy in the literature surrounding the function of nucleus accumbens D2 neurons.

Disclosures: Y. Yao: None.

Poster

773. Dopamine, Reward, and Reinforcement

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 773.07/U15

Topic: G.02. Motivation

Title: Effect of sexual behavior on seizures and dopamine levels in male rats

Authors: *M. L. RAMÍREZ-RENTERÍA[1], E. HERNANDEZ-ARTEAGA[2], M. HERNANDEZ[3], M. OLVERA-CORTES[5], M. A. GUEVARA[4], A. AGMO[6];
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Abstract: Sexual interaction is a motivated behavior that has been associated with increases in serum testosterone and dopamine levels in the brain of male rats. Various environmental and pathological conditions produce alterations in hormonal and dopaminergic secretions, with seizures being one of the most common neurological disorders, often triggered by neural hyperexcitability. Studies in both humans and animals have reported that the presence of seizures occur in association with alterations in cerebral dopamine levels. Considering that sexual behavior is associated with increases in cerebral dopamine levels (DA) and that this neurotransmitter is involved in inducing seizures, the aim of this study was to determine the effect of sexual behavior on the induction of seizures and the dopamine levels in the prefrontal cortex and amygdala of male rats. For purposes of this study, 46 Wistar rats were classified into four groups: 1) the 3-MPA group (with one i.p. injection of 40mg/kg of 3-mercaptopropionic acid, 3-MPA); 2) the SEX3-MPA group (subjects that had sexual interaction prior to administration of 3-MPA); 3) the SAL group (which received one i.p. injection of saline solution); and 4) the SEXSAL group (subjects that had sexual interaction prior to administering the saline solution). Behavioral recording of seizures was done for 20 minutes post-injection. Dopamine concentrations were determined using the HPLC technique. Results showed that prior performance of sexual behavior decreased the number of subjects that presented seizures (only 39.5%). Also, in the case of the rats that did have seizures, both frequency and duration were lower, accompanied by longer latency and less severity, compared to the 3-MPA group. Regarding DA quantification, the subjects that had seizures showed higher concentrations in both the PFC and the amygdala than the SAL group and the animals that did not present seizures. While the effect of sexual behavior on seizures is not yet fully understood, there is evidence that this type of conduct increases dopaminergic levels in certain brain structures. Moreover, several studies have shown that both increases in DA levels and the administration of DA are associated with lower incidence and severity of seizures. Therefore, these results suggest a possible

neuroprotective effect of sexual behavior on pharmacologically-induced seizures in male rats, likely mediated by increases in dopamine levels.

Disclosures: M.L. Ramírez-Rentería: None. **E. Hernandez-Arteaga:** None. **M. Hernandez:** None. **M. Olvera-Cortes:** None. **M.A. Guevara:** None. **A. Agmo:** None.

Poster

773. Dopamine, Reward, and Reinforcement

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 773.08/U16

Topic: G.02. Motivation

Support: Leibniz Society (LIN Postdoc Network)
Priority Program 1665 of the DFG/OH 69/1-2
CBBS, FKZ ZS/2016/04/78120

Title: Temporal evolution of reward prediction error signals during reward and punishment learning

Authors: *M. BROSCH[1], F. W. OHL[1,2,3], M. T. LIPPERT[1,2];
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Abstract: Mesolimbic dopamine neurons have long been associated with encoding a universal reward prediction error (RPE) signal necessary for reinforcement learning. Several recent studies have, however, called into question the universality of such a signal, for example by demonstrating that it evolves only gradually during learning (Coddington, L.T. & Dudman, J.T. Nat Neurosci. 2018). Typically, these studies have used conditioning paradigms with appetitive reinforcement. This approach leads to a potential confound of movement-related responses and valence-related responses, obscuring the nature of the dopaminergic signal. Here we investigate how neuronal responses in the medial ventral tegmental area (VTA) of mice evolve during classical Pavlovian conditioning using a paradigm containing both, actively consumed reward as well as passively received punishment. Since it is especially unclear to what degree medial VTA neurons encode RPE signals in the initial phase of learning, faithful tracking of identified dopaminergic cells during this phase of the experiment is a necessity. We have therefore developed a novel optrode drive which combines tetrode unit recordings and optogenetic confirmation of dopamine-cell identity. The construction of the drive prevents electrode tip movements and associated loss of units from the plugging forces of electrical and optogenetic plugs, resulting in a higher yield of identified units over multiple sessions. The drive was implanted in the posterior medial portion of the VTA in DAT-Cre mice. Selective expression of ChR2 in dopaminergic cells from a floxed viral vector allowed the optical identification of

individual dopaminergic units during each session. The mice underwent a head-fixed reward and punishment learning paradigm. In this paradigm, an auditory stimulus preceded either rewarding water delivery or punishing air puffs in a trace conditioning manner. Recording unit activity throughout the VTA then allowed us to evaluate the relationship of dopamine cell firing and RPE coding during the early to late stages of conditioning.

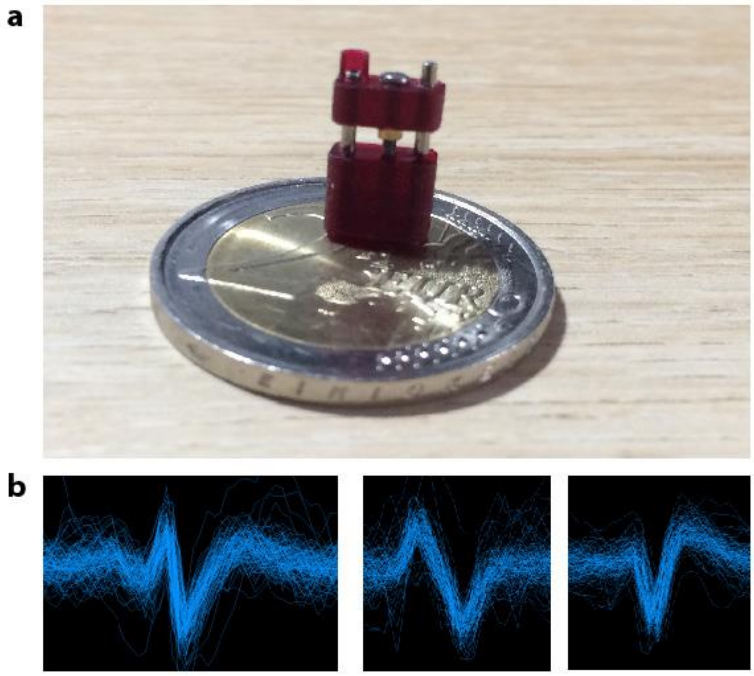

Fig 1 | Newly developed optrode microdrive **(a)** and single trial overlay of different VTA sorted single-units **(b)** exemplary spike traces are overlaid and aligned, recorded in one session of the Pavlovian conditioning paradigm

Disclosures: M. Brosch: None. **F.W. Ohl:** None. **M.T. Lippert:** None.

Poster

773. Dopamine, Reward, and Reinforcement

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 773.09/U17

Topic: G.02. Motivation

Support: NIH Grant AG061691-01

Title: Overexpression of protein kinase inhibitor alpha in nucleus accumbens increases low voluntary running motivation

Authors: *X. MAO;
Dept. of Biomed. Sci., Univ. of Missouri-Columbia, Columbia, MO

Abstract: Objective and rationale: Physical inactivity is associated with the risk of 40 chronic diseases and has been identified as the fourth leading risk factor for global mortality. Therefore, efforts to increase physical activity level would be beneficial to health. In an effort to reverse the physical inactivity to promote the health, Booth's Lab has developed a low voluntary running (LVR) rat line in order to study the genetic factors contributing to the low physical activity. Therefore, current study attempts to examine the regulatory role of PKIa in determining voluntary wheel running behavior along with the motivation for voluntary running behavior in both WT and LVR male rats. We hypothesize that overexpression of PKIa increases male rats voluntary running distance by increasing the motivation for running. **Methods**: 11 weeks old WT and LVR male Wistar rats were injected with either adeno-associated virus (AAV) expressing an empty-vector (EV) or AAV driving the overexpression of PKIa within the NAc. Following 3 weeks running observation, a running wheel based operant runway test (ORT) was deployed to determine the voluntary running motivation. Endogenous genes expression were then assayed via qRT-PCR. **Results**: WT and LVR male rats following AAV-PKIa overexpression showed no running distance difference compared with their AAV-EV control during the course of 3 weeks. Yet, LVR male rats following overexpression of PKIa spent significantly less time to approach the running wheel than AAV-EV control. **Conclusions**: Overexpression of PKIa did not increase nightly running distance in both WT and LVR male rats; however, the low motivation of LVR males were significantly increased in approaching the running wheel induced by the overexpression of PKIa in NAc. It is possible that the larger body weight of male rats prevents them from increasing the actual running distance following the overexpression of PKIa even under the increased voluntary running motivation. Future study should also investigate the both voluntary running distance and motivation in female rats following the overexpression of PKIa.

Disclosures: X. Mao: None.

Poster

773. Dopamine, Reward, and Reinforcement

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 773.10/U18

Topic: G.02. Motivation

Support: IN307417

Title: Apomorphine as a discriminative stimulus

Authors: *B. L. PACHECO GÓMEZ[1], W. A. ZEPEDA-RUIZ[2], D. N. VELÁZQUEZ-MARTÍNEZ[2];
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Abstract: Drug discrimination is a procedure where subjects learn to discriminate between the interoceptive stimulus of a drug and its vehicle. Male Wistar rats were trained to discriminate the dopamine agonist apomorphine (0.1778 mg/kg IP) from saline injection for sucrose reward under a FR10 schedule of reinforcement. When the discrimination was acquired (more than 80% accuracy to both drug or vehicle conditions), generalization gradient to 0.031 mg/kg, 0.056 mg/kg and 0.10 mg/kg doses was obtained. The response rate under apomorphine was depresed in comparison to the response rate of the days when saline was administered. However, lever selection was a dose dependent function: the lowest dose (0.031 mg/kg) showed a similar discrimination index to saline while the dose of 0.10 mg/kg produced a similar discrimination index to the training dose.

Disclosures: B.L. Pacheco Gómez: None. **W.A. Zepeda-Ruiz:** None. **D.N. Velázquez-Martínez:** None.

Poster

773. Dopamine, Reward, and Reinforcement

Location: Hall A

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Topic: G.02. Motivation

Support: Vanderbilt University startup funds
NIH Grant DA042111
Brain and Behavior Research Foundation
Whitehall Foundation
Edward J. Mallinckrodt Jr. Foundation

Title: Sex differences in cholinergic regulation of nucleus accumbens circuit function controlling motivation

Authors: *L. J. BRADY, M. G. KUTLU, J. E. ZACHRY, E. S. CALIPARI;
Pharmacol., Vanderbilt Univ., Nashville, TN

Abstract: In recent years we have made great strides towards our understanding of psychiatric disease states; however, a majority of these studies have focused almost entirely on male subjects. In a large number of psychiatric disorders, such as anxiety, depression, and addiction, sex is a critical biological variable and women represent a particularly vulnerable population. At the core of these disorders is a dysregulation in reward and motivation, yet there is a disparity between the prevalence and prognosis of these disorders in females. The paucity of data describing the unique neural circuitry underlying these sexual dimorphisms highlight the critical need for preclinical investigation of reward learning and motivation in female subjects. There are a variety of factors that could contribute to these sex differences - including estrous cycle

dependent ovarian hormone fluctuations - but the precise neural circuits and neurobiological mechanisms that underlie these differences in reward and motivation are largely unknown. The mesolimbic dopamine pathway, which connects the ventral tegmental area (VTA) to the nucleus accumbens (NAc), is an essential component of the process that controls motivation and reward-seeking behavior. In the NAc specifically, tonic/phasic dopamine release is known to play a critical role in converting information about environmental reward-predictive cues to anticipated positive outcomes, and is heavily modulated by the activity of cholinergic interneurons signaling through nicotinic acetylcholine receptors (nAChRs). Using fast-scan cyclic voltammetry (FSCV) paired with site-specific pharmacology we measured subsecond dopamine kinetics in male and female mice in either diestrus (low circulating hormones) or estrus (high circulating hormones) and defined sex-differences in local circuit regulation of dopamine release in the NAc. We show that the ability of the cholinergic system to regulate tonic/phasic dopamine activity via nAChRs is enhanced in females. Further, the ratio of phasic-to-tonic evoked dopamine release varied between estrus and diestrus females. Finally, cholinergic regulation of dopamine signaling via nAChRs in the NAc was altered in a way that promotes and enhances dopamine release in estrus females. Together this work will expand our understanding of the sex differences in cholinergic regulation of local NAc circuit function underlying reward learning, aiding in the development of better and more effective pharmacotherapies to counter psychiatric disease states in women.

Disclosures: L.J. Brady: None. **M.G. Kutlu:** None. **J.E. Zachry:** None. **E.S. Calipari:** None.

Poster

773. Dopamine, Reward, and Reinforcement

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 773.12/U20

Topic: G.02. Motivation

Support: Deutsche Forschungsgemeinschaft (DFG): postdoctoral fellowship grant to Sarah Starosta (STA 154/1-1)

Title: Dopamine's role in foraging decisions

Authors: *S. STAROSTA[1], S. A. SHUVAEV[1], D. KVITSIANI[2], A. KOULAKOV[1], A. KEPECS[1];
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Abstract: We are continually confronted with decisions about whether to stay engaged in our current behavior or switch to a new course of action. These stay-or-leave decisions have been mostly studied in behavioral ecology as foraging decisions but little is known about their neural basis. Therefore, we set out to study the neural mechanisms underlying stay-or-leave decisions in

a behavioral paradigm inspired by foraging theory from neuroethology.
Optimal choice strategies for foragers facing diminishing returns can be described by the marginal value theorem (MVT), a classic theoretical framework proposed by Charnov (1976). MVT describes how to maximize reward rate on average but it does not address how individual decisions are made. Therefore, we designed a task that allowed us to infer the trial-to-trial choice strategy in a foraging behavior so we could link neural activity with choice behavior.
Mice were allowed to run back and forth between two water ports connected by a variable-height bridge. With each re-entry into the same port the amount of water dispensed decreased according to a preset depletion rate, while switching to the other port reset water to the full amount. Additionally, we manipulated the effort of switching between ports by changing the height of the bridge that had to be crossed between the ports. Using a range of manipulations we show that mouse behavior follows the predictions made by the MVT: both an increase in the average reward rate as well as an increase in harvesting time led animals to leave a depleting port earlier, while increasing the switching effort was associated with staying longer. In addition, the average leaving threshold was similar across ports even when ports were set to deplete at different rates. To describe the observed behavior formally, we constructed a theoretical model that formalizes MVT predictions on a trial-by-trial basis. The model is able to account for the behavioral data described above and suggests that animals use the last ~10 trials to compute the average reward rate proposed by MVT.
Next, we examined the responses of dopaminergic (DA) neurons in the ventral tegmental area (VTA) during foraging because of their key role in reward-guided behavior. We recorded population activity of VTA DA neurons with fiber photometry while mice were foraging for water rewards. We observed that phasic responses in VTA DA neurons reflected the size of reward received and that this reward response was predictive of whether an animal would stay at or leave a port.
We conclude that foraging behavior in mice can be described by an MVT-like decision rule and dopaminergic signaling in the VTA contributes to the decision when to leave a depleting resource.

Disclosures: **S. Starosta:** None. **S.A. Shuvaev:** None. **D. Kvitsiani:** None. **A. Koulakov:** None. **A. Kepecs:** None.

Poster

773. Dopamine, Reward, and Reinforcement

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 773.13/U21

Topic: G.02. Motivation

Support: PROAP/CAPES
UFCSPA

Title: Restriction and hypercaloric diets modulate the expression of genes related to the dopaminergic system in the ventral tegmental area of mice dams

Authors: *V. FEISTAUER, J. FISH, C. K. D. OLIVEIRA, *M. GIOVENARDI, S. DE ALMEIDA;
UFCSPA, Porto Alegre, Brazil

Abstract: Eating is necessary to maintain physiological processes, but it is also pleasurable. Many individuals are unable to control food intake, leading to an excessive adipose tissue accumulation, long associated with increased morbidity and mortality. Contrary, caloric restriction have been associated with increased life expectancy and reduced incidence of chronic diseases. The dopaminergic system is related to addictive-like behaviors and food reward. Therefore, we aim to evaluate the effects of restrictive and hypercaloric diet during pregnancy and lactation on the expression of dopaminergic system genes in the ventral tegmental area (VTA). We also measured the effect of these diets in locomotor activity and innate fear in the open field (OF) test. BALB/c albino female mice were divided into three dietary groups: control (CONT), restriction (RD) and hypercaloric (HD). Isogenic male mice were used for mating. Dams received their specific diets throughout pregnancy and lactation. On the 9th post-partum day, dams were tested in the OF, and after weaning, dam's VTA was collected. Gene expression was analyzed by reverse transcription real-time polymerase chain reaction. RD and HD dams had increased lateral and central locomotion in the OF. HD had reduced innate fear when compared to RD and CONT dams. RD and HD dams had higher levels of *Th, Slc6a3* and *Drd2* mRNA, and HD dams had increased *Drd1* mRNA, but no significant difference in *Drd3, Comt,* and *Maob* genes. Our results show that restriction and hypercaloric diets modulate the expression of dopaminergic system genes and alter locomotor activity of mice dams.

Disclosures: V. Feistauer: None. **J. Fish:** None. **C.K.D. Oliveira:** None. **M. Giovenardi:** None. **S. de Almeida:** None.

Poster

773. Dopamine, Reward, and Reinforcement

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 773.14/U22

Topic: G.02. Motivation

Support: NHMRC Grant 1138062

Title: Roles of midbrain dopamine neurons in relapse

Authors: *Y. LIU, P. JEAN-RICHARD-DIT-BRESSEL, J. YAU, G. D. GIBSON, S. KILLCROSS, G. P. MCNALLY;
Univ. of New South Wales, Sydney, Australia

Abstract: Return to drinking after a period of abstinence remains a key impediment to successful treatment of alcohol use disorders. Dopamine projections from the ventral tegmental area to nucleus accumbens, which comprise the mesolimbic dopamine system, play an important role in motivated behaviors and reinforcement learning, but their role in context-induced reinstatement remain poorly understood. We assessed the roles of ventral tegmental area dopamine neurons (VTA^{Th}) during two different forms of relapse to alcohol-seeking: renewal (context induced reinstatement) and reacquisition in freely moving rats. Using gCaMP fibre photometry, we show that reacquisition, but not renewal, of alcohol-seeking is associated with calcium transients in VTA^{Th} neurons. Then, using dLight fibre photometry, we mapped dopamine transients in nucleus accumbens medial shell, core, and lateral shell during relapse. Calcium transients in VTA^{Th} neurons were temporally specific to behaviors that earned alcohol-associated stimuli and ingestion of alcohol. They were not observed to the same behaviour in the same sessions that did not earn these stimuli or alcohol ingestion. Optogenetic inhibition of VTA^{Th} neurons during the periods in which they showed increased calcium transients reduced reacquisition, but the same silencing at equivalent times had no effect on renewal. Using chemogenetics (KORDs), we confirmed that silencing VTA^{Th} neurons reduced reacquisition but not renewal of alcohol seeking. Taken together, these findings show the role of VTA^{Th} neurons can be dissociated across different forms of relapse in the same animals. Renewal proceeds largely independent of VTA^{Th} neurons whereas the presence of alcohol during reacquisition restores activity (calcium transients) of VTA^{Th} neurons to alcohol-seeking behaviors as well as alcohol-related stimuli and this restoration underpins the rapid return to alcohol-seeking and ingestion.

Disclosures: Y. Liu: None. **P. Jean-Richard-dit-Bressel:** None. **J. Yau:** None. **G.D. Gibson:** None. **S. Killcross:** None. **G.P. McNally:** None.

Poster

773. Dopamine, Reward, and Reinforcement

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Topic: G.02. Motivation

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The Pharmacological Research Foundation
The Uehara Memorial Foundation

Title: Involvement of dopamine D1 and D2 receptor-dependent activation of mitogen-activated protein kinase (MAPK) signaling in the nucleus accumbens in stimulus-reward learning and motivation

Authors: *M. SAIFULLAH[1], T. NAGAI[2], K. YAMADA[2];
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Abstract: Abused drugs, food, and other reward-associated stimuli activate mitogen-activated protein kinase (MAPK) signaling pathway in the mesolimbic dopaminergic system (reward circuit) which projects from the ventral tegmental area to the nucleus accumbens (NAc). NAc is of particular interest because of its role in controlling affective and motivational aspects of behavior. Majority of the neurons in the NAc are GABAergic medium spiny neurons (MSN), which express either dopamine D1- or D2-class receptors. Although mitogen-activated protein kinase (MAPK) signaling plays an important role in several types of learning, the cell type-specific role of MAPK pathway in stimulus-reward learning and motivation remains unclear. In this study, we used adeno-associated virus (AAV)-FLEX mediated conditional transgene expression technology to manipulate MAPK signaling. We expressed wild-type (wt) and constitutively active (ca) MAP2K1 gene exclusively in either D1R- or D2R-MSNs in the NAc and analyzed the effect on methamphetamine-induced conditioned place preference (CPP) as well as on operant behavior for a food reward. The behavioral analyses revealed that D1R-MSN specific expression of caMAP2K1 gene in the NAc potentiated methamphetamine-induced CPP while the D2R-MSN specific expression in the same region did not affect the CPP score. In this test, animals learn to associate the rewarding effect of drug of abuse with the distinct contextual cue. Similar results were observed in Pavlovian conditioning for food reward as well, in which mice learn to associate reward outcome with a predictive cue. Both D1R and D2R mediated caMAP2K1 enhanced motivation to perform an instrumental task. These results suggest that D1R-dependent MAPK signaling pathway in the NAc may play an important role in both natural and drug reward-associated learning and memory, but motivation to perform an instrumental task is modulated by both D1R and D2R mediated MAPK signaling.

Disclosures: **M. Saifullah:** None. **T. Nagai:** None. **K. Yamada:** None.

Poster

773. Dopamine, Reward, and Reinforcement

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 773.16/U24

Topic: G.02. Motivation

Support: Virginia Tobacco Settlement Foundation
Virginia Youth Tobacco Programs

Title: Alternative splicing of D2 dopamine receptor mRNA shows little difference between neuronal cell types, but is modulated by nicotine and the sex of the individual

Authors: A. D. HUDSON[1], R. L. MURPHY[2], M. T. PEGLAR[1], *K. J. FRYXELL[1];
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Abstract: Alternative splicing of D2 dopamine receptor mRNA produces two protein isoforms ($Drd2_L$ and $Drd2_S$). $Drd2_L$ contains a 29 amino acid segment in the third cytosolic loop, encoded by exon 6, that is absent from $Drd2_S$. $Drd2_S$ receptors are primarily presynaptic, while $Drd2_L$ receptors are primarily postsynaptic. It is unclear whether this pattern of localization is due to differences in transport or synthesis, or at the level of mRNA or protein. What is clear is that significant alterations in the ratio of *Drd2S* to *Drd2L* are associated with schizophrenia, depression, and bipolar disorder. Moreover, SNPs that influence this ratio are associated with increased incidence of cocaine abuse and schizophrenia. Here we developed a novel computational method of analyzing RNA sequencing data, to assess the extent to which alternative splicing of D2 mRNAs differs between brain areas and cell types. In male C57BL/6J mice, samples of the ventral tegmental area (VTA) had a *Drd2L/ Drd2S* mRNA ratio = 5.1, which was somewhat lower than the ratio of 8.6 in the cell bodies of striatal D2 medium spiny neurons (MSN). However, in male FBA/NJ mice, a larger data set from D2 MSN yielded a ratio of 4.9. Overall, there was not any consistent evidence of a much lower *Drd2L/ Drd2S* ratio in VTA, as would have been expected if the presynaptic localization of $Drd2_S$ were regulated at the level of mRNA splicing. We extended these results by qRT-PCR analysis in both male and female C57BL/6J mice, 24 hr after a single injection of either 0.5 mg/kg nicotine or saline. In saline controls, qRT-PCR measurements showed a *Drd2L/ Drd2S* mRNA ratio of 0.7 in male ventral tegmentum (1.0 in females), and 0.8 in male ventral striatum (1.6 in females). Although these two methods differed in their detection sensitivity for the *Drd2S* and *Drd2L* isoforms, both sets of results agreed in finding that the differences between brain areas and cell types were too small to support the hypothesis that the pre-synaptic localization of $Drd2_S$ was regulated at the level of mRNA splicing. We conclude that the predominantly pre-synaptic localization of $Drd2_S$ is likely to be determined at the level of molecular transport and/or stability. On the other hand, we also found that a single nicotine injection significantly altered the *Drd2L/Drd2s* mRNA ratio in all brain areas tested. The effect of nicotine differed between brain areas, sexes, and left/right sides of the brain. Overall, males produced more *Drd2S* than females, and males also showed a greater nicotine effect on the *Drd2L/ Drd2S* ratio. These effects of sex, nicotine, and left/right sides of the brain on the *Drd2L/ Drd2S* ratio have important implications for the etiology of addiction and mental health disorders.

Disclosures: A.D. Hudson: None. **R.L. Murphy:** None. **M.T. Peglar:** None. **K.J. Fryxell:** None.

Poster

773. Dopamine, Reward, and Reinforcement

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 773.17/U25

Topic: G.02. Motivation

Support: Intramural Research Grant

Title: Functional and spatial diversity of dopamine neurons in the substantia nigra for different aspects of behavior

Authors: *M. COSTELLO, D. B. T. MCMAHON, O. HIKOSAKA;
Lab. Sensorimotor Res., Natl. Eye Inst., Bethesda, MD

Abstract: Previous work in our laboratory showed that dopamine (DA) cells show a diverse range of functional properties that vary according to anatomical location within the substantia nigra pars compacta (SNc). The rostral ventromedial region (rvmSNc) contains DA neurons that show the classic dopamine features of reward prediction error signaling and suppressed responses to aversive conditioned stimuli ("Value cells"). Conversely, DA neurons in the caudal dorsolateral region (cdlSNc) show little reward prediction error signaling and respond strongly to both appetitive and aversive conditioned stimuli ("Salience cells") (Matsumoto and Hikosaka 2009). The same axis of the SNc segregates DA neurons with connections to the head and tail regions of the caudate nucleus respectively, and likewise shows a gradient of sensitivity to either the short-term current value of objects ("Update cells" in rvmSNc") or the long-term historical value of objects ("Sustain cells" in cdlSNc) (Kim et al. 2015). To further characterize the functional specialization of dopamine cells within the dorsal and ventral SNc we screened individual neurons with a broad spectrum of behavioral tasks including Pavlovian conditioning, passive viewing of previously conditioned stimuli, and reversal learning tasks. We found Value-Update DA neurons in the rvmSNc that show the "classic" profile of dopamine neurons, namely (1) excitation to reward-predicting but not punishment-predicting stimuli, (2) enhanced responses to unpredicted rewards, (3) no clear spatial selectivity, and (4) cessation of responses to previously learned stimuli in contexts where reward is absent. In contrast the Salience-Sustain DA neurons in cdlSNc show markedly different functional properties, namely (1) brisk responses to both reward- and punishment-predicting stimuli, (2) little sensitivity to the predicted or unpredicted status of rewards, but sensitive to unpredicted airpuff, (3) spatial selectivity for stimuli presented in the contralateral visual field, and (4) sustained responses to historically rewarded stimuli even in tasks where no reward was expected or forthcoming. Taken together, this pattern of results points to a division of labor within the midbrain DA system whereby DA neurons in rvmSNc are specialized for responding to the current expectation of reward and provides new information about motivational value. Conversely, DA neurons in cdlSNc are

specialized for maintaining a long-term historical record of past experience and sending a salience signal marking the significance of upcoming events.

Disclosures: M. Costello: None. **D.B.T. McMahon:** None. **O. Hikosaka:** None.

Poster

773. Dopamine, Reward, and Reinforcement

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 773.18/U26

Topic: G.02. Motivation

Title: Simultaneous measurement of ventral tegmental area activity and nucleus accumbens dopamine release reveals patterns of neuron firing associated with dopamine release

Authors: *D. F. HILL[1], Z. OLSON[2], M. J. BARTLETT[5], T. FALK[6], M. L. HEIEN[3], S. L. COWEN[4];
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Abstract: Dopamine neuron activity in the ventral tegmental area (VTA) and dopamine release in the nucleus accumbens (NAc) are essential for economic decision making, error-driven learning, and addiction. Though considerable evidence suggests a direct link between VTA neuron activity and dopamine release, little is known about the specific patterns of activity exhibited by midbrain neurons that lead to the release of dopamine in the NAc. Similarly, it is unclear how the activities of cells in proximal nuclei, such as the rostromedial tegmental nucleus (RMTg), known as the master-brake of the VTA, contribute to release. To address this, we developed novel instrumentation capable of measuring dopamine release and single-unit activity simultaneously to elucidate the characteristics of VTA and RMTg activity that give rise to dopamine release. Spontaneous phasic dopamine release was induced pharmacologically in anesthetized male Sprague Dawley rats (n = 22, 3 - 4 months old, 1 - 1.5 % isoflurane) using a dopamine transporter inhibitor GBR-12909 (17.5 mg/kg, *i.p.*) and the dopamine receptor 2-like antagonist eticlopride (0.75 mg/kg, *i.p.*). As predicted, a portion of recorded dopaminergic neurons (15%) exhibited changes in firing at the time of dopamine release onset. Interestingly, many of these cells exhibited changes in firing at both the onsets and the peaks of dopamine release events. These data suggest that the mechanisms involved in the initiation of dopamine release also contribute to the signal that terminates release. We also hypothesized that most non-dopaminergic neurons of the VTA and RMTg, many presumed to be local GABAergic neurons, would decrease firing just prior to dopamine release in order to release dopamine neurons from local inhibition. Instead, we observed that most responsive non-dopaminergic neurons in both regions increased firing at the onset of dopamine release events, suggesting that a more complex

network of inhibitory and excitatory neurons in the VTA and RMTg controls dopamine release than previously thought. These data support a link between VTA neuron activity and dopamine release, but also suggest that VTA-mediated dopamine release in the NAc is not a simple function of dopamine neuron firing activity.

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Poster

773. Dopamine, Reward, and Reinforcement

Location: Hall A

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Topic: G.02. Motivation

Support: NIH Grant NS083815
NIH Grant MH119312

Title: Action-induced inhibition of nigrostriatal dopamine release by goal-directed behavior

Authors: ***N. G. HOLLON**[1], E. W. WILLIAMS[1], H. LI[1], T. I. TRAUT[1], C. D. HOWARD[1,2], X. JIN[1];
[1]Mol. Neurobio. Lab., Salk Inst. for Biol. Studies, La Jolla, CA; [2]Neurosci., Oberlin Col., Oberlin, OH

Abstract: Nigrostriatal dopamine plays critical roles in voluntary movement, motivation, and reinforcement learning, but its exact role in instrumental learning and how it interacts with actions remain poorly understood. Here we examined how self-initiated goal-directed action influences nigrostriatal dopamine transmission during instrumental behavior with minimal overt changes in the external environment. Mice expressing channelrhodopsin in their dopamine neurons learned to press a lever on a continuous reinforcement schedule to deliver blue-light stimulation into their substantia nigra pars compacta (SNc). This free-operant optogenetic self-stimulation of nigrostriatal dopamine was sensitive to changes in the action-outcome contingency, demonstrating that performance was goal-directed. Using fast-scan cyclic voltammetry, we monitored changes in dorsal striatal dopamine concentration during both self-stimulation and subsequent playback of stimulations delivered in the same temporal sequence but not contingent upon any action. Self-stimulated dopamine release was markedly lower than that evoked by non-contingent playback, indicating that self-initiated action causes a robust suppression of dopamine release, even when driven by direct optogenetic depolarization of dopamine neurons themselves. This suppression of the expected neurochemical consequence of one's own action, likely through an efference copy, is consistent with a feedforward inhibition triggered by the goal-directed action. Electrophysiological recordings of optogenetically

identified SNc dopamine neurons provided evidence for inhibition of somatic firing activity contributing to the observed effects on terminal release. Non-reinforced presses of the typically active lever revealed transient dips below baseline dopamine levels. This inhibition was action-specific and was not observed to presses of the inactive lever. Probes with delayed stimulation or varied magnitude demonstrated that the action-induced suppression is precisely timed to counteract the expected consequence of that action. Recordings in mice performing heterogeneous action sequences for nigrostriatal self-stimulation further revealed the sequence-specificity of this inhibition, which was strongest during the sequence element most proximal to outcome delivery. Collectively, these findings demonstrate that nigrostriatal dopamine signals prediction errors in action-outcome associations, and have fundamental implications for instrumental behavior and movement control.

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Poster

773. Dopamine, Reward, and Reinforcement

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Program #/Poster #: 773.20/U28

Topic: G.02. Motivation

Support: NSF IOS1557755
NIGMS 5T34GM096958

Title: Characterization of the effects of systemically increasing dopamine, serotonin, and noradrenaline levels on the valuation of reward vs. avoidance

Authors: *J. B. ROBERTS[1], O. CHAMAN[1], E. B. OLESON[2];
[1]Biol., [2]Psychology, Univ. of Colorado Denver, Denver, CO

Abstract: Optimal behavior and overall survival require obtaining highly-valued outcomes from our environment. These action-outcome situations are often driven by either the pursuit of reward or the avoidance of harm. The three primary monoamine neurotransmitter systems that modulate such motivated behaviors are dopamine (DA), serotonin (5-HT), and noradrenaline (NA). Here, we are using selective uptake inhibitors GBR-12909, fluoxetine, and desipramine, to block the uptake of DA, 5-HT, and NA respectively. To investigate how these uptake inhibitors influence the value of avoidance vs. reward, we combined operant behavior with behavioral economic theory. In our avoidance task, rats were trained to respond to avoid electrical foot-shock across a range of prices (response requirement/mA shock avoided); in our reward-seeking task, rats were trained to respond for sugar across a range of prices (response requirement/mg sugar received). We then fit data with demand curves and solved for alpha. Demand curves are a

common tool used by economists to measure price sensitivity depicting the relationship between consumption and price. Alpha represents the rate at which demand curves decay and can be used to make inferences regarding the value individuals place on the commodity being consumed. If the slope decays at a faster rate, we would infer that the value to avoid or seek reward is decreased because consumption became more sensitive to price. Conversely, if slope decays at a slower rate, we would infer that the value to avoid or seek reward is increased because consumption become less sensitive to price. Preliminary data suggest that GBR-12909 increased avoidance value; whereas desipramine decreased avoidance value. Investigating whether these pathways produce distinct effects on reward vs. avoidance valuation will provide novel insight into how the brain controls these fundamental aspects of behavior. The implications of this work may also advance our understanding of major psychiatric conditions such as depression and drug addiction. After completing the reward valuation component of this study, we attempt to replicate our findings using chemogenetics to add anatomical specificity to our exploration of this research question.

Disclosures: **J.B. Roberts:** None. **O. Chaman:** None. **E.B. Oleson:** None.

Poster

773. Dopamine, Reward, and Reinforcement

Location: Hall A

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Program #/Poster #: 773.21/U29

Topic: G.02. Motivation

Support: HFSP CDA00029/2013-C
EC Marie Curie DopaPredict
FWO PhD scholarship 11ZA317N

Title: Dopamine cue salience responses promote associative learning

Authors: J. MORRENS, C. AYDIN, A. JANSE VAN RENSBURG, ***S. HAESLER**;
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Abstract: Dopamine neurons mediate the association of conditioned stimuli (CS) with reward (unconditioned stimuli, US) by signaling the discrepancy between predicted and actual reward during the US (i.e. reward prediction errors, RPE), a fundamental parameter of reinforcement learning models. Alternative models suggest, learning is influenced by the salience or associability of the CS. A hallmark of CS associability models is that they provide a simple explanation for latent inhibition, i.e. the observation that novel CS are more effectively learned than familiar CS. Novel CS are known to activate dopamine neurons, but whether those CS salience responses affect associative learning has not been investigated. Moreover, pharmacological evidence has implicated the dopamine system in latent inhibition. but the circuit

mechanism by which the activity of dopamine neurons causes a learning bias towards novel stimuli remains unknown. Here, we measured dopamine transients with fiber photometry across the midbrain ventral tegmental area (VTA) and substantia nigra pars compacta (SNc) in a non-associative novelty exposure paradigm, in which animals show spontaneous orienting responses to novel but not familiar stimuli. We found dopamine responses to novel stimuli are graded, with no distinct pattern across SNc and VTA, thus not supporting the notion of a distinct anatomical subpopulation responding to novel stimuli. We then performed olfactory conditioning, using stimulus novelty and familiarity to experimentally manipulate CS salience. With bidirectional optogenetic manipulation of dopamine neurons selectively during the CS period, we demonstrated that dopamine CS salience signals promote associative learning. The function of dopamine in associative learning thus involves stimulus salience signals in addition to US RPE signals. This idea is consistent with dopamine response properties recorded previously in primates and with theoretical models combining stimulus associability and error terms (Lak et al., 2016; Le Pelley, 2004; Schultz, 2016), but it has lacked an experimental confirmation. It has been suggested that latent inhibition results from the reduced associability of stimuli experienced without any consequence. Given our findings, it seems however more plausible it is not the reduced CS associability of familiar stimuli but the increased associability of novel stimuli, which underlie the learning bias towards novel stimuli in latent inhibition. Latent inhibition might thus merely result from the absence of dopamine CS salience responses to familiar stimuli.

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Poster

773. Dopamine, Reward, and Reinforcement

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 773.22/U30

Topic: G.02. Motivation

Support: NIH 5R01MH068073
NARSAD

Title: Dopamine encodes the state of reward availability in a modified condition inhibition paradigm

Authors: ***A. KALMBACH**[1,2], P. D. BALSAM[3], E. H. SIMPSON[1,2];
[1]Psychiatry, Columbia Univ., New York, NY; [2]Developmental Neurosci., New York State Psychiatric Inst., New York, NY; [3]Barnard Coll Columbia Univ., New York, NY

Abstract: Inhibition of dangerous or wasteful behavior is necessary for allocating energy to situations that are less dangerous or more productive and rewarding. This inhibition requires

observation of environmental cues and adjustment of behavior accordingly. Behavioral inhibition deficits are observed in ADHD, addiction, and schizophrenia. Here, we investigated whether and how dopamine signaling encodes the conditioned stimulus that signals when rewards cannot be earned and the extent to which the dopamine signal correlated with behavioral responses. In our behavior paradigm, the animals pressed a lever to earn a reward on a random interval schedule (RI 20s) but when a prolonged tone was present (3.5kHz; 80s), rewards could not be earned. Animals learned to suppress lever pressing during the tone. Throughout learning, we utilized fast scan cyclic voltammetry to measure extracellular dopamine in the ventral striatum or fiber photometry to monitor calcium dynamics in dopamine neuron cell bodies and axons using GCaMP6f or dopamine release from dopamine axons using dLight. Unexpectedly, we found that, after learning stabilized, both dopamine release and dopamine somatic and axonal activity decreased to a steady state that persisted throughout the duration of the tone. Immediately following tone cessation, dopamine release and neuronal activity rebounded to pre-tone levels. Thus, these measurements of dopamine activity suggest that dopamine encodes reward availability and not proximity to reward. Furthermore, the dynamics of lever pressing during the conditioned tone did not correlate with the dynamics of dopamine release and neuronal activity, which suggests that dopamine activity and behavior are not tightly coupled in this behavioral paradigm. These results also indicate that measurements usually performed to detect phasic changes in dopamine can also be utilized to detect relatively long lasting changes in dopamine.

Disclosures: A. Kalmbach: None. **P.D. Balsam:** None. **E.H. Simpson:** None.

Poster

773. Dopamine, Reward, and Reinforcement

Location: Hall A

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FRC ‘‘espoir en tête’’ 2012
Laboratoire d’Excellence LABEX BIO-PSY - ANR-11-IDEX-0004-02.

Title: Electrophysiological analysis of the dynamics of mesocortical circuits during decision making under uncertainty in mice

Authors: *E. BOUSSEYROL, S. DIDIENNE, S. TAKILLAH, C. PRÉVOST-SOLIÉ, J. NAUDÉ, P. FAURE;
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Abstract: The ability to adapt to the unfamiliar or uncertain is fundamental, and entails that animals actively explore their environment. This adaptation requires to balance the exploitation of the best option so far with the exploration of alternative choices (1). Dopaminergic (DA) neurons of the ventral tegmental area (VTA) (2) and frontal cortices such as the orbitofrontal (OFC) (3) and prefrontal (PFC) (4) play crucial roles in this balance. However, little is known about their functional coordination as part of an interconnected mesocortical circuit. In this project, we ask whether specific dynamics in this network (VTA, OFC, and PFC) support decision-making and exploratory behavior in uncertain environments. We used a behavioral paradigm that allows computational modeling of exploratory choices in a decision-making task in mice with simultaneous quantification of electrophysiological activity. Using intracranial self-stimulation of the medial forebrain bundle, mice were trained to obtain rewards on three explicit locations in an open-field. Mice could not obtain two consecutive rewards at the same location, forcing them to navigate between locations. After a learning period, locations were associated with distinct reward probabilities (e.g. 100%, 50% and 25%), offering mice three different binary choices. Local field potentials (LFP) and multi-unit activity were recorded in the OFC and PFC, as well as in VTA DA neurons from mice performing the task. We analyzed transient oscillations from LFPs and neuron firing rate and correlated them with behavior and decision parameters (e.g. reward probability and uncertainty of the available locations). Animals adopted a specific behavioral strategy to deal with the uncertainty of the environment (2). Our results indicate that specific activity patterns emerged in frontal cortices and VTA DA neurons during the learning process, at the time of the decision, when animals engage in a new trial. These activities were temporally organized and locked on specific behaviors. Moreover, we show that this sequence of activities correlates with choices in the probabilistic setting of the task. Finally, in order to disentangle the relative roles of these different structures, we showed that optogenetic manipulation of VTA DA cells biased choices. Our results suggest a specific sequence of activation in the VTA-OFC-PFC network that is related to mouse choices. (1) Cohen et al., Phil. Trans. R. Soc. B 2007 (2) Naudé et al., Nat. Neurosc. 2016 (3) Wilson et al., Neuron 2014 (4) Euston et al., Neuron 2012

Disclosures: **E. Bousseyrol:** None. **S. Didienne:** None. **S. Takillah:** None. **C. Prévost-Solié:** None. **J. Naudé:** None. **P. Faure:** None.

Poster

773. Dopamine, Reward, and Reinforcement

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 773.24/U32

Topic: G.02. Motivation

Title: Cue encoding patterns of brain stimulation reward compared to sucrose rewards

Authors: *D. N. TAPP, S. M. THOMPSON, M. S. MCMURRAY;
Psychology, Miami Univ., Oxford, OH

Abstract: Dysfunctional reward processing can lead to obesity or psychiatric diseases such as anorexia and addiction.
Thus, it is critical that we understand the neurobiological systems that are responsible for the processing of food rewards. Food rewards recruit complex neural systems responsible for taste reactivity, energy homeostasis, and satiety, in addition to reward processing. Thus, the processing of food rewards is confounded by these other signals, making it challenging to tease apart reward signals from other activators of these circuits. Unlike food rewards, brain stimulation reward (BSR) provides direct electrical stimulation to discrete areas of the mesocorticolimbic reward circuit in a controllable manner. Further, BSR activates dopaminergic cue encoding circuitry in a more direct manner than food rewards. To aid in our understanding of the neural systems responsible for the complex encoding of food rewards, we examined how food rewards activate neural circuitry differently than (BSR), which is free of sensory processes, is more temporally precise, and activates only selected neural circuits. We compared encoding of BSR and food-reward on one critical aspect of reward processing: reward-predictive cue encoding. By combining a classical conditioning paradigm with *in vivo* electrophysiological recordings, we found that the encoding of food-predictive cues by the nucleus accumbens (NAc) is biased by non-reward processes (which BSR is free of). To control for variation in reward intensity, all animals performed behavioral tests after recording to determine reward sensitivity and match subjective reward magnitudes across reward types. By comparing the timescale and intensity of food-evoked cue encoding to BSR, we found that food rewards produce less intense, yet longer-lasting phasic changes in neural activity in the NAc compared to BSR. Such results suggests that food rewards activate neural circuitry for a briefer and less powerful manner than BSR, highlighting how the complex neural encoding of foods may bias reward encoding. These findings shed light on the basic neurobiology controlling both food reward and BSR, which are widely used in reinforcement research.

Disclosures: D.N. Tapp: None. **S.M. Thompson:** None. **M.S. McMurray:** None.

Poster

773. Dopamine, Reward, and Reinforcement

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 773.25/U33

Topic: G.02. Motivation

Title: Sex differences in an effort-related decision making task

Authors: *E. L. ERRANTE[1], M. CHAKKALAMURI[1], O. I. AKINBO[1], S. E. YOHN[2], J. D. SALAMONE[3], L. MATUSZEWICH[1];

[1]Dept. of Psychology, Northern Illinois Univ., Dekalb, IL; [2]Vanderbilt Univ., Nashville, TN; [3]Dept Psychological Sci., Univ. of Connecticut, Storrs Mansfield, CT

Abstract: Major Depressive Disorder (MDD) is characterized by debilitating symptoms, including anxiety, fatigue and anhedonia. Interestingly, there are sex differences in the prevalence rates of MDD with 8.5% of females reporting symptoms compared to 4.8% of males (NIH, 2016). One component of MDD is lowered motivation or interest for pleasurable activities, which can be difficult to treat. An approach previously used to assess motivation is to compare performance on tests of effort-related decision-making, where subjects are presented with a choice between high effort/high reward and low effort/low reward options. Prior research in males has found that dopamine (DA) underlies the motivated behaviors assessed in the effort-related task with antagonism of DA D2 receptors resulting in motivational deficits. However, whether DA antagonism reduces performance in effort-based decision-making tasks in females is not known. The aim of the present study was to investigate motivation for a sucrose reward in an effort-related decision-making task after administration of the DA D2 receptor antagonist haloperidol (HAL). Adult male and female Sprague Dawley rats were randomly assigned to a non-food restricted or a food restricted condition in order to assess sex differences and the motivation for a sucrose reward. A progressive ratio choice procedure was used to assess effort-related decision-making. In this task, rats were trained in operant chambers to either lever press for a highly valued sucrose reward on a progressing fixed ratio schedule or to approach and consume freely available lab chow. Once responding was stable, HAL was administered at varying doses (vehicle, 0.05, 0.1, or 0.2 mg/kg) prior to the test. Our initial findings show that HAL significantly reduced all appropriate parameters in males and females-- lever pressing ($p < 0.05$), highest ratio achieved ($p < 0.05$), and breakpoint ($p < 0.05$)-- without any significant change in chow consumption. There were also significant interactions on lever pressing between drug dose, food restriction and sex ($p < 0.05$) as well as significant interactions on highest ratio achieved between drug dose and sex ($p < 0.05$) and chow consumption between drug dose and food deprivation ($p < 0.05$). Importantly, female rats that were food restricted showed a different pattern of behavior than males in terms of general performance. Overall, these data suggest that DA antagonism produces motivational deficits in both sexes, but that food restriction may not increase responding in female rats as it does in male rats. These findings may provide a better understanding of motivational dysfunction in both sexes and potential treatment targets for MDD.

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Poster

773. Dopamine, Reward, and Reinforcement

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Program #/Poster #: 773.26/U34

Topic: G.02. Motivation

Support: NSERC Grant
CIHR Grant

Title: D2 agonism in the nucleus accumbens, but not the prefrontal cortex, restores reward responsiveness following chronic stress

Authors: *S. J. LAMONTAGNE, S. H. IRWIN, M. C. OLMSTEAD;
Queen's Univ., Kingston, ON, Canada

Abstract: Anhedonia, “a loss of interest or pleasure in previously rewarding activities” (DSM-5, 2013), is characteristically preceded by chronic stress (Hamen, 2005). Recent literature suggests that stress-induced deficits may be alleviated by activating distinct dopaminergic (DA) receptor subtypes. Recently (2019), we showed that chronic mild stress (CMS)-induced reward dysfunction was restored through systemic injections of a D2/3 agonist in rats; however, it remains unclear how this effect is mediated centrally. Although it is well known that the nucleus accumbens (NAcc) and prefrontal cortex (PFC) are sensitive to the effects of chronic stress, their role in mediating reward dysfunction following stress is elusive (Lucas et al., 2004; Chen et al., 2013). Using the rat probabilistic reward task (PRT; Der-Avakian et al., 2013), we investigated the neuroanatomical specificity of D2 agonism on reward learning following CMS.
Eighteen rats were exposed to Willner’s (1992) CMS regime and 18 rats were left undisturbed (no-stress control). Prior to testing in the PRT, animals from each condition received intra-NAcc (n=9 per group) or intra-PFC (n=9 per group) infusions of D2 agonist, quinpirole (QUIN; 1ug/side). We found that both CMS groups showed greater adrenal gland and lower thymus gland weights relative to control groups. There was a strong inverse relationship between adrenal gland weight and reward learning following CMS in the intra-PFC-QUIN group, but not in the intra-NAcc-QUIN group, suggesting that D2 activation in the PFC does not restore reward learning in stress-susceptible animals. Relative to no-stress and CMS animals that received NAcc infusions of QUIN, animals that received PFC infusions showed impaired reward learning with respect to reward response bias, accuracy and reaction time for the rewarding stimulus. CMS animals that received NAcc infusions did not differ from no-stress control animals on any behavioural measure.
Collectively, these findings suggest that the restoration of reward learning following chronic stress is mediated by D2 agonism in the NAcc. Future research should investigate whether other receptor subtypes, such as D1, in the PFC differentially affect reward learning following chronic stress.

Disclosures: S.J. Lamontagne: None. **S.H. Irwin:** None. **M.C. Olmstead:** None.

Poster

773. Dopamine, Reward, and Reinforcement

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 773.27/U35

Topic: G.02. Motivation

Support: NIH Grant MH107126

Title: Catechol-o-methyltransferase function regulates palatable food consumption in male mice

Authors: *M. NOBACK[1], G. ZHANG[2], N. WHITE[3], G. V. CARR[4], J. C. BARROW[5];
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Abstract: Catechol-*O*-methyltransferase (COMT) is a critical enzyme involved in the metabolism of dopamine and other catecholamine neurotransmitters. COMT is a particularly important regulator dopaminergic signaling in regions of the brain with low expression of the dopamine transporter, such as the prefrontal cortex (PFC). Due to this regional specificity, COMT activity is a potent modulator of PFC-dependent cognitive function, including inhibitory control. In humans, expression of the high activity Val isoform is associated with increased risk of obesity, consumption of high-fat food, and craving of self-described “unhealthy” food. In these experiments, we measured palatable food consumption under fixed and progressive ratio schedules of reinforcement in two separate mouse models characterized by increased COMT activity. First we found that wild-type C57BL/6J mice singly housed for two weeks following weaning (postnatal day 21-35) have more COMT protein in the PFC than their littermates who were continuously group housed when measured as adults (postnatal day 63). Additionally, the socially isolated (SI) mice displayed increased consumption of a palatable food (strawberry milk) under an FR1 schedule of reinforcement. The SI mice showed additional signs of increased willingness to work for the palatable food in a progressive ratio task and a continuous performance test (CPT) of vigilance. To determine if the SI phenotype is related to COMT function, we tested transgenic mice that overexpress COMT in the FR1 and CPT. In a preliminary cohort, we found effects similar to those seen in the SI mice. The COMT transgenic mice consumed more strawberry milk on the FR1 schedule and demonstrated increased vigilance in the CPT. These results indicate that COMT activity may regulate palatable food consumption. Future experiments will examine whether the relationship between COMT activity and palatable food consumption can be regulated by acute changes in COMT activity or if it results from long-term adaptations in neurocircuitry.

Disclosures: M. Noback: None. **G. Zhang:** None. **N. White:** None. **G.V. Carr:** None. **J.C. Barrow:** None.

Poster

773. Dopamine, Reward, and Reinforcement

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 773.28/U36

Topic: G.02. Motivation

Support: Grinnell College

Title: Time course of D2DR levels in the nucleus accumbens during the development and maintenance of high-fat diet-induced obesity

Authors: M. M. MARCUS, I. BUTZIRUS, D. N. A. OKINE, *A. L. TRACY;
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Abstract: The mesolimbic dopaminergic pathway is implicated in the development and maintenance of obesity. In particular, dopamine (DA) receptor genotype has been shown to affect food reinforcement in humans and food motivation is increased by DA agonism in rats (Epstein et al., 2007; Zhang et al., 2003). Chronic obesity appears to reliably reduce striatal dopamine D2 receptor (D2DR) availability in humans, as well as in high-fat diet (HFD) induced chronically obese rats (Wang et al., 2001; Johnson & Kenny, 2010). However, changes in D2DR during the development of obesity have not yet been studied. The purpose of the present study is to examine the changes in D2DR-positive cells in the nucleus accumbens (NAcc) over an 8-week period of exposure to HFD. Four Long-Evans rats fed a 40% butterfat diet and four rats fed standard chow were euthanized and brain tissue was collected after 0, 7, 14, 21, 28, 35, 42, 49, and 56 days of ad libitum consumption of their respective diet. D2DR positive cells were visualized and quantified in 40 μm slices through the NAcc using immunohistochemical staining. D2DR levels were compared across diet type and duration. In contrast to findings in chronic obesity, our results indicate no difference in D2DR levels between rats consuming the HFD and rats consuming standard chow at early time points following introduction of the HFD (≤ 4 weeks). This finding supports the idea that obesity-induced changes in D2DR are a result of chronic consumption of HFD and/or increases in adiposity, and are not a short-term response to exposure to palatable foods. These changes are consistent with findings that novel food motivation remains similar between diet conditions in the short-term following HFD exposure, dropping off only after chronic intake (> 6 weeks; Tracy et al., 2015), and follow the behavioral pattern of initial binge eating of the HFD, followed by an intake plateau during maintenance of chronic obesity.

Disclosures: M.M. Marcus: None. **I. Butzirus:** None. **D.N.A. Okine:** None. **A.L. Tracy:** None.

Poster

773. Dopamine, Reward, and Reinforcement

Location: Hall A

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Program #/Poster #: 773.29/U37

Topic: G.02. Motivation

Support: NIH DP2MH113095
NIH 5T32 NS007433

Title: Rare rewards drive enhanced dopamine responses and learning

Authors: *K. M. ROTHENHOEFER[1], A. ALIKAYA[1], W. R. STAUFFER[2];
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Abstract: Dopamine neurons code reward prediction errors (RPEs), the differences between received and predicted values. However, it is not known how estimated (predicted) uncertainty affects value updating or the neural coding of RPEs. To investigate this, we created two reward size sets represented by two distinct visual cues, with the same expected value but different 'shapes.' One reward set consisted of three reward sizes that were delivered with equal probability (p = 1/3, 1/3, 1/3). The other reward set consisted of the same three reward sizes, but with the middle value more certain to be delivered (p = 2/15, 11/15, 2/15). Thus, the two sets coarsely simulated uniform and normal distributions, respectively. Distinct images predicted the reward sets. Monkeys made choices between one of the reward sets and an alternative option. At un-signaled intervals during a session, we shifted all the reward sizes in a reward set by a constant factor. This manipulation forced animals to learn the shifted mean in order to maximize reward value. The choice behavior indicated monkeys learned faster from RPEs generated by rare rewards drawn from the tails of normal-like distributions - compared to the more frequent, but same magnitude RPEs generated by rewards drawn from uniform-like distributions. We recorded 87 dopamine neurons across two monkeys; 81 were significantly activated by reward ($p < 0.05$, Wilcoxon). Recordings in a Pavlovian task (n = 51 neurons) revealed that dopamine responses, across the population and within single neurons, were magnified by infrequent positive and negative RPEs generated in the normal-like distribution, compared to the identical positive and negative RPEs generates with greater frequency from the uniform-like distribution. Crucially, we observed bi-directional modulations in the same neurons. Therefore, the modulations in the dopamine responses could not be explained by different subjective values assigned to the predictive stimuli. Thus, rare rewards enhance the dopamine RPE responses, even when the conventional RPE is identical. This neuronal effect corresponded to the faster behavioral learning and together these results indicate that reward updating is modulated by estimated uncertainty.

Disclosures: K.M. Rothenhoefer: None. **A. Alikaya:** None. **W.R. Stauffer:** None.

Poster

773. Dopamine, Reward, and Reinforcement

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Program #/Poster #: 773.30/U38

Topic: G.02. Motivation

Support: NIH grant R01-DA042889
Wayne and Gladys Valley Foundation

Title: Decoding the influence of dopamine in different NAc subregions on cue-driven behaviors and behavioral inhibition

Authors: *J. W. DE JONG[1], I. CERNIAUSKAS[1], S. OBAYASHI[1], J. P. H. VERHAREN[1], L. TIAN[2], S. LAMMEL[1];
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Abstract: The mesolimbic dopamine (DA) system, which is comprised of ventral tegmental area (VTA) DA neurons projecting to the nucleus accumbens (NAc), is associated with reward, appetitive motivation, and hedonic processes. Mesolimbic VTA DA neurons signal reward prediction errors (RPEs); they are excited in response to rewards and reward-predicting cues and are inhibited by aversive events. However, we have recently identified a novel subtype of mesolimbic DA neuron projecting to the ventral NAc medial shell (vNAcMed), which is excited by unexpected aversive outcomes and cues that predict them (*de Jong et al., 2019; Neuron*). To further explore the functional role of these non-canonical mesolimbic DA neurons, we performed multi-site fiber photometry recordings in different NAc subregions using the DA sensor dLight during an operant conditioning assay. Specifically, we trained head-fixed mice in an operant reward-seeking task, in which a conditioned stimulus (CS+) predicts the availability of a reward. Consistent with the RPE theory, we find that after conditioning the CS+ evokes transient DA release in the lateral shell of the NAc (NAcLat), whereas reward omission inhibits DA release. In contrast, no changes in DA release were observed in the vNAcMed in direct response to the CS+. Surprisingly, however, DA release in the vNAcMed increased gradually during reward seeking. Furthermore, when we trained mice on a conditioned suppression paradigm to show behavioral restraint and inhibit reward-seeking behavior, which is normally evoked by the CS+, we found that presentation of the CS+ continued to evoke DA release in the NAcLat. However, in this case mice did not initiate reward seeking and there was no increase in DA release in the vNAcMed. Together, these results suggest that while canonical NAcLat-projecting DA neurons signal a reward prediction error, vNAcMed-projecting DA neurons are excited concurrent with reward seeking and possibly reflect either action initiation or the anticipation of a proximal reward. We are currently studying how NAcLat and vNAcMed integrate cortical glutamatergic inputs with

local DA release to mediate cue-driven behavior and behavioral inhibition. Developing a detailed understanding of the role of DA in different NAc subregions underlying cue driven behavior represents an important step towards the identification of clinically relevant targets for treating impulse control disorders such as binge eating disorder and substance use disorder.

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Poster

774. Social Behavior: Systems and Circuits

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 774.01/U39

Topic: G.03. Emotion

Support: NIH grant HD088411
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Title: Oxytocin neurons enable social transmission of maternal behavior

Authors: *I. C. CARCEA[1], N. LOPEZ[2], B. J. MARLIN[3], R. OYAMA[4], J. MENDOZA-NAVARRO[5], M. OPENDAK[6], A. L. FALKNER[7], D. LIN[8], K. NISHIMORI[9], T. KIKUSUI[10], K. MOGI[10], R. M. SULLIVAN[11], R. C. FROEMKE[12];
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Abstract: Maternal care is profoundly important for mammalian survival, and one critical molecular signal for this behavior is oxytocin, released by hypothalamic paraventricular nucleus (PVN) and enabling plasticity within auditory cortex for recognizing infant vocalizations. Maternal behaviors can be expressed by non-biological parents, after experience with infants. To determine how these behaviors can be acquired during natural experience, we continuously monitored homecage behavior of female virgin mice co-housed for days with an experienced mother and litter, synchronized with in vivo recordings from virgin PVN/oxytocin neurons. Mothers engaged virgins in maternal care by directing the virgins toward the nest (shepherding), and demonstrated maternal behavior by self-generating pup retrieval episodes. We found that shepherding led to activation of oxytocin neurons in two stages, first at the start of the physical

social interaction (~ 20% of optogenetically-identified oxytocin neurons), and then when the virgin entered the nest with pups (~ 33% of oxytocin neurons). Similarly, we found that exposure to maternally-executed pup retrievals activated oxytocin neurons in virgin PVN (~30% of oxytocin neurons). This socially triggered increased firing of oxytocin neurons gated behaviorally-relevant cortical plasticity for pup distress calls. Pharmacogenetic suppression of oxytocin neurons delayed the acquisition of pup retrieval behavior via these social interactions. Thus rodent maternal behavior can be learned by social transmission, and our results describe a mechanism for adapting the brains of new parents to infant needs via endogenous oxytocin.

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Poster

774. Social Behavior: Systems and Circuits

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 774.02/U40

Topic: G.03. Emotion

Support: NIH Grant 3R01HD08841102S1

Title: Social transmission of maternal behaviors through observation

Authors: *N. LÓPEZ CARABALLO[1], R. FROEMKE[2];
[1]Sackler Inst. of Biomed. Sciences; Neurosci. Inst., [2]Dept. of Otolaryngology-Head and Neck Surgery; Dept. of Neurosci. and Physiol., New York Univ. Sch. of Med., New York, NY

Abstract: Our laboratory studies the mechanisms by which social experience leads to neuroplasticity to promote learning and pro-social behavioral changes. We focus on maternal care by mice, enabling reliable measurements of various social behaviors combined with experimental approaches such as neural recordings and optogenetics. When mouse pups are out of the nest, they emit vocalizations that prompt the mother to fetch them back to the nest. Virgin females do not initially retrieve pups, but usually begin retrieving after several days of co-housing with an experienced mother and pups.
To understand the social experiences that lead to virgin co-parenting, we first built a new system for combining continuous video-audio-neural recordings from co-housed animals over days. We found that mothers appear to demonstrate maternal behaviors to virgins. To explore the potential for social transmission of maternal behavior, we developed a new paradigm for virgins to learn retrieval through observation. A non-co-housed virgin observes a mother retrieve pups through a transparent barrier that allows visual, odor and auditory cues to go through. Virgin female mice

can learn retrieval through observation. When the visual input was impaired, animals did not learn to retrieve via observation. Also, if the observer was an oxytocin receptor knockout animal, there was also minimal acceleration in time to first retrieval via observational learning (Carcea et al., in review).
We define successful retrieval as a mouse placing the pup safely inside the nest. Although mothers are proficient retrievers, some fail to retrieve accurately, sometimes placing the pups in the outside border of the nest. After observing some virgins mimicked mother's retrieval errors, we developed a setup for virtual simulation of observational learning, consisting of retrieval videos and pup calls audio playback. It allows us to manipulate the sensory stimuli presented to the virgins and further explore experience-related effects on behavior and neural activity. Our data (n=3) shows that virgins can learn to retrieve in the virtual setup. Furthermore, our lab showed that the neuromodulator oxytocin has a role in sensitizing the sensorial cortex promoting learning of pup retrieval (Marlin et al. Nature 2015). Sensory cortices and hypothalamic-oxytocin-releasing regions seem to be activated during observational learning in virgins, as shown by expression of the intermediate-early gene *c-fos* in auditory, visual and piriform cortices and the paraventricular nucleus of the hypothalamus. Our research will help parse out the specific experiences and sensory modalities required for learning of maternal behaviors.

Disclosures: **N. López Caraballo:** None. **R. Froemke:** None.

Poster

774. Social Behavior: Systems and Circuits

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 774.03/V1

Topic: G.03. Emotion

Support: NIH/NIMH 1R56MH115681

Title: From discriminative to affective touch: A mesoscale perspective of the somatosensory pathway to the primate amygdala

Authors: ***A. B. MARTIN**[1], K. R. ANDERSEN[1], J. K. MORROW[1], E. A. HILLIER[2], M. A. CARDENAS[2], S. LEE[1], S. L. COWEN[3], K. M. GOTHARD[4];
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Abstract: The role of the primate amygdala in processing touch has only recently been addressed. The neural processes that transform the objective, discriminatory features of tactile inputs, presumably originating from area 3b, into a representation of emotional significance in the amygdala are unknown. To address this question, we have recorded local field potentials in response to the same tactile stimuli from the primary somatosensory cortex (area 3b), secondary

somatosensory cortex (SII), and the amygdala. The tactile stimuli included 1-s long, non-aversive airflow stimuli and brief sweeping touches by human experimenters. These stimuli were delivered to the face and head of the monkey. The experimenters wore instrumented gloves that signaled the contact force and sweep duration of each touch. In area 3b, the airflow and the touch stimuli elicited similar responses: a brief elevation of power in the 4-30 Hz frequency range, followed by a suppression of the power the 8-30 Hz range, and then a suppression of power in the 4-7 Hz range. As expected, the high-frequency broadband was highly correlated with spiking activity. In the amygdala, the airflow and the touch stimuli also elicited similar responses. However, these responses were different from the responses in 3b and showed stronger modulation in response to touch compared to airflow. Specifically, in response to tactile stimulation we observed an increase in power followed by a suppression in the 4-7 Hz (theta) and 30-70 Hz (gamma) frequency ranges. The most prominent finding was a reliable suppression in the 12-30 Hz (beta) range. None of these responses depended on the presence (airflow) or absence (touch) of stimulus-related spiking activity (see adjacent poster) or the associated high frequency broadband modulations. These features of mesoscale neurophysiology in the amygdala have not been previously reported. We took advantage of the simultaneously recorded LFP's from area 3b and the amygdala to explore the processing flow of tactile signals between these areas. We found a strong correlation in beta modulation at the time of stimulation, especially for human touch. In parallel, we found a weaker correlation in theta between these areas and an associated anti-correlation between cortical theta and amygdalar beta, indicating a temporal link in tactile processing between area 3b and the amygdala. While these findings are preliminary, they suggest that the LFP's in the amygdala map onto the canonical features of sensory information processing found in the cortex.

Disclosures: A.B. Martin: None. **K.R. Andersen:** None. **J.K. Morrow:** None. **E.A. Hillier:** None. **M.A. Cardenas:** None. **S. Lee:** None. **S.L. Cowen:** None. **K.M. Gothard:** None.

Poster

774. Social Behavior: Systems and Circuits

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 774.04/V2

Topic: G.03. Emotion

Support: NIH/NIMH 1R56 MH115681

Title: From discriminative to affective touch: A single-unit perspective of the somatosensory pathway to the primate amygdala

Authors: *R. ANDERSEN[1], J. K. MORROW[2], A. B. MARTIN[1], E. A. HILLIER[1], M. A. CARDENAS[3], S. LEE[1], K. M. GOTHARD[4];

[1]Physiol., [2]Neurosci., [3]Univ. of Arizona, Tucson, AZ; [4]Physiol., Univ. of Arizona Col. of Med., Tucson, AZ

Abstract: The role of the primate amygdala in processing touch has only recently been addressed. The neural processes that transform the objective, discriminatory features of tactile inputs, presumably originating from area 3b, into a representation of emotional significance in the amygdala are unknown. To address this question, we have recorded neural responses to the same tactile stimuli from the primary somatosensory cortex (area 3b), secondary somatosensory cortex (SII), and amygdala. The tactile stimuli included 1-s long, non-aversive airflow and brief sweeping touches by human experimenters. These stimuli were delivered to the face and head of the monkey. The experimenters wore instrumented gloves that signaled the contact force and sweep duration of each touch. Both the airflow and the human touch reliably activated neurons in area 3b. A large proportion of touch-responsive neurons in 3b (35 of 61) responded to deflections of the whiskers and facial hairs (mainly in the perioral area). A subset of neurons in 3b (approximately 30%) showed significant correlations with the contact forces applied to their receptive fields. In contrast, simultaneously recorded neurons in the amygdala responded reliably to airflow (22 of 110) but failed to respond to human touch delivered to the same area, suggesting a gating mechanism for social touch in the amygdala. To test for the role of social factors, 10 human experimenters, with different levels of familiarity with the subject monkey, delivered similar patterns of touches to the same skin area. Only 2 amygdala neurons of the 151 tested exclusively with human touch responded. These neurons appeared to differentiate between the individuals delivering the touch stimuli. The autonomic state of the animal in response to being touched by different individuals was considered as a factor for the observed gating. Indeed, less familiar individuals caused higher elevations of heart and respiratory rates than more familiar individuals. Compared to human touch, airflow stimuli appeared less arousing. It is possible, therefore, that the autonomic arousal during human touch is related to an intra-amygdala process by which responses to social but not mechanical touch are gated out. This purported gating mechanism may not be universal. In previous studies, we found that 30-40% of the neurons in the amygdala of other monkeys responded to human touch. Ongoing studies will shed light on the sources of the observed individual variation and will determine whether social and non-social tactile stimuli are processed differentially in the amygdala.

Disclosures: R. Andersen: None. **J.K. Morrow:** None. **A.B. Martin:** None. **E.A. Hillier:** None. **M.A. Cardenas:** None. **S. Lee:** None. **K.M. Gothard:** None.

Poster

774. Social Behavior: Systems and Circuits

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 774.05/V3

Topic: G.03. Emotion

Support: NIMH/NIH P50 100023

Title: Statistically separable components of the local field potential show sensory-modality specific spike-field coherence in the primate amygdala

Authors: *J. K. MORROW[1], M. X. COHEN[2], K. M. GOTHARD[3];
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Abstract: Electrophysiological signals recorded via depth electrodes are often separated into two components: a low-frequency component (often called the local field potential or LFP) produced by the aggregate activity of thousands of nearby cells; and a high-frequency component that reflects action potentials (a.k.a., “spikes”) of individual neurons. Spike-field coherence examines the relationship between these signals to determine if spiking activity is synchronized with, or modulated by, lower frequency oscillations. While numerous studies have found spike-field coherence in well-organized structures like the hippocampus or cortex, next to nothing is known about this important phenomenon in the primate amygdala. To address this issue, we recorded single-unit and LFP activity from 16 sites that spanned the entire dorsal-ventral axis of the amygdala while monkeys received visual, tactile, or auditory stimuli. We then isolated statistically independent sources of LFP signals using a generalized eigendecomposition-based (GED) analysis that has recently been validated using empirical and simulated neural datasets. We found significant spike-field coherence in several low-frequency bands (1-10 Hz) in both the channel-wise and GED-based LFP signals. Visual, tactile, and auditory stimuli often, but not always, elicited spike-field coherence in different frequency bands. The channel-wise LFP showed spike-field coherence at high frequencies (>100 Hz), which is often due to contamination of this frequency range by components of the action potential signal; however, the GED-based signal rarely showed this high-frequency artifact. These results demonstrate that 1) single-unit activity can be synchronized to LFP oscillations within the primate amygdala, 2) spike-field coherence was prominent at low frequencies and appeared to be related to the sensory modality of the stimulus in this particular experiment, and 3) GED-based LFP signals may be more resistant to high-frequency artifacts in spike-field coherence.

Disclosures: J.K. Morrow: None. **M.X. Cohen:** None. **K.M. Gothard:** None.

Poster

774. Social Behavior: Systems and Circuits

Location: Hall A

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Program #/Poster #: 774.06/V4

Topic: G.03. Emotion

Support: R01 MH105624

Title: Inclusion of dlPFC and vlPFC inputs in cortico-amygdala topography

Authors: *A. C. MCHALE, J. L. FUDGE;
Neurosci., Univ. of Rochester Sch. of Med., Rochester, NY

Abstract: The primate amygdala is a collection of nuclei that work together to interpret a range of salient stimuli, including social cues such as faces and social group hierarchies. The basal nucleus is of particular interest in primates, including humans, because it is disproportionately enlarged and complex. It contains 3 subdivisions: the magnocellular (Bmc), intermediate (Bi,) and parvicellular (Bpc). These subdivisions are distinguished by a gradual dorsal-ventral cellular gradient based on pyramidal cell size and cell-packing density.
In previous work, we found that the topography of projections from "limbic cortex" (orbital and medial prefrontal cortex (omPFC) and insula) to the basal nucleus subdivisions is determined by cortical differentiation rather than lobar assignment. The least differentiated cortices project throughout the basal nucleus, with successively more differentiated cortices overlapping these inputs along a ventral to dorsal gradient.
Our current work seeks to understand whether more highly differentiated "non-limbic" prefrontal cortex, specifically the dorsolateral prefrontal cortex (dlPFC) and ventrolateral prefrontal cortex (vlPFC), fits into this organization. We examined the distribution of labeled cells throughout the dlPFC and vlPFC following small injections of retrograde tracer into different subdivisions of the basal nucleus. We then analyzed them with respect to previous data documenting omPFC and insula inputs. In line with the literature, there is an overall lower density of dlPFC and vlPFC projections into the basal nucleus compared to omPFC and insula projections. However, a topographical pattern of inputs into the basal nucleus was observed. Bpc received few to no projections, Bi received light projections, and Bmc received light to moderate projections from dlPFC and vlPFC regions. The majority of retrogradely labeled cells were in areas 12, 45, and 8A, and there were scattered retrogradely labeled cells in areas 9 and 46. Taken together, the results indicate an overall topography in cortico-amygdala projections wherein relatively more differentiated inputs overlap less differentiated inputs progressing from Bpc to Bi to Bmc.

Disclosures: A.C. McHale: None. **J.L. Fudge:** None.

Poster

774. Social Behavior: Systems and Circuits

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Program #/Poster #: 774.07/V5

Topic: G.03. Emotion

Support: NIH DC04845
NIH MH105624
Univ. Roch. Center for Visual Sciences

Univ. Roch. Schmitt Program for Integrative Neuroscience

Title: Specificity of an amygdala-prefrontal projection for integrating emotional and multisensory information in the macaque

Authors: *K. K. SHARMA[1], M. M. DIEHL[3], J. L. FUDGE[4], L. M. ROMANSKI[2];
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Abstract: The ventrolateral prefrontal cortex (VLPFC) is a site of multisensory integration that is highly responsive to species-specific faces and vocalizations in both monkeys and humans. Face cells and face patches have been found in the macaque VLPFC and studies in humans indicate that a subregion of the VLPFC is critical for the identification of facial expressions. The amygdala is also highly active during the processing of facial and emotional expressions. Within the amygdala, the basal nucleus is a key input to the prefrontal cortex and is massively expanded in primates. In macaques, the basal nucleus has three sub-nuclei with unique and overlapping projections to the prefrontal cortex, thereby participating in distinct but complementary microcircuits. To achieve precise insight into the potential circuit function of amygdala projections to the VLPFC, we injected bidirectional tracers into face and vocalization-responsive regions of the VLPFC and mapped retrogradely labeled cells within the amygdala. In previous electrophysiology experiments, macaques viewed or heard vocalizations, facial gestures, or audiovisual combinations of faces and vocalizations as part of a presentation task or an audiovisual working memory task. Injections of dextran-conjugated tracers were subsequently placed at VLPFC sites with a high concentration of cells responsive to species-specific vocalizations (auditory), faces (visual), or simultaneous presentations of both stimuli (multisensory). 14-21 days post-injection, animals were perfused and the brain was processed for immunocytochemical localization of labelled cells and fibers. In addition to connectivity with auditory association and inferotemporal cortex (previously presented), tracer injections resulted in dense concentrations of retrogradely labeled cells that were consistently found in the basal nucleus and were highly restricted to the intermediate (Bi) and magnocellular (Bmc) subdivisions of the basal nucleus. Our results establish a direct connection between the basal nucleus of the amygdala and VLPFC sites that process and integrate faces and voices. Furthermore, this projection arises from a highly specific portion of the basal nucleus that has established connections to occipital and temporal sensory and association cortices. Our findings illustrate a pathway by which the amygdala may participate in the processing of multisensory, social stimuli in the prefrontal cortex.

Disclosures: K.K. Sharma: None. **M.M. Diehl:** None. **J.L. Fudge:** None. **L.M. Romanski:** None.

Poster

774. Social Behavior: Systems and Circuits

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 774.08/V6

Topic: G.03. Emotion

Support: NIMH IRP

Title: Chemogenetic investigation of ventral hippocampus and orbitofrontal cortex interaction in social behavior

Authors: *A. ALIBRO, G. LARYEA, O. ABUBAKARE, Y. CHUDASAMA;
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Abstract: Fronto-temporal interactions are critical for the normal expression of cognitive and socioemotional behaviors. In rats, lesions of the hippocampus have a large impact on social behavior causing disorganized nest building, altered social interactions and abnormal social learning and memory (e.g., Bunsey and Eichenbaum, 1995; Hippocampus, 5: 546-556). Lesions of the orbitofrontal cortex (OFC) also affect social behavior by altering emotional responsiveness towards other rats which in some cases expresses as heightened aggression (e.g., Rudebeck et al., 2007, EJN, 26:2315-2326). The ventral hippocampus (vHC) sends a direct projection to the OFC suggesting that these two regions work closely together in controlling certain aspects of social interactive behavior. To date, the functional interaction between the vHC and OFC with respect to social behavior has not been systemically addressed.
In this study, we used a DREADDs mediated approach to disconnect the interaction between the vHC and OFC. Rats received unilateral injections of the inhibitory DREADDs construct, AAV8-hSyn-hM4D(Gi)-mCherry, in either opposite hemispheres (contralateral, n= 10) or the same hemisphere (ipsilateral, n= 6) while the control group was injected with AAV8-hSyn-GFP (n= 8) in contralateral hemispheres. The animals were first tested on discrimination learning, flexibility and decision-making to assess basic cognitive functions. Subsequently, the animals were tested on a social interaction task to examine how the rats behaved towards familiar or novel conspecifics. Ten minutes prior to the beginning of each tasks, rats were administered clozapine or vehicle (20% DMSO in water) in a counterbalanced design. Preliminary data indicates that although DREADDS mediated inhibition of the vHC and OFC interaction does not impact associative learning and decision-making per se, it appears to influence the degree of social affiliation in rats.

Disclosures: A. Alibro: None. **G. Laryea:** None. **O. Abubakare:** None. **Y. Chudasama:** None.

Poster

774. Social Behavior: Systems and Circuits

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 774.09/V7

Topic: G.03. Emotion

Support: NIMH IRP

Title: Cingulotomy alters postnatal development of vocalizations in infant marmosets

Authors: *Y. CHUDASAMA, G. NAGARAJAN;
Section on Behavioral Neurosci., Natl. Inst. of Mental Hlth., Bethesda, MD

Abstract: Marmosets have a rich repertoire of vocalizations used to convey positive and negative emotional information to family members. Vocal development is easily modulated by environmental changes such as social interaction. Like all mamammalian species, infant marmosets cry to produce reactions from the mother or care-giver. From a developmental perspective, not responding appropriately to the cries of an infant may have detrimental effects on the animals social behavior when adult. Studies using functional ultrasound in adults (Takahashi et al., 2018) and immediate early gene expression in infants (Neuman, 2016) implicate the cingulate cortex (area 24) in the normal expression of vocal calls. Here we examined changes in vocal calls (acoustics) of infant marmosets (postnatal day 10 - 16) before and after a cingulate lesion (NMDA 0.12 M). Vocalizations were recorded using Sennheiser ME 64 and acoustics analysed using Raven Pro. Vocal calls such as phee, tsik, trill and cry were preserved before and after the lesion. One day after the lesion, the acoustic structure of the calls and preference of call types changed substantially; phee calls became unstructured and longer in duration, cries became more frequent, and the number of tsik and trills were reduced. Five days after the surgery, there was a higher rate of tsik and trill calls. In addition, we found that physical contact with a stuffed toy induced a 90-95% reduction in vocalization. Without physical contact, there was a dramatic increase in the number of calls. These data suggest that physical contact for neonatal infants reduces emotional distress and that cingulate cortex lesion does not eliminate vocalizations but rather influences the call by altering its structure and frequency. This alteration in the overall integrity of the vocalization may influence the information or message conveyed to family members and may also influence how family members interact with the infant during development.

Disclosures: Y. Chudasama: None. **G. Nagarajan:** None.

Poster

774. Social Behavior: Systems and Circuits

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 774.10/V8

Topic: G.03. Emotion

Support: NIMH IRP

Title: Connections of the medial and lateral septum in the rat: A viral tracing study

Authors: *J. GOODING[1], G. NAGARAJAN[2], Y. CHUDASAMA[1];
[2]Section on Behavioral Neurosci., [1]Natl. Inst. of Mental Hlth., Bethesda, MD

Abstract: The septal region attracts much attention because of its involvement in the control of a variety of motivational, emotional and cognitive behaviors. Many of these studies involved septal lesions that resulted in extensive damage to both medial and lateral septal nuclei. The behavioral effects of large septal lesions may represent a composite phenomenon that reflects the loss of normal, but different functions of the medial and lateral septal regions. The septohippocampal pathway has been best characterised in anatomic and physiological terms but the anatomic localization of the septum makes it an important relay station between brainstem structures and the telencephalon. To date, there have been no systematic analyses of the anatomical
organization of the medial and lateral septal nuclei. Here we used a retrograde viral tracer called pseudorabies (PRV) to determine their major inputs. We injected PRV-614 (DS Red) and PRV-152 (GFP) into the medial and lateral septum, respectively. The preliminary data show that both lateral and medial septal nuclei receive major input from the piriform cortex consistent with previous reports, and both are densely innervated by the entorhinal cortex. The observed differences between these two regions relate to the hippocampus with only the ventral portion projecting to the lateral septum only. In addition, unlike the medial septum, tracer injections in the lateral septum caused extensive retrograde labelling in the ventral regions of the prefrontal cortex, the pre- and postgenual cingulate cortex, as well as the paraventricular and paratenial nulclei of the midline thalamus. Together, these data indicate the medial and lateral septum can be anatomically differentiated on the basis of their selective diencephalic and telencephalic inputs.
Further studies will disentangle the multisynaptic pathways by which the medial and lateral septum are anatomically organized.

Disclosures: J. Gooding: None. **G. Nagarajan:** None. **Y. Chudasama:** None.

Poster

774. Social Behavior: Systems and Circuits

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 774.11/V9

Topic: G.03. Emotion

Support: NIMH IRP

Title: Galanin receptor 1 in the ventral prefrontal cortex and ventral hippocampus: Implications for fronto-temporal modulation of impulse control

Authors: *K. E. BERKUN[1], F. MESSANVI[1], H. A. WANG[1], H. TEJEDA[1], R. FIELDS[2], Y. CHUDASAMA[1];
[1]NIMH, [2]NINDS, NIH, Bethesda, MD

Abstract: We recently demonstrated that the neuropeptide galanin modulates ventral prefrontal cortex (vPFC) and ventral hippocampal (vHC) actions on impulse control mechanisms in rats. Specifically, we showed that while local infusion of M617, a selective agonist of the galanin receptor 1 (Gal-R1) in the vPFC made rats impulsive, intra-vHC Gal-R1 stimulation had the opposite effect of making rats more controlled and less impulsive. This finding was in the absence of compulsive perseverative responding suggesting a selective mechanism of Gal-R1 mediated modulation of impulse control in prefrontal-hippocampal circuitry. This prompted us to examine the characteristics of vPFC and vHC neurons expressing the galanin 1 receptor. We first used multiplex fluorescent in situ hybridization to determine the expression of Gal-R1 in vPFC and vHC as well as their co-localization with glutamatergic and GABAergic neuron markers. The preliminary results showed that vPFC Gal-R1 mRNA were mostly found in glutamatergic neurons, whereas vHC Gal-R1 mRNA were located in CA1 pyramidal layer and the subiculum. Some signal was also observed in the dentate gyrus granular layer. We then made an adeno-associated virus (AAV) expressing cre under the promoter of Gal-R1and injected this virus, together with another cre-dependent AAV expressing a fluorescent protein, into the vPFC or the vHC. This analysis will be used to characterize the virus and verify its cellular specificity, which will then allow us to determine connectivity of the infected neurons and later optically stimulate or silence them to assess their functions.

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Poster

774. Social Behavior: Systems and Circuits

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 774.12/V10

Topic: G.03. Emotion

Support: NIMH IRP

Title: Sexual dimorphic effects of ventral lateral septal lesions on anxiety related vocalization

Authors: *G. NAGARAJAN, J. GOODING, Y. CHUDASAMA;
Natl. Inst. of Mental Hlth., Bethesda, MD

Abstract: Anxiety disorders pose a major health concern in society with an increased prevalence in the female population and are comorbid with other psychiatric illnesses including depression and schizophrenia. According to one prominent view, the expression of anxiety is caused by anomalies in the septo-hippocampal neural connections associated with conflict resolution. In particular, the ventral hippocampus has been implicated in conflict resolution and rats with large septal lesions display anxiolytic behavior. Accordingly, anatomical studies including our own show that the ventral lateral septum (vLS) is densely innervated by the ventral hippocampus in both male and female rats. While these studies implicate an important role for septal-hippocampal interactions, there has been no systematic attempt to establish sex differences in the behavioral expressions of anxiety. In the first of a series of studies, we examined the effect of vLS lesions on standard anxiety tasks in male and female rats and recorded their vocalizations as a potential index of anxiety. The vLS was lesioned bilaterally using NMDA (n=5/group). Soon after recovery, lesioned males were highly aggressive towards their conspecific lesioned cage mate and had to be separated. In the open field test, lesioned-male rats spent more time in the periphery of the box indicating an anxious state whereas the lesioned-females were less anxious as evidenced by spending more time in the center of the box. With respect to vocalization, after receiving the lesion, the males vocalized more than sham males and lesioned females. Together, these data suggest that despite the normal perseveration of the hippocampal-septal projections, lesions to the vLS show clear sexual dimorphic behavioral changes in anxiety.

Disclosures: G. Nagarajan: None. **J. Gooding:** None. **Y. Chudasama:** None.

Poster

774. Social Behavior: Systems and Circuits

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 774.13/V11

Topic: G.03. Emotion

Title: Alteration of brain connectivity associated with the magnitude of the romantic love in couple

Authors: *J. KIM[1], J. OH[1,2], H. EOM[2], M.-K. KIM[2], J.-J. KIM[1,2];
[1]Yonsei Univ., Seoul, Korea, Republic of; [2]Inst. of Behavioral Sci. in Med., Yonsei Univ. Col. of Med., Seoul, Korea, Republic of

Abstract: Introduction: Romantic love is the evoking one of the most overwhelming affective states and is associated with a desire to enter or maintain a close relationship. Resting state functional magnetic resonance imaging (rsfMRI) studies have found that increased regional homogeneity and functional connectivity (FC) in brain regions involved in the processing of reward, motivation, and emotion regulation network and social cognition network when comparing “in-love” group from “ended-love” and “single” group. However, how the magnitude of the love in the couple is related to the brain, functional structures are not well known. We studied the association between the brain connectivity and the magnitude of the love for one’s partner and from one’s partner. **Method:** rsfMRI and passionate love scale (PLS) were obtained from the 40 couples in the plan of the marriage (Female: N=40, Male: N=40). After standardized preprocessing, region of interest (ROI)-based approach was used to do the ROI to ROI connectivity analysis. The 10 ROIs known as reward, motivation and emotion regulation network [dorsal anterior cingulate cortex (dACC), insula, caudate, amygdala, and nucleus of accumbens] and social cognition network network [temporo-parietal junction (TPJ), posterior cingulate cortex(PCC), medial prefrontal cortex (MPFC), inferior parietal, precuneus] were defined. Correlation analysis was run to explore the association between PLS scores and ROIs’ connectivity. **Results:** 1) One’s PLS score had a positive correlation with the connectivity-strength of ROI to ROI within both insula and dACC but had no correlation with connectivity-strength within the ROI’s of social cognition network. 2) Partner’s PLS score had a positive correlation with connectivity-strength in ROI’s of social cognition network (TPJ and PCC) and reward, motivation and emotion regulation network (dACC, insula and caudate). **Discussion:** This study first provides empirical evidence of the alteration in brain functional architecture associated with the magnitude of love in the couple. Reward, motivation and emotion regulation network is the critical brain region with the degree of love for one’s partner and from one’s partner. Our results may also suggest that partner’s love is more related to social cognition process than one’s love.

Disclosures: **J. Kim:** None. **J. Oh:** None. **H. Eom:** None. **M. Kim:** None. **J. Kim:** None.

Poster

774. Social Behavior: Systems and Circuits

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 774.14/V12

Topic: G.03. Emotion

Support: NIH Grant R01-MH098348

Title: Neural reactivity varies with physical and sexual abuse

Authors: ***H. FREEMAN**[1], J. B. PURCELL[2], D. C. KNIGHT[3];
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Abstract: Physical and sexual abuse during childhood are widespread issues that have been linked to negative psychological, physical, and behavioral outcomes later in life. Approximately 18% of adolescents in the United States have been physically abused, while 12% have been sexually abused. Dysfunction of emotional processes appear to underlie the stress-related symptoms of those exposed to abuse in childhood. Therefore, it is important to investigate the neural function that supports emotion processes in those who have experienced abuse during childhood to better understand the neural basis of abuse-related emotional dysfunction in adulthood. The current study investigated brain activity using functional magnetic resonance imagining (fMRI) with participants who were physically and/or sexually abused during childhood and compared them to non-abused controls. 301 participants between the ages of 17-23 completed a psychosocial stress task based on the Montreal Imaging Stress Task (MIST; Dedovic et al., 2005) during fMRI. Stress-related brain activity was compared between participants who had experienced abuse and a control group that had not experienced the same type of abuse. Physical abuse was associated with decreased orbitofrontal cortex reactivity to stress. Sexual abuse was linked to decreased neural activation within the ventromedial prefrontal cortex, dorsolateral prefrontal cortex, cingulate cortex, and hippocampus. The present results suggest that childhood physical and sexual abuse alters the stress-related neural function of young adults in brain regions associated with emotion expression and regulation. These findings may lead to better understanding of the adult psychopathology that is associated with adverse childhood events.

Disclosures: **H. Freeman:** None. **J.B. Purcell:** None. **D.C. Knight:** None.

Poster

774. Social Behavior: Systems and Circuits

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 774.15/V13

Topic: G.03. Emotion

Support: NIMH Grant MH109545
NIMH Grant MH119422

Title: Corticotropin-releasing factor in the insular cortex increases social exploration in rats

Authors: *N. S. RIEGER, J. A. VARELA, A. DJERDJAJ, J. P. CHRISTIANSON;
Boston Col., Chestnut Hill, MA

Abstract: Assessing affective state is important to complex social behaviors such as empathy and deficits in these evaluations are implicated in a number of disorders including autism. The insular cortex (IC) is a region with myriad sensory inputs that is important to both social behavior and evaluating the emotional state of others. Corticotropin-releasing factor (CRF) is integral to emotion, valence signaling and social behavior. Importantly, CRFR1 receptors are present in IC but the role of CRF in the IC on social behavior is unknown. In acute whole cell recordings of IC pyramidal neurons, bath application of CRF (50 nM) depolarized the resting potential, reduced action potential amplitude and reduced afterdepolarization without affecting other intrinsic properties (i.e. I/O curve); these effects were evident in cells from male and female rats. In acute recordings on a perforated multielectrode array, CRF (50 and 300nM) increased synaptic fEPSP amplitude. This effect was blocked by both the coapplication of a CRFR1 antagonist (CP154526, 10 µM) and the presence of a GABAa receptor antagonist (SR-95531, 2 µM). In whole cell recordings CRF reduced sIPSC frequency and amplitude further indicating a net excitatory effect of CRF on the IC via CRFR1 mediated inhibition of GABAergic interneurons. We tested for insular CRF induced behavioral changes by giving bilateral infusions of CRF (either 50 or 300 nM) to rats and exposing them to either juvenile (~PN31) or adult (~PN51) conspecifics in a social exploration paradigm. Both 50 nM and 300 nM doses increased the amount of time spent interacting with conspecifics indicating a gain of function role of CRF in the insula in social behavior. Taken together, these results show that CRF increases IC excitability leading to increased social exploration of both juveniles and adults.

Disclosures: N.S. Rieger: None. **J.A. Varela:** None. **A. Djerdjaj:** None. **J.P. Christianson:** None.

Poster

774. Social Behavior: Systems and Circuits

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 774.16/V14

Topic: G.03. Emotion

Support: KAKENHI JP 18K10852

Title: Long-term voluntary exercise affected helping behavior mediated by activity of oxytocin neurons in rats

Authors: *Y. LIU, N. KUBOTA, S. AMEMIYA, T. NISHIJIMA, I. KITA;
Tokyo Metropolitan Univ., Tokyo, Japan

Abstract: Several studies have suggested that physical exercise may facilitate prosocial behavior, which is defined as the voluntary behavior intended to be benefit for another, but there are few experimental studies focusing on the effect of exercise on prosocial behavior, conducting in controlled laboratory settings. Hence, whether long-term voluntary exercise affects prosocial behavior and the neural mechanisms underlying the effect of the exercise on prosocial action remain unclear. Previous researches have suggested that empathy is one of the most essential factors for the prosocial behavior and is mediated by activity of oxytocin (OXT) neurons. Thus, it is possible that long-term voluntary exercise may affect the prosocial behavior via the activity of OXT neurons. In the present study, we examined the effect of long-term voluntary exercise for 4 weeks on helping behavior for soaked conspecifics in male rats, and measured neuronal activity of OXT neurons in the hypothalamic paraventricular nucleus (PVN) during helping situation using immunohistochemistry. We also measured neuronal activities in the central nucleus of the amygdala and corticotropin-releasing factor neurons in the PVN in both helping (observer) and soaked (demonstrator) rats in order to evaluate neuronal activities related to empathetic concern in the prosocial behavior. Helping rats were assigned one of two groups to alter the exercise condition; individually housing in the cage with running wheel (EX) or without running wheel (no-EX) for 4 weeks. Then, we observed a helping behavior that a helping rat opens the door for a soaked rat, for 6 consecutive days (maximum for 5 min/day). The time to door-opened and the rate of door-opened were recorded. In addition, the time spent in interaction zone and the duration of grooming were also observed to evaluate helping intention and empathy based on emontional contagion, respectively. Although no significant difference between the groups was obtained in the time to door-opened, the rate of door-opened in EX group was more than that in no-EX group. Furthermore, the time spent in interaction zone and the duration of grooming in the EX group were longer than those in the no-EX group. These results suggest that long-term voluntary exercise may facilitate prosocial behavior by enhancing an ability of empathy. The results of neuronal activity are under consideration.

Disclosures: **Y. Liu:** None. **N. Kubota:** None. **S. Amemiya:** None. **T. Nishijima:** None. **I. Kita:** None.

Poster

775. Mood Disorders: Circuits and Synapses

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 775.01/V15

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: MH101180

Title: Prelimbic medial prefrontal cortex disruption during adolescence increases susceptibility to helpless behavior in adult rats

Authors: *D. L. ULIANA, F. V. GOMES, A. A. GRACE;
Neurosci., Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Background: Major depressive disorder (MDD) is a disabling mental disorder worldwide. Several stress animal models have been used to study the neurobiology of this disorder, including learned helplessness (LH), in which susceptible animals show a failure to escape along with a downregulation of ventral tegmental area (VTA) dopamine (DA) system activity. In LH, the prelimbic portion of the prefrontal cortex (plPFC) plays an important role in the modulation of helpless behavior, but so far there is no evidence indicating that its developmental disruption alters susceptibility to this behavior. **Methods:** Male adolescents (PND 31-33) and adult (PND 70-72) Sprague-Dawley rats were submitted to plPFC lesion surgery and during adulthood (>PND 65) or 1 week later were evaluated in the elevated plus maze. Two days following, the rats were submitted to the LH model to evaluate helpless behavior. Electrophysiology recording in the VTA of DA neurons in adult rats was performed after four days of LH. **Results:** Whereas adult plPFC lesion induced neither anxiety responses (% Time and Entries in open arms) nor increased susceptibility to helpless behavior (Number of escape failures and Latency to escape), adolescent plPFC lesions induced an anxiety response. The plPFC lesion increased the proportion of animals showing helpless behavior in LH at adulthood (adolescent plPFC lesion: 92.3% of helplessness; control group: 42.1% of helplessness rats), increasing the latency to escape and the number of escape failures. In the saline-injected group, the latency to escape and the number of escapes failures were significantly different between helpless and nonhelpless rats. plPFC lesions decreased the number of spontaneously active DA neurons compared to the control group in VTA, similar to that observed in other depression models. No effect of condition was found on firing rate and percentage of spikes in burst. Helpless animals with adolescent plPFC lesion showed a decreased DA population activity in VTA compared to naive rats and nonhelpless rats. **Conclusion:** These data suggest that the disruption of plPFC activity during adolescence increases susceptibility to helpless behavior in

adult rats. Therefore, a predisposition or early life adverse events that impair plPFC activity may enhance susceptibility to depression in adulthood. **Financial support:** MH101180.

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Poster

775. Mood Disorders: Circuits and Synapses

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 775.02/V16

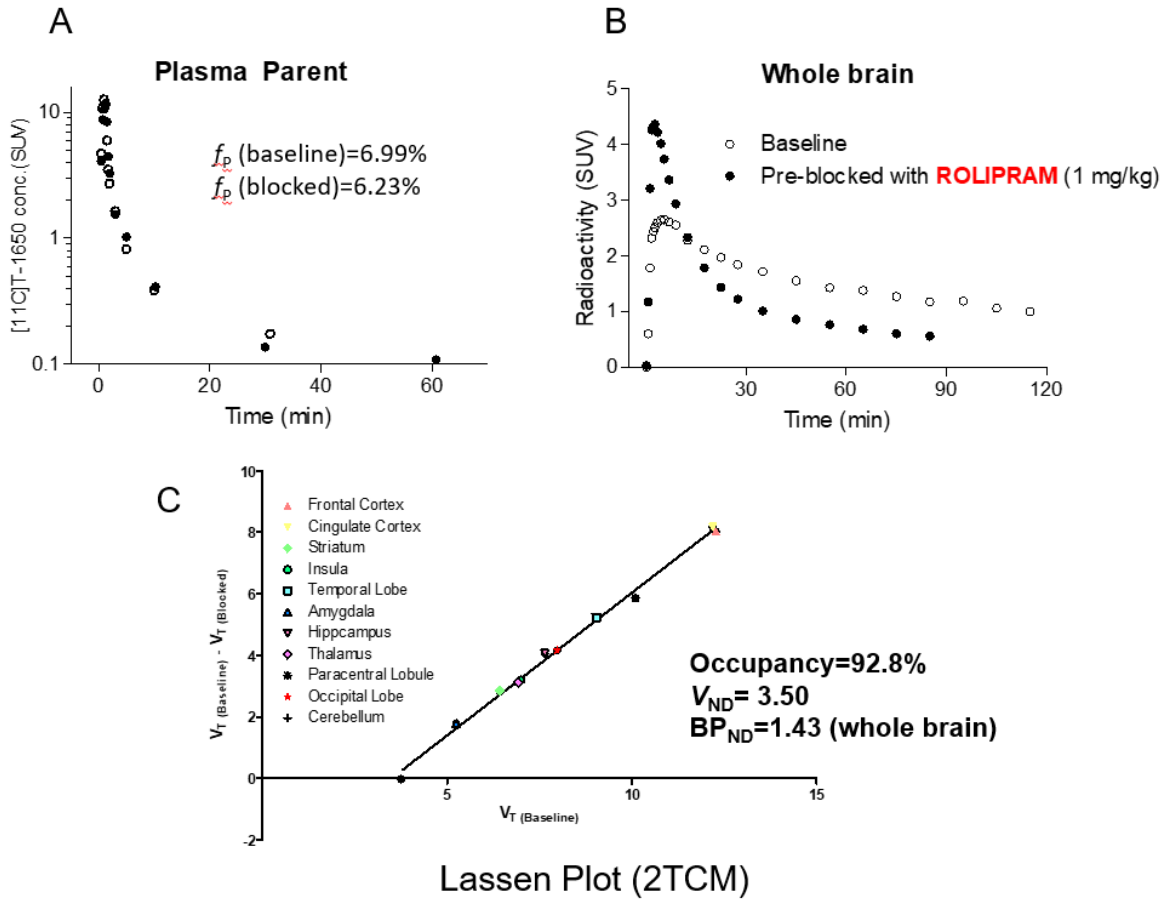
Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Title: Development and initial *in vivo* evaluation in monkey brain of [^{11}C]T-1650, a novel positron emission tomography ligand for phosphodiesterase-4 subtype D

Authors: *R. DICK[1], Y. WAKABAYASHI[1], S. TELU[1], M. FUJITA[2], C. MORSE[1], S. S. ZOGHBI[1], R. L. GLADDING[1], R. NUGENT[3], M. GURNEY[3], V. W. PIKE[1], R. B. INNIS[1]; [1]Mol. Imaging Br., Natl. Inst. of Mental Hlth., Bethesda, MD; [2]Hyogo Col. of Med., Nishinomiya, Japan; [3]Tetra Discovery Partners, Grand Rapids, MI

Abstract: Objective: Phosphodiesterase-4 (PDE4) is an enzyme that metabolizes and terminates the actions of the second messenger cyclic adenosine monophosphate (cAMP). Binding of the PDE4 inhibitor [^{11}C](*R*)-rolipram was previously found to be globally decreased in unmedicated subjects with major depressive disorder (MDD) compared to controls, a finding consistent with the cAMP theory of depression. However, rolipram inhibits all four PDE4 subtypes (4A, 4B, 4C, and 4D). Prior research has shown that type D (PDE4D) may play a key role in cognitive function and depression. This study used positron emission tomography (PET) to assess the newly developed PDE4D-selective radioligand [^{11}C]T-1650 in rhesus monkey. **Methods:** Two brain scans were obtained in one monkey using [^{11}C]T-1650. To measure enzyme-specific uptake, one scan was performed after injection with a selective PDE4 inhibitor, rolipram. Concurrent arterial samples were obtained to measure parent radioligand concentrations. **Results:** The tracer readily entered the brain and showed widespread distribution, with lower binding in the cerebellum. Radioactivity concentration in whole brain peaked at 2.65 SUV (standardized uptake value units) at baseline and 4.37 SUV after rolipram administration (1.0 mg/kg). The plasma parent peaked at 12.6 SUV and 11.8 SUV, respectively, and the plasma parent free fraction was estimated at 6.99% and 6.23%, respectively. In the pharmacokinetic analysis, target enzyme density was quantified as total distribution volume (V_T) using the two-tissue compartment model. V_T was well-identified in all brain regions and showed strong time stability. A Lassen plot was used to graphically estimate occupancy of PDE4D by rolipram for several brain regions. PDE4D occupancy was 92.8% and non-displaceable distribution volume

(V_{ND}) was estimated as 3.50 mL/cm^3 (Fig.1). **Conclusions**: [^{11}C]T-1650 was able to successfully image and quantify PDE4D in monkey brain, thus warranting further investigation of this novel radioligand.



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Poster

775. Mood Disorders: Circuits and Synapses

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 775.03/V17

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: NIH Grant DA045463
NARSAD Independent Investigator Award

Title: Characterization of the long-term effects of inflammatory pain on depressive-like behaviors

Authors: *D. BUREK, N. MASSALY, J. A. MORON-CONCEPCION;
Anesthesiol., Washington Univ. Sch. of Med., St. Louis, MO

Abstract: The rates of suicide and unintentional lethal overdose have doubled in the last 15 years, paralleling increases in reported pain and prescribed opioids. Limited insights into the mechanisms of pain and depression comorbidity underlie inadequate efforts to prevent these fatalities. Both chronic pain and depression involve dynamic recruitment of and allostatic changes to mesolimbic reward circuitry. Emotional responses to pain are associated with activity in the nucleus accumbens (NAcc), which integrates information from multiple brain areas to play a critical role in emotion and motivation, making this structure an ideal candidate for studying pain and depression comorbidity. Interestingly, discrete regions of the NAcc differentially regulate reward and aversion through the kappa opioid receptor (KOR) and its endogenous neuropeptide ligand dynorphin (DYN), by modulating dopamine, glutamate, and serotonin release. Our laboratory recently demonstrated that pain actively recruits this system to drive negative affective states. However, the role of the DYN-KOR system in pain-induced depressive-like behaviors modeled as passivity during acute and inescapable stressors remains to be investigated. Here we demonstrate that persistent inflammatory pain results in longer latency to eat in the novelty-suppressed feeding task, suggesting greater conflict between anxiety and motivation. Persistent inflammatory pain also results in more immobility in the forced swim test but does not impact exploratory behavior in the open field and elevated zero maze, indicating a predominantly depressive-like state. To further uncover NAcc DYN-KOR circuitry, we use retrograde tracing and characterization of KOR-expressing afferents into the NAcc during prolonged inflammatory pain. In parallel, we use the KOR antagonist norBNI directly in the NAcc in an effort to block the effects of pain in the novelty-suppressed feeding, forced swim, and tail suspension tests. This foundation for future studies on specific afferents will elucidate targets to treat pain-induced depressive-like behavior and ultimately improve quality of life for patients and prevent life-threatening episodes.

Disclosures: D. Burek: None. **N. Massaly:** None. **J.A. Moron-Concepcion:** None.

Poster

775. Mood Disorders: Circuits and Synapses

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 775.04/V18

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: NRF Grant 2015R1A5A2008833

Title: Streptozotocin-induced hyperglycemia causes depressive-like behaviors with glial alterations in the medial prefrontal cortex

Authors: H. SON, J. BAEK, J. KANG, ***H. KIM**;
Anat. and Convergence Med. Sci., Gyeongsang Natl. Univ. Med. Sch., Jinju, Korea, Republic of

Abstract: Depression is a devastating psychiatric illness that reduces the quality of life and sometimes leads to suicide. The prevalence of depression is more than three times higher in people with diabetes. The global rising prevalence of diabetes could deteriorate the prevalence of depression. However, the nature of the relationship between depression and diabetes remains unclear. In the present study, we investigated the effect of hyperglycemia on depressive behaviors and related brain regions. To induce hyperglycemia, a core symptom of diabetes, we injected streptozotocin (STZ, 100 mg/kg, i.p.) once. We confirmed that the blood glucose levels were two times higher in STZ-injected mice than the control group and the high blood glucose levels were maintained for at least three weeks. We found that preference about novel social interaction decreases in STZ-injected mice, but not in the basal preference of the social interaction, which could represent anhedonic behavior. Thereafter, we measured anhedonic behaviors using the sucrose preference test and female urine sniffing test to confirm anhedonic symptom. We found that sniffing time of STZ-injected mice decreases while sucrose preference does not change. We also found despair behavior in STZ-injected mice by confirming increased immobility during tail suspension test. We found increased expression of glial fibrillary acidic protein and Iba1 in the medial prefrontal cortex (mPFC) of STZ-induced mice. These results suggest that hyperglycemia could induce depressive-like behaviors and it might be due to glial alteration in the mPFC.

Disclosures: H. Son: None. **J. Baek:** None. **J. Kang:** None. **H. Kim:** None.

Poster

775. Mood Disorders: Circuits and Synapses

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 775.05/V19

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: NIH Grant F31AA025827
NIH Grant R01AA013983
NIH Grant R01DA031734
NIH Grant R01MH108665

Title: Fighting females: Neural and behavioral effects of chronic social defeat stress in female mice

Authors: *E. L. NEWMAN[1], H. E. COVINGTON, III[1], L. CART[1], M. B. BICAKCI[1], K. BURK[1], J. SUH[2], K. J. RESSLER[2], J. F. DEBOLD[1], K. A. MICZEK[1];
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Abstract: Despite the two-fold higher prevalence of mood disorders in females compared to males, most clinical and preclinical research focuses on male subjects. We introduce an ethological murine model to study several cardinal symptoms of affective disorders in the *female targets* of *female aggression*. Housed with a castrated male conspecific, most intact Swiss Webster (CFW) females readily attack unfamiliar C57BL/6J (B6) females, inflicting more than 40 bites/5-min. These highly aggressive CFW females were housed in resident pairs with castrated CFW males and used as stimulus animals for a 10-day female social defeat stress procedure. Daily 5-min defeats occurred in large cages divided by perforated Plexiglas partitions; CFW males were temporarily removed and intruder experimental B6 females were exposed to unfamiliar aggressive CFW females. Following defeats, B6 females were housed opposite the CFW females that defeated them and CFW males were returned to be pair-housed with CFW females. Non-defeated B6 females were housed opposite unfamiliar resident CFW pairs daily, but were never physically attacked. Compared to controls, defeated B6 females exhibited elevated concentrations of plasma corticosterone and increased c-Fos activation in the medial amygdala, ventral lateral septum, ventromedial hypothalamus, and hypothalamic paraventricular nucleus following the final defeat episode. Defeated females also showed vigilance-like behavior and deficits in social interactions, novel object investigation, and nesting as well as greater alcohol intake compared to controls. The duration of social contact increased 24 hrs after defeated females received a single dose of ketamine (20 mg/kg). Ongoing work evaluates the reinforcing strength of aggression in CFW females that work for the opportunity to defeat a submissive female opponent. These novel behavioral methods will encourage further studies of sex-specific neural, physiological, and behavioral adaptations to social stress and on the biological bases for interfemale aggression.

Disclosures: E.L. Newman: None. **H.E. Covington:** None. **L. Cart:** None. **M.B. Bicakci:** None. **K. Burk:** None. **J. Suh:** None. **K.J. Ressler:** None. **J.F. DeBold:** None. **K.A. Miczek:** None.

Poster

775. Mood Disorders: Circuits and Synapses

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 775.06/V20

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: NIMH R01 MH114882
NIMH R01 MH090264

Title: Neural circuitry of social reward deficits following chronic social defeat stress

Authors: *L. LI, M. FLANIGAN, K. B. LECLAIR, L. F. PARISE, K. CHAN, Y. SHIMO, F. CATHOMAS, M. PINTO-KASTER, C. BURNETT, R. DURAND-DE CUTTOLI, H.-Y. LIN, A. AUBRY, S. J. RUSSO;
Nash Family Dept. of Neurosci., Icahn Sch. of Med. At Mount Sinai, New York, NY

Abstract: Major Depressive Disorder (MDD) is one of the most common mental disorders. Social stressors often increase the incidence of depression in humans, and repeated exposures to social defeat stress in rodents causes a strong depression-like phenotype marked by anhedonia and social-avoidance. One of the fundamental questions arising from these studies in rodents is whether social avoidance could occur due to a loss of social reward. To test this possibility, we measured social conditioned place preference (CPP) in susceptible and resilient mice following chronic social defat stress. Here we show that CSDS, impairs formation of social CPP in susceptible, but not resilient, male and female mice. We next performed a whole brain c-Fos study and found several brain regions showing differential activation of c-Fos expression between susceptible and resilient mice, such as the prelimbic (PL), infralimbic (IL), Nucleus accumbens (NAc), lateral Hypothalamus (LH), supraoptic nucleus (SON) and Periaqueductal gray (PAG). Interestingly, we find different c-Fos expression patterns in the paraventricular hypothalamus (PVH), between susceptible and resilient mice. Our next step is to determine the molecular identity of cell types in the PVH differentially activated by stress and to then to test whether PVH circuitry in causally linked to loss of social reward in susceptible mice. This research may provide a circuit-level framework to understanding deficits in social behavior across a range of stress-related illnesses such as depression and anxiety.

Disclosures: L. Li: None. **M. Flanigan:** None. **K.B. LeClair:** None. **L.F. Parise:** None. **K. Chan:** None. **Y. Shimo:** None. **F. Cathomas:** None. **M. Pinto-Kaster:** None. **C. Burnett:** None. **R. Durand-De Cuttoli:** None. **H. Lin:** None. **A. Aubry:** None. **S.J. Russo:** None.

Poster

775. Mood Disorders: Circuits and Synapses

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 775.07/V21

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Title: Reduced synaptic inhibition onto CA1 pyramidal neurons induces anti-despair-like behavior in RalBP1 mutant mice

Authors: *S. YOON, W. SONG, S. OH, M.-H. KIM;
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Abstract: Balanced excitatory and inhibitory (E/I) neurotransmission is critical for normal brain functions including mood regulation in animals. Here we show that the deficiency of RalBP1 reduces the density of interneurons in the hippocampus and behavioral despair in mice. Mice deficient of RalBP1 ($RalBP1^{-/-}$), a multifunctional protein that interacts with the small GTPase RalA and RalB, displayed fewer interneurons in hippocampal CA1 regions and reduced inhibitory synaptic events in CA1 pyramidal neurons but normal excitatory synaptic transmission. Behaviorally, $RalBP1^{-/-}$ mice were less immobile during both the tail suspension test and the forced swimming test. Bilateral infusion of Muscimol, the $GABA_AR$ agonist, into hippocampal CA1 regions induced despair-like behaviors in WT mice, while knockdown of Gabrg2 in CA1 neurons reduces behavioral despairs. Chemogenetic activation and suppression of interneurons in CA1 areas produced despair-like and anti-depressant behaviors, respectively. Together, these results suggest that the E/I balance in hippocampal CA1 neuron influences behavioral despairs and mood regulation.

Disclosures: S. Yoon: None. **W. Song:** None. **S. Oh:** None. **M. Kim:** None.

Poster

775. Mood Disorders: Circuits and Synapses

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 775.08/V22

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Title: Inhibition of the medial prefrontal cortex attenuates symptoms of depression in Long Evans rats

Authors: *J. J. CORTRIGHT, S. ACKERMAN, L. LANDAETA, L. WILLARD;
Univ. of Wisconsin-River Falls, River Falls, WI

Abstract: Self-focus (i.e. the process by which one engages in self-referential processing) is a core issue in the psychopathology of major depression, which affects 350 million people worldwide. Previous studies have used functional neuroimaging to identify that the cortical midline structures, including the medial prefrontal cortex (mPFC), play a key role in self-referential processing in depressed subjects. The current study investigates the hypothesized link between the mPFC and depression using an animal model of learned helplessness to measure self-referential processing. It is hypothesized that a decrease in symptoms of depression will be seen in animals that have undergone inhibition of the mPFC. This research holds significance in that it builds on previous studies, with conflicting results, that have aimed to link specific patterns of activity to the PFC as mediating symptoms of depression. Further examination of the

mPFC is therefore warranted not only as a possible precursor to the implication of its involvement in mediating depression, but also in order to provide support for a theory of dominant pattern of brain activity (inhibition) which interacts with symptoms of depression. The current study utilized female Long Evans rats in order to more accurately generalize findings to the population of women, which make up the majority of depressed individuals in humans. Subjects were exposed to 28 days of randomized stressors during adulthood including forced swim, cage tilt, wet bedding, mild restraint and restriction of food and water. Control animals were housed in pairs, while animals exposed to randomized stress were housed in isolation. Following surgical placement of guide cannula animals were either infused with an inhibitory cocktail (0.3 nmol/0.5µl/side baclofen/0.3 nmol/0.5µl/side muscimol) or sham (artificial cerebrospinal fluid) before being tested for resiliency against learned helplessness. Subjects were tested for latency in a forced swim test and hot plate test, for motivation in a radial arm maze, for lethargy in an open field test, and for anhedonia using sugar pellets. To date, a significant decrease in latency in the forced swim test and hot plate test has been found in stress-exposed animals which had undergone inhibition of the mPFC compared to controls. Currently, attenuation of learned helplessness symptoms in other tests is being analyzed. Collectively, these findings hold significance in that they build on recent research that has aimed to link areas of the PFC to symptoms of depression.

Disclosures: J.J. Cortright: None. **S. Ackerman:** None. **L. Landaeta:** None. **L. Willard:** None.

Poster

775. Mood Disorders: Circuits and Synapses

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 775.09/V23

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Title: The topography of GABA/glutamate co-release in the rodent and primate lateral habenula

Authors: *L. RIOS, C. TAN, K. GLEASON, C. TAMMINGA, S. SHABEL;
UT Southwestern Med. Ctr., Dallas, TX

Abstract: The lateral habenula (LHb) responds to aversive stimuli, and its hyperactivity is hypothesized to contribute to depression. Recent studies in rodents have shown that inputs from the basal ganglia and ventral tegmental area to the lateral habenula co-release GABA with glutamate; the balance of GABA and glutamate at these synapses may regulate LHb responses to aversive stimuli and mood. In the present study, we investigated whether the magnitude and topography of co-release of GABA and glutamate in the LHb is conserved in primates. Our data indicate substantial co-labeling of GAD (the synthesizing enzyme for GABA) and VGLUT2 (vesicular glutamate transporter) in synaptic terminals in the monkey and human LHb, consistent

with co-release of GABA and glutamate from individual terminals onto primate LHb neurons. Preliminary data suggest that there are differences in the topography of co-release in the primate and rodent LHb, perhaps due to expansion of the LHb in primates. Thus, co-release of GABA with glutamate may be a conserved mechanism for regulation of LHb activity and mood in rodents and primates.

Disclosures: L. Rios: None. **C. Tan:** None. **K. Gleason:** None. **C. Tamminga:** None. **S. Shabel:** None.

Poster

775. Mood Disorders: Circuits and Synapses

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 775.10/V24

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Title: Epigenetic regulation of hippocampal Bdnf predicts behavioral vulnerability to chronic stress

Authors: *C. LI[1,2], F. MENG[2], W. WANG[2], J. LIU[2], X. LIU[2], M. GUO[2], X.-Y. LU[1];
[1]Dept. of Neurosci. & Regenerative Med., Med. Col. of Georgia at Augusta Univ., Augusta, GA;
[2]Inst. for Metabolic and Neuropsychiatric Disorders, Binzhou Med. Univ. Hosp., Binzhou, China

Abstract: Chronic stress can cause depression in susceptible individuals, however, the underlying mechanisms remain elusive. Chronic social defeat stress (CSDS) and chronic unpredictable stress (CUS) are the most widely used animal models of depression. Using these two animal models, we examined expression of brain-derived neurotrophic factor (*Bdnf*) exon I, II, III, IV and VI-containing transcripts and histone modifications at individual *Bdnf* promoters in the hippocampus. Both CSDS and CUS mice were separated into stress-susceptible and resilient subgroups based upon their social interaction ratios and sucrose preference ratios, respectively. While CSDS decreased expression of total *Bdnf* mRNA in the hippocampus of both susceptible and resilient groups, only susceptible CUS mice showed reduced total mRNA levels. CSDS and CUS mice displayed distinct patterns of expression of exon-specific *Bdnf* transcripts and histone acetylation and methylation at their corresponding promoters. Furthermore, deletion of *Bdnf* specifically in the hippocampal dentate gyrus increased behavioral susceptibility to subthreshold CUS. These results suggest that histone modifications of the *bdnf* gene may underlie differential expression of exon-specific *Bdnf* transcripts and stress susceptibility in the CSDS and CUS models of depression.

Disclosures: C. Li: None. **F. Meng:** None. **W. Wang:** None. **J. Liu:** None. **X. Liu:** None. **M. Guo:** None. **X. Lu:** None.

Poster

775. Mood Disorders: Circuits and Synapses

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 775.11/V25

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

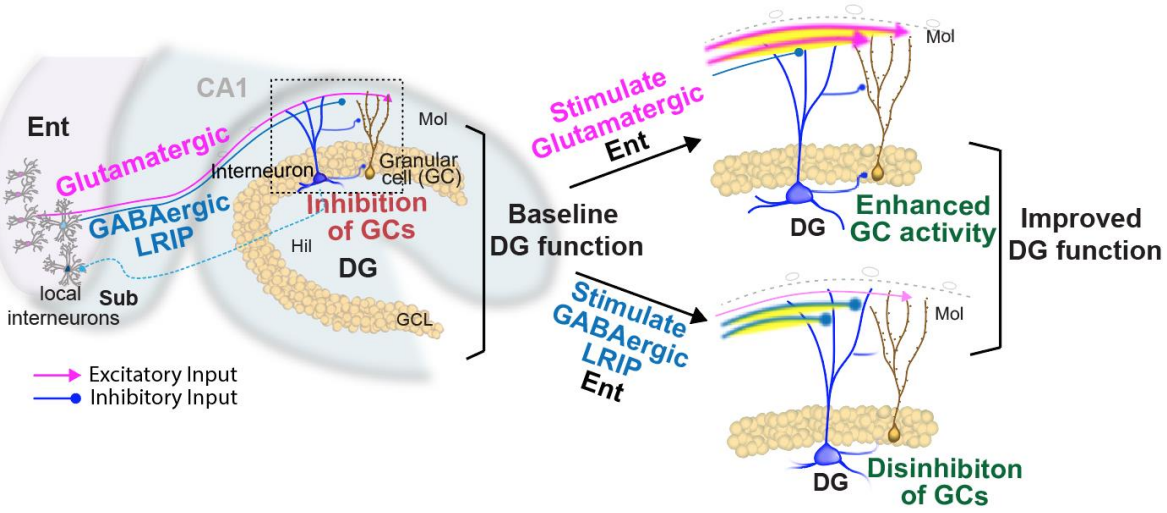
Support: 80NSSC17K0060 (NASA; AJE)
CHOP Department of Anesthesiology and Critical Care Development Funds (AJE)
PENN McCabe award (SY)

Title: GABAergic entorhinal cortex control of hippocampal function in stress-induced behavior adaptations: Cellular and circuitry mechanisms

Authors: *S. YUN[1,2], F. H. TRAN[1], I. SOLER[1,2], R. P. REYNOLDS[1], M. SUAREZ[1], A. J. EISCH[1,2];
[1]Children's Hosp. of Philadelphia Res. Ctr., Philadelphia, PA; [2]Perelman Med. Center, Univ. of Pennsylvania, Philadelphia, PA

Abstract: Humans with and rodent models for Major Depressive Disorder (MDD) are marked by dysregulated hippocampal circuitry, and several successful antidepressant treatments (antidepressant medication or brain stimulation techniques) ameliorate these hippocampal changes. Thus, a promising framework for discovery of new antidepressants has emerged: find treatments that "recalibrate" depression-linked dysfunctional neural circuits and behavior. Strikingly, while direct stimulation of the hippocampus has generally negative effects, we recently discovered that chronic stimulation of glutamatergic entorhinal cortex [Ent]-DG circuitry is antidepressive in a mouse model for depression (Yun et al., 2018 Nature Med). In addition to Ent-DG glutamateric neurons, it is known that a subset of Ent-hippocampus GABAergic long-range projecting neurons (LRIP) contribute to hippocampal network activity and function (i.e. memory). However, it is unknown if Ent GABAergic LRIPs regulate depressive-like behaviors. Here we used chemogenetics to control the excitability of either Somatostatin (SST) or Parvalbumin (PV) Ent cells via AAV-DIO-hM3Dq or AAV-DIO-mCherry infusion into the Ent of male mice. Repeated stimulation of Ent-CA1/CA3 LRIPs (SST+ or PV+ cells) increased immobility in FST after chronic restraint stress, implying depressive-like behavior. In contrast, stimulation of Ent-DG LRIPs (SST+ cells) decreased FST immobility. Given these data, we now are examining psychosocial stress-induced DG dysfunction (e.g. pattern separation, social and non-social approach behavior, neurogenesis) after stimulation of SST+ Ent-DG projecting LRIPs and neuroanatomical functional complexity of Ent GABAergic LRIPS via monosynaptic tracing and *in vivo* Ca^{2+} imaging. Our study is

revealing the broad implications that Ent-hippocampus projecting GABAergic LRIPs have for understanding MDD and may guide future treatments.



Disclosures: **S. Yun:** None. **F.H. Tran:** None. **I. Soler:** None. **R.P. Reynolds:** None. **M. Suarez:** None. **A.J. Eisch:** None.

Poster

775. Mood Disorders: Circuits and Synapses

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 775.12/V26

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: NIMH MH105910

Title: Role of cortical somatostatin and parvalbumin interneurons in the rapid antidepressant actions of scopolamine

Authors: *M. V. FOGAÇA, M. WU, X.-Y. LI, R. S. DUMAN;
Psychiatry, Yale Univ., New Haven, CT

Abstract: Currently available antidepressants have relatively low efficacy and delayed therapeutic responses to alleviate Major Depressive Disorder (MDD) symptoms. A single dose of scopolamine, a nonselective muscarinic acetylcholine receptor antagonist induces rapid antidepressant effects in patients. Scopolamine was shown to act through blockade of M1-type receptors on GABA interneurons, and we have recently found that chemogenic activation of somatostatin (SST) and parvalbumin (PV) interneurons abolishes the antidepressant responses of scopolamine. Using Cre-dependent Design Receptors Exclusively Activated by Designer Drugs

(DREADD), we tested if the inhibition of GABA interneurons in the medial prefrontal cortex (mPFC) could mimic the antidepressant actions of scopolamine, as well as its molecular changes. Using Sst-Cre M1 deletion mice, we also evaluated if scopolamine effects could be mediated by M1 receptors specifically located in SST interneurons and if there are sex differences guiding these responses. Here we used mice that express Cre-recombinase in GABA interneurons (Gad1-Cre) or in specific subpopulations, such as PV (Pv-Cre) and SST (Sst-Cre). The viral vector (pAAV-hSyn-DIO-hM4D(Gi)-mCherry) was infused into mice mPFC to induce Cre-recombinase-dependent expression of Gi-coupled hM4Di receptors, which are sensitive to clozapine-N-oxide (CNO). Two weeks later, mice were tested in three different timepoints, receiving 3 injections of CNO (2.5 mg/kg) with the first administration starting ~24 h before the test, one injection of CNO 4 h before the test or one injection of CNO 30 min before the test. After injections, the mice were subjected to the forced swim test (FST) or to the novelty suppressed feeding test (NSFT). The efficiency of viral infusion was confirmed at the end by histology and electrophysiological recordings. Stimulation of Gad1-, Pv- and Sst-Cre interneurons using the protocol of 3 CNO injections induced antidepressant-like effects, but was ineffective after 4h or 30 min of administration. In addition, the actions of scopolamine in the FST and NSFT were blocked in the Sst-Cre M1 deletion mice in both male and female. Moreover, scopolamine increased levels of the glutamatergic and GABAergic-related proteins in the mPFC. We are currently testing if similar molecular changes could be found in hM4Di animals. The results are consistent with the hypothesis that the initial trigger for the rapid antidepressant action of scopolamine is antagonism of M1 receptors on mPFC GABA interneurons, which then promotes an enhancement in glutamatergic neurotransmission and rapid synaptic changes.

Disclosures: **M. V. Fogaça:** None. **M. Wu:** None. **X. Li:** None. **R.S. Duman:** None.

Poster

775. Mood Disorders: Circuits and Synapses

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Program #/Poster #: 775.13/V27

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: NIH DA009082

Title: Ultrastructural localization of serotonergic 5-HT3 receptors in the rat locus coeruleus

Authors: *I. HORRILLO[1], B. A. REYES[2], T. LHAMO[3], E. J. VAN BOCKSTAELE[4]; [1]Pharmacol., Univ. of the Basque Country UPV/EHU; Ctr. de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Bilbao, Spain; [2]Pharmacol. & Physiol., [3]Pharmacol. and Physiol., Drexel Univ., Philadelphia, PA; [4]Dept. of Pharmacol. & Physiol., Drexel Univ. Col. Of Med., Philadelphia, PA

Abstract: Deficiency of monoamines, norepinephrine (NE) and serotonin (5-HT) has been implicated in the pathophysiology of depressive disorders. Neurochemical studies show interactions between serotonin and NE systems. Lesioning of the serotonergic nuclei increases LC neuronal firing whereas electrical stimulation of the serotonergic pathways inhibits noradrenergic neurotransmission. Serotonin has been shown to modulate noradrenergic pathways through the involvement of the serotonin receptors. Pharmacological studies have shown that activation of the 5-HT3 receptor (5-HT3) in the locus coeruleus (LC), the primary noradrenergic nucleus in the brain, decreases the firing of LC neurons and release of NE in prefrontal cortex. A recent pharmacological study shows a functional role of 5-HT3 in the LC. However, the cellular substrates for interactions between 5-HT3 and noradrenergic LC has not been elucidated. In the present study, we investigated the cellular sites for interactions between 5-HT3 and noradrenergic neurons in the LC using immunofluorescence and immunoelectron microscopy. Tissue sections were collected through the LC and processed for immunocytochemical detection of tyrosine hydroxylase (TH), a marker for catecholaminergic neurons, and 5-HT3. Immunofluorescence microscopy revealed that TH-containing perikarya and somatodendritic processes exhibited 5-HT3 immunoreactivity. Ultrastructural analysis using immunoperoxidase labeling for TH and immunogold-silver labeling for 5-HT3 confirmed that 5-HT3 are localized within TH-containing somatodendritic processes. Taken together, these results indicate anatomical substrates for proposed interactions between the noradrenergic and serotonergic systems in the LC.

Disclosures: I. Horrillo: None. **B.A. Reyes:** None. **T. Lhamo:** None. **E.J. Van Bockstaele:** None.

Poster

775. Mood Disorders: Circuits and Synapses

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 775.14/V28

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: R01MH112716-01

Title: Nucleus accumbens expression of SIRT1 mediates cell-type specific alterations in neuronal morphology in a mouse model of depression

Authors: *T. CALL, H.-D. KIM, A. SUMMERS, N. T. QUINTUS, R. JOHNSON, D. FERGUSON;
Univ. of Arizona Col. of Medicine- Phoenix, Phoenix, AZ

Abstract: Major depressive disorder (MDD) affects over 300 million people worldwide and is the leading cause of lost productivity and workplace disability. The nucleus accumbens (NAc) is

the reward processing center in the brain. Disruption of function in the NAc has been tied to many psychiatric disorders, including MDD and drug addiction. The NAc is comprised mostly of medium spiny neurons (MSNs) which can be divided into two subtypes based on the enrichment of dopamine receptors, D1- or D2- type receptors. While studies have found differing responses between these neuronal subtypes in animal models of MDD, the exact role of these different subtypes in MDD remains elusive. Recent studies have illuminated sirtuin-1 (SIRT1) as a protein of interest affected by chronic social defeat stress that, when elevated in the NAc, results in susceptibility to depressive-like symptoms. Indeed, SIRT1 has been found to play a role in altering neuronal morphology in other brain regions, such as the hippocampus and prefrontal cortex. However, the role and effects that SIRT1 plays in modifying neuronal morphology within the NAc has yet to be established. Here we seek to elucidate the action of SIRT1 on neuronal morphology following overexpression or knock out in D1 or D2 cell-types. To this end, we used transgenic and viral (HSV) approaches to precisely increase or decrease SIRT1 expression in D1 and D2 neurons within the NAc. Morphological changes in these neurons were evaluated via DiOlistic labeling. We found SIRT1-mediated changes in spine densities and dendritic complexities. Understanding the morphology of the NAc in models of MDD will facilitate the generation of novel targeted treatments and the next generation of antidepressant interventions.

Disclosures: T. Call: None. **H. Kim:** None. **A. Summers:** None. **N.T. Quintus:** None. **R. Johnson:** None. **D. Ferguson:** None.

Poster

775. Mood Disorders: Circuits and Synapses

Location: Hall A

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Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

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Grants-in-Aid for Scientific Research on Innovative Areas “Adaptive Circuit Shift” (26112009)
the Strategic Research Program for Brain Sciences (SRPBS)

Title: The measurement of motivational level by using a modified version of the Brinkman board test in monkeys

Authors: *S. NAKAMURA, K.-I. TSUTSUI;
Lab. of Systems Neurosci., Grad. Sch. of Life Sciences, Tohoku Univ., Sendai, Japan

Abstract: In this study, we aimed to quantify the motivational level of monkeys by introducing a modified version of the Brinkman board test, which was originally developed to test manual dexterity. We required monkeys to grasp a piece of food reward placed in vertically and

horizontally oriented wells on the board. The board consisted of 50 slots, and the food pieces were randomly placed in 12 slots per session. Two types of boards were used to change the difficulty of the test: one had narrow (difficult) and the other had wide (easy) wells. Multiple sessions were continued until the monkeys spontaneously stopped performing. Two parameters were quantified: the number of sessions the monkey performed as an index of the motivational level and the average time the monkey spent to finish a single session as an index of the motor ability. In order to validate this paradigm, we examined how a decrease in the motivational level of the monkeys would affect the performance of the behavioral test. To lower their motivational level to the behavioral test, we gave the monkeys a moderate amount of the same food reward before the behavioral test. As a result, we found a significant decrease in the number of sessions the monkey performed in difficult condition, compared with the baseline level. However, such change was not observed in easy condition. The average time consumption did not change in both conditions. We further examined how the inhibition of the activity of the ventral medial frontal cortex (MFC) including the rostroventral area of the anterior cingulate cortex (ACC), which has long been implicated in motivational behavior, would affect the performance of the behavioral test by applying low-frequency repetitive transcranial magnetic stimulation (LF-rTMS). The LF-rTMS (1 Hz, 1200 pulses in total) targeting this brain region induced a significant decrease in the number of sessions in the difficult condition, but not in the easy condition, whereas the average time consumption per session did not change. In contrast, such change was not observed following the LF-rTMS to the other MFC regions. Together, these results indicate the importance of the ventral MFC including the rostroventral part of the ACC in motivational control, and show the validity of this behavioral test as the measurement of the motivational level in monkeys.

Disclosures: **S. Nakamura:** None. **K. Tsutsui:** None.

Poster

775. Mood Disorders: Circuits and Synapses

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 775.16/V30

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

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National Key Research and Development Program of China 2017YFC0803608

Title: Perineuronal nets in the prefrontal cortex regulate vulnerability to stress in rats

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Abstract: Major depressive disorder is a leading cause of disease burden globally. Studies have shown that the prefrontal cortex (PFC) plays an important role in the resilience and susceptibility to depression, but the underlying mechanisms remain unknown. In the present study, we found that an extracellular matrix structure, perineuronal nets (PNNs), that is localized on parvalbumin-positive (PV+) interneurons in the PFC mediated the vulnerability to stress. The maturation of PNNs alleviated the vulnerability to stress. Adolescent rats exhibited a lower level of PNNs in the medial PFC (mPFC) compared with adult rats and also exhibited greater vulnerability to chronic stress. The degradation of PNNs in the mPFC promoted vulnerability to stress in adult rats and impaired GABAergic transmission in the mPFC. Administration of the noncompetitive N-methyl-D-aspartate receptor antagonist ketamine exerted rapid antidepressant-like effects in rats and promoted the structural recovery of PNNs. A single administration of ketamine also reversed the changes in PV+ interneuron activity following chronic stress. These findings indicate that PNNs are important structures in the susceptibility and resilience to stress and highlight a possible neuron-specific target for the antidepressant effect of ketamine.

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Poster

775. Mood Disorders: Circuits and Synapses

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

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Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

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Title: Orexinergic projection to the dorsal raphe regulates affective behaviors in an animal model of SAD

Authors: *F. SAMAD[1], H. XIONG[1], S. DAOUD[1], K. LINNING-DUFFY[1], F. P. MANFREDSSON[2], J. S. LONSTEIN[3], L. YAN[3];
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Abstract: The neuropeptide orexin/hypocretin has been implicated in many functions including wakefulness, reward, and mood. The objective of the present study was to probe the role of hypothalamic orexinergic projections to the midbrain dorsal raphe nucleus (DRN) in regulating anxiety- and depression-like behavior in an animal model of Seasonal Affective Disorder (SAD). SAD is a major depressive disorder recurring in winter when there is lower intensity of sunlight. Our group has developed an animal model of SAD utilizing the diurnal Nile grass rat (*Arvicanthis niloticus*), which shows increased depression- and anxiety-like behaviors when housed in a 12:12 hr light:dark (LD) cycle but with a winter-like low daylight intensity (dimLD) compared to those housed in a 12:12 hr LD cycle involving bright, summer-like daylight intensity (brLD). We also found that the depressive behaviors were accompanied by a reduction in central orexin in grass rats. In this study, we tested the hypothesis that light modulates affective behaviors through an orexin receptor 1 (OX1R) pathway from the hypothalamus to the DRN. Grass rats were injected with an AAV expressing OX1R-shRNA or scrambled control (SC)-shRNA into the DRN, followed by 4 weeks of brLD housing prior to behavioral assessment in an open field test (OFT) and forced swim test (FST). During the OFT, animals injected with OX1R-shRNA into the DRN spent less time in the center of the OFT arena and deposited more fecal boli compared to either a group of DRN-missed OX1R-shRNA controls or scrambled shRNA controls. During the FST, the DRN OX1R-shRNA group spent less time climbing the wall (escape behavior) and more time immobile (behavioral despair), compared to the control groups. These results revealed that AAV-mediated knockdown of OX1R within the DRN leads to increase depression- and anxiety- like behaviors in grass rats housed in the summer-like brLD. The results suggest that the antidepressant/mood-lifting effects of bright sunny days are partly mediated by orexinergic pathways, particularly the orexinergic input to the serotonin-rich DRN.

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Poster

776. Mood Disorders: Molecular Mechanisms and Approaches

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 776.01/V32

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Title: Manipulation of resilient key drivers alters susceptibility to chronic social defeat stress

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Abstract: Major depressive disorder (MDD) is a significant public health problem. Though MDD incidence varies with ethnicity, as many as 18% of Americans will experience MDD during their lifetime. Genetics and environmental factors like chronic social stress play a role in the development of MDD. Chronic social defeat currently serves as the best animal model stress paradigm to study depressive like behaviors. Using a Weighted Gene Co-expression Network Analysis (WGCNA) on mice resilient to social defeat determined a unique enrichment of gene expression within the brown module. A undirected key driver analysis was then conducted using ARACNE (algorithm for reconstruction of accurate cellular networks) based on gene-gene correlations, GPRIN1 was found to be one of 3 key drivers within the module. The expression of key drivers within the resilient specific brown module were manipulated in order to determine the role of resilient-specific modules in preventing depression like behavior in animal models of MDD. To accomplish this, GPRIN1 was overexpressed using a Herpes Simplex Virus (HSV) in 20 mice. As a control a group of 20 mice were given the same HSV virus with Green Florescent protein (GFP). To test the effect of viral overexpression mice were exposed to four days of accelerated social defeat, along with a social interaction test. It was determined that the viral overexpression of GPRIN1 promotes resiliency to social defeat stress.

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Poster

776. Mood Disorders: Molecular Mechanisms and Approaches

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Program #/Poster #: 776.02/V33

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: NIMH R01MH106500

Title: The BDNF-TrkB pathway acts through nucleus accumbens D2 expressing neurons to mediate susceptible behavior to social defeat stress

Authors: *M. O. F. PAGLIUSI, Jr[1,2], G. MORAIS-SILVA[3], R. CHANDRA[4], C. R. SARTORI[1], M. LOBO[5];
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Abstract: Depressive disorders affect a significant portion of the world's population. In the United States, for example, 16.2% of inhabitants will experience at least one depressive episode during their lifetime. In addition, according to WHO, depressive disorders are the leading cause of disability in the world, which also highlights the economic relevance associated with

depression. Social defeat stress (SDS), which involves a resident intruder paradigm, has been widely used to induce negative affective states that model symptomatology of depression. Previous studies demonstrate that increased levels of BDNF from the ventral tegmental area (VTA) to the nucleus accumbens (NAc) mediates susceptible behavior to SDS. While it is known that BDNF acts on NAc medium spiny neurons (MSNs) it is unclear if it is acting through dopamine receptor 1 or 2 (D1 or D2) expressing MSNs. To provide insight into this we generated a Cre-inducible adenoassociated virus (AAV) expressing truncated TrkB (Trkb.T1), which lacks the kinase domain thus preventing downstream TrkB signaling. We infused this virus into the NAc of D1-Cre or A2A-Cre mice. Following viral expression we performed SDS followed by social interaction, the splash test, sucrose preference, and the forced swim test. Our data demonstrate that blocking BDNF-TrkB signaling, through TrkB.T1 overexpression, in D2-MSNs prevents stress susceptibility and causes resilient behavior to SDS. In contrast TrkB.T1 expression in D1-MSNs causes a susceptible outcome to a subthreshold (S)SDS. Our studies implicate D2-MSNs as mediating the BDNF-TrkB effects of stress susceptibility, while BDNF acting on D1-MSNs has a protective role in stress.

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Poster

776. Mood Disorders: Molecular Mechanisms and Approaches

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Support: NSFC Grant 31271198, 81121001, 81421061
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Title: Antidepressant effects and underlying mechanisms of roman chamomile essential oil in depressive rats

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Abstract: Depression is called ‘the common cold of mental illness’, which is easy to be neglected, and the pathogenesis of depression remains unclear. Essential oils have long been used as a means of helping people fall asleep and alleviating anxiety, and are considered as a possible antidepressant treatment. At present, our understanding on the mechanism of action of essential oils is scarce; despite their widespread use in alleviating depression no study existed reporting the underlying mechanisms of how essential oils may alleviate depression. In this

study, we aimed to investigate the antidepressant effects and possible underlying mechanisms of Roman chamomile essential oil (RCEO) on depressive-like behaviors in Wistar-Kyoto (WKY) rats. We found that the inhalation of RCEO, or α-pinene, one of the main components of RCEO, for two weeks considerably attenuated the depressive-like behaviors, as witnessed by open-field test, sucrose preference test, and forced swim test. We used isobaric tags for relative and absolute quantitation analysis (iTRAQ), quantitative polymerase chain reaction (qPCR), and western blot (WB) to measure the changes in different mRNA/protein expression levels before and after the inhalation of α-pinene in WKY rats, and compared their expression levels in the hippocampus and prefrontal cortex (PFC) with control Wistar rats. Our iTRAQ analysis showed that inhalation of α-pinene increased the expression of proteins that are involved in oxidative phosphorylation, such as cytochrome c oxidase subunit 6C-2, cytochrome c oxidase subunit 7A2, and ATPase inhibitor in the hippocampus. iTRAQ analysis also revealed an upregulation of the calcium-binding protein, parvalbumin (PV, 2.8-fold upregulation in the hippocampus), which is known to regulate animal behavior, following α-pinene treatment. Upregulation of PV at its transcriptional and translational levels following α-pinene treatment were also confirmed by qPCR (Vehicle, 1±0.06, n=3; α-pinene, 1.28±0.06, n=3; P=0.013) and WB (Vehicle, 1±0.09, n=4; WKY, 0.86±0.03, n=4; P<0.01, one-way ANOVA). However, it had no effect on the number of PV^+ neurons in the hippocampus of WKY rats. Taken together, our results suggest that inhalation of RCEO relieves depression-like behaviors in WKY rats possibly via modifying the oxidative phosphorylation-related pathways and by increasing the level of PV. By overexpression or knockdown of PV in the hippocampus or PFC, the involvement of PV in depression is investigated.

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Poster

776. Mood Disorders: Molecular Mechanisms and Approaches

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Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: MH049698
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Title: Molecular neurobiology of enrichment loss

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Abstract: Psychological loss impacts nearly all of our lives, yet little is known about what happens in the brain during this experience. Loss occurs when one is deprived of something perceived as important, such as a loved one, home, or job, and its symptomology resembles depression. We can simulate loss in rats by removing environmental enrichment, producing a unique phenotype of depression-like behaviors. Here we probe the molecular neurobiology of enrichment loss with a multidimensional approach that spans big data techniques, brain regions, and sex.

Male and female rats were divided into 3 groups: environmentally enriched (EE), enrichment removed (ER), and control (CON). EE and ER animals were housed in groups of 10 in large, multi-level cages with toys. CON animals were pair-housed. ER animals were removed from enriched housing after 4 weeks and moved to single-housing. Two weeks after removal, brains were collected. Bilateral micropunches were taken of regions implicated in loss by c-fos expression, including the infralimbic prefrontal cortex, basolateral amygdala, and medial amygdala. These regions were run on parallel RNAseq, shotgun proteomics, and kinomics platforms. A series of bioinformatics analyses were then used to derive molecular signatures of loss that span RNA, protein, and kinase activity levels. Tools used include GSEA, iLINCS, OmiClust, and KRSA. The resulting multi-level signatures yield in-depth information about the proteins and pathways that are altered in loss.

The ER group exhibited differential expression in several pathways that may contribute to loss. At the RNA level, we observed modulation of pathways associated with synaptic transmission, neuroinflammation, cytoskeletal organization, lipid homeostasis, and angiogenesis. Sex-specific changes were present within each of these categories. Continued bioinformatic analyses at the protein and activity levels will build upon these results to generate more detailed region- and sex-specific signatures for ER.

Taken together, these results allow us to start to understand what is happening in a rat's brain during enrichment loss, offering insight into the mechanisms that could underlie psychological loss in humans. They also point to potential therapies that may offer relief to people experiencing loss.

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Poster

776. Mood Disorders: Molecular Mechanisms and Approaches

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Program #/Poster #: 776.05/V36

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Title: NMDA receptor GluN2B tyrosine phosphorylation invoved in depression related behaviour

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Abstract: Abstract
NMDA receptors mediate various physiological and pathological functions, and studies have shown that phosphorylation of different subunits of NMDA receptors can regulate the processes of receptor membrane trafficking and channal gating.In recent years, it has been found that GluN2 subunit has multiple tyrosine phosphorylation sites. Our previous study reported that the phosphorylation at Tyr-1070 of GluN2B can change the expression of receptor on cell membrane by coordinating the phosphorylation at Tyr-1472, but the in vivo function of this site on NMDA receptor-mediated function remains unclear. In this study, we first prepared GluN2B subunit mice with NMDAR receptor c-terminal tyrosine 1070 mutation mice (hereinafter referred to as 1070 KI mice),Behavioral tests showed that the mutant mice did not affect hippocampal related behaviors, but showed an antidepressant like phenotype. 1070 KI mice after chronic restraint stress model still exist antidepressant phenotypic stability, show in forced swimming test the immobile time significantly shorter than WT mice, anhedonia in sucrose preference test . It is suggested that phosphorylation of GluN2B Tyr-1070 is involved in and regulates the process related to depression. Biochemical results showed that at the basic level, the mutant mice reduced the phosphorylation level at Tyr-1472 only in the mPFC region. the phosphorylation Tyr-1070 of WT mPFC region is increased after CRS,but Tyr-1472 phosphorylation level without any change, it also suggests that tyrosine phosphorylation in regulating at baseline and after the stress is very different. we found that After the mutation at Tyr-1070, the function of NMDARs was not affected on the synapses of pyramidal neurons at layer 5-6 in this brain region, but the function of extrasynaptic GluN2B-containing NMDAR receptor is down-regulated, the number of functional synapses is increased and the excitatory synaptic transmission is enhanced, which was directly related to the enhanced activity of mTORC1 after the mutation at site Tyr-1070.Combined with the above data, we reveals a new mechanism of NMDAR receptor tyrosine phosphorylation in mPFC region in the regulation of depression and provides a new way to elucidate the NMDA receptor-mediated MDD disease.
Keywords:tyrosine phosphorylation, Tyr-1070, mPFC region, depression

Disclosures: X. Shi: None. **J. Luo:** None. **W. Yang:** None. **Q. Zhang:** None.

Poster

776. Mood Disorders: Molecular Mechanisms and Approaches

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Title: Chemogenetic manipulation of Npas1-neurons in the ventral pallidum is related to social defeat stress susceptibility

Authors: *G. MORAIS-SILVA[1,2], H. NAM[2], M. F. PAGLIUSI, JR[3,2], S. CHAN[4], M. T. MARIN[1], M. LOBO[2];
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Abstract: Depression is a serious disorder intrinsically related to stressful events, with an enormous impact on individual wellbeing and public health services worldwide. However, we are still seeking to understand how stress experience impacts the brain and develop more effective treatments for depression. Recent studies using the animal model of social defeat stress demonstrate an important role of the nucleus accumbens (NAcc) and ventral pallidum (VP), key brain areas in motivated behaviors, in the etiology of depression. Considering the extensive and reciprocal connections that exist between these regions, VP projections to NAcc could be interesting targets related to the susceptibility to stress. To address this question, we used a chemogenetic approach to activate or inactivate VP Npas1 neurons, which heavily projects to NAcc, during a subthreshold protocol of social defeat stress. Male Npas1-Cre-2A-tdTomato mice (n = 44) stereotaxically received AAV2-hSyn-DIO-hM3Dq (excitatory Designer Receptor Exclusively Activated by Designer Drugs - DREAAD), AAV2-hSyn-DIO-hM4Di (inhibitory DREADD) or AAV2-hSyn-DIO-eYFP (control groups) into the VP (0.3 uL infused over 15 min) 2 weeks before being exposed to a subthreshold social defeat stress (SSDS) protocol. Briefly, in the SSDS protocol animals were defeated for 2.5 min by three different aggressors (CD1 retired breeders) on a single day, each session separated by 15 min of sensory interaction. Thirty minutes before the SSDS, animals received Clozapine N-Oxide (CNO) i.p. at a dose of 1 mg/kg. Twenty-four hours later the animals underwent a social interaction test (SI) and a forced swim test (FST). Chemogenetic activation of Npas1 neurons during SSDS decreased time spent in the interaction zone and increased the time spent in the corners in the SIT when a social target was presented. It also increased immobility time in the FST. In contrast, inactivation of Npas1 neurons had no effect on such behaviors. Our results demonstrate that increased activity of Npas1 neurons during stressful events induces susceptibility to social defeat stress.

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Poster

776. Mood Disorders: Molecular Mechanisms and Approaches

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Title: Asparagus extract ameliorates menopausal depression in ovariectomized rats under chronic unpredictable mild stress

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Abstract: Depression is a serious illness and one of the most prevalent psychiatric disorders. Women are more vulnerable to depression than men. Moreover, a woman's risk of developing depression increases with age, likely due to hormonal fluctuations associated with menopause. To investigate the effects of asparagus extract on menopausal depression, we induced menopause in rats via ovariectomy and exposed them to chronic unpredictable mild stress (CUMS) for 4 weeks. After 2 weeks of initial CUMS exposure, asparagus extract (1000 mg/kg, 2000 mg/kg, PO) and imipramine (IMI, 10 mg/kg, IP) were administered for 4 weeks. Thereafter we measured depression-associated behaviors using the sucrose preference test (SPT), elevated plus maze (EPM) and forced swim test (FST). We then measured the levels of corticosterone and inflammatory cytokines using ELISA. We report that CUMS promoted depression-like behavior and significantly increased corticosterone and inflammatory cytokines levels in ovariectomized (OVX) rats. Treatment with asparagus extract, however, effectively rescued the CUMS induced depression-like behavior and corticosterone levels in OVX rats. Furthermore, we found that CUMS down-regulates the expression levels of brain-derived neurotrophic factor (BDNF) and its primary receptor, tropomyosin receptor kinase B (TrkB), in OVX rats. Treatment with asparagus extract also rescues the expression levels of BDNF and TrkB. These results suggest that asparagus extract exerts antidepressant effects by modulating the BDNF-TrkB signaling pathway in a rat model of menopausal depression.

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Poster

776. Mood Disorders: Molecular Mechanisms and Approaches

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Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: PAICYT-UANL SA103-15

Title: Activation of CB1 receptors and quantification of the cnr1 gene in a depression model

Authors: A. VILLARREAL ZUÑIGA[1], D. MONTIEL CONDADO[2], A. GONZALEZ HORTA[2], M. BERMUDEZ DE LEON[3], *B. GONZALEZ HERNANDEZ[2];
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Abstract: It is estimated that about 300 million people suffer from unipolar major depression, which in the worst case can lead to suicide; also is one of the major causes of ill-health and economic burden worldwide. Besides, after half a century of intensive research since antidepressant drugs were introduced into clinical practice, their efficacy remains low, at around 70% (compared with a no-treatment recovery rate of around 50%); and the onset of action remains slow, at around 4-6 weeks; Recently the CB1 cannabinoid receptors (RCB1) have been explored, because preclinical studies suggest that, agonists for RCB1 possess antidepressant properties and the antagonist are pro-depressant. The objective of this work is to study the participation of CB1 receptors and the cnr1 gene in a depression model. Young male Sprague-Dawley rats (200-250g) were used. The model of depression used was the forced swimming test combined with a "time-sampling" analysis, which consists in forcing the rats to swim individually on two occasions: 1) pre-session of 15 minutes and 24 hours later, 2) experimental session of 5 minutes, in which three behaviors are recorded in intervals of 5 seconds (or counts): climbing, swimming and immobility. The following drugs were administered intraperitoneally: 1) ACEA (3mg/mL/kg), agonist for RCB1; and 2) imipramine, tricyclic antidepressant (30mg/10mL/kg). For the analysis of the cnr1 gene, an RT-PCR of the following nuclei was performed: pre-frontal cortex and hippocampus. The administration of imipramine had the expected antidepressant effect, reducing the immobility behavior, increasing the swimming behavior (no change in climbing) and increase expression of the cnr1 in the hippocampus and pre-frontal cortex. Interestingly, the application of ACEA presented a similar effect, decreasing the immobility and increasing the swim (no change in climbing). Besides was observed, increase expression of the cnr1 in pre-frontal cortex, but in hippocampus was high significative. These results indicate that the activation of CB1 receptors have an antidepressant effect, which may be due to an increase in

expression of the cnr1 gene. Suggesting they have a very important role in the pathophysiology of depression and be a new pharmacological target for its treatment.

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Poster

776. Mood Disorders: Molecular Mechanisms and Approaches

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NARSAD #26950 (DAP)

Title: Social defeat affects transcription of nociceptin peptide and Oprl1 receptor in reward-processing brain areas

Authors: B. ROMOLI[1], N. PRAKASH[1], S. BERRETTA[2], A. DER-AVAKIAN[1], D. A. PIZZAGALLI[2], ***D. DULCIS**[1];
[1]Psychiatry, Univ. of California San Diego, San Diego, CA; [2]Translational Neurosci. Lab., McLean Hosp., Belmont, MA

Abstract: Anhedonia, the reduced ability to experience pleasure, is a core symptom of depression and other mood disorders often triggered by chronic stress. Nociceptin/orphanin FQ peptide (pNoc) has been classically thought to be involved in pain processing, but its role in stress and depression has recently gained attention. Altered levels of pNoc and its receptor Oprl1 have been associated with stress-induced deficits, including blunted reward learning (Der-Avakian et al., 2017). Here, we investigated whether chronic social defeat induced changes in pNoc/Oprl1 transcription in rats that were either susceptible or resilient to stress-induced anhedonia.
Adult male Wistar rats (n=12) underwent 21 days of social defeat and anhedonia was assessed using the intracranial self-stimulation (ICSS) procedure. Stress-exposed animals clustered into susceptible or resilient subgroups (n=6 each) based on their ICSS reward thresholds (unbiased k-means method). Brain sections of ventral tegmental area (VTA), dorsal striatum (CPu) and prefrontal cortex (PFC) were processed for RNA-scope *in-situ* hybridization (ISH) to detect mRNA levels of pNoc, Oprl1, cFos, and neurotransmitter (NT) markers for dopamine (tyrosine hydroxylase, TH), glutamate (vesicular glutamate transporter1, VGLUT1), and GABA (vesicular GABA transporter, VGAT).
Quantification of ISH-reactive cells in stress- and reward-related brain regions revealed that

stress significantly reduced pNoc-expressing cells in VTA, CPu and PFC, while no significant changes were detected in the number of Oprl1-expressing cells. When stressed animals were clustered into susceptible and resilient subgroups, analyses revealed that pNoc transcriptional reduction in all 3 brain regions was driven by the resilient group, while Oprl1 expression was differentially regulated in specific brain regions and conditions. Susceptible rats had significantly fewer VTA Oprl1-expressing cells than resilient rats, while resilient rats had significantly fewer CPu Oprl1-expressing cells than susceptible rats.
We are currently implementing multiple RNAscope NT markers (TH, VGAT, VGLUT1) in combination with activity gene, cFos, to quantify such pNoc/Oprl1 transcriptional changes in specific neuronal subtypes differentially cFos-activated by stress in susceptible and resilient rats, when compared to non-stressed animals (n=6).
Given the heterogeneity of regulation displayed by different brain regions in response to chronic stress, a region- and cell-specific analysis of pNoc/Oprl1 expression patterns is fundamental to begin to understand its function and generate new targets with a potential translational value.

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Poster

776. Mood Disorders: Molecular Mechanisms and Approaches

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 776.10/V41

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: CIHR Project Grant

Title: Transcriptomic analysis of cortical microcircuit cell-types reveals differential cellular responses to chronic stress

Authors: *D. F. NEWTON[1], H. OH[3], R. SHUKLA[4], K. A. MISQUITTA[5], C. J. FEE[2], G. BADER[6], M. BANASR[7], E. SIBILLE[8];
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Abstract: Background: Depression is characterized by disrupted gene expression in cortical brain regions. Such genes are involved in GABAergic and glutamatergic signaling, neurotrophic support, oxidative stress, and other functions. Similar changes occur in UCMS, a depression-

relevant mouse model. Currently, the coordinated changes occurring within and across cell-types of the cortical microcircuitry (CM) are unknown.
Methods: We examined the transcriptomic changes occurring in the principal 4 cell-types comprising the CM of UCMS-exposed C57Bl/6J male mice versus controls (n=10/group). Depressive-like behaviour (emotionality) was assessed through a battery of 7 behavioural tests after 5-weeks of UCMS. Pyramidal (PYR)-cells and GABAergic interneurons expressing somatostatin (SST), parvalbumin (PV), or vasoactive-intestinal-peptide (VIP) were collected using fluorescent in-situ hybridization and laser-capture microdissection. Gene expression was determined by RNA sequencing. Differential expression, biological pathway enrichment, and co-expression network analyses were performed.
Results: UCMS-exposed mice exhibited elevated emotionality versus controls (p=0.002). Differentially expressed genes were largely unique to each cell-type. UCMS induced an upregulation of synapse structure and neurotransmission-related genes in PYR-cells and a dysregulation (up/down-regulation) in SST-cells. UCMS increased co-expression between PYR-cells and both PV (p=0.00048) and SST-cells (p=0.0026) and decreased co-expression between VIP and SST-cells (p=0.014). A co-expression hub module of 1048 genes in PYR-cells, enriched in axon guidance-related genes, correlated with emotionality in UCMS-exposed mice (r=0.78, p=0.010).
Conclusions: CM cell-types undergo different responses to chronic stress. Synaptic changes in between PYR-cells and both SST and PV-cells may underlie the long-term neurobiological adaptations to UCMS. In vivo pharmacological validation studies targeting key disrupted pathways are warranted.

Disclosures: D.F. Newton: None. **H. Oh:** None. **R. Shukla:** None. **K.A. Misquitta:** None. **C.J. Fee:** None. **G. Bader:** None. **M. Banasr:** None. **E. Sibille:** None.

Poster

776. Mood Disorders: Molecular Mechanisms and Approaches

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 776.11/V42

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: NIMH Grant MH112861

Title: Chemogenetic activation of medial prefrontal cortex excitatory neurons improves chronic corticosterone-induced behavioral deficits

Authors: *A. DIETERICH[1], K. STECH[2], B. A. SAMUELS[2];
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Abstract: The medial prefrontal cortex (mPFC) is less active in individuals with major depressive disorder and acute optogenetic activation of all mPFC neurons has antidepressant-like effects in mice that are susceptible to chronic social defeat stress (Covington et al., 2010). Here we take a chemogenetic approach to specifically target excitatory neurons in the mPFC. To this end, we exposed C57BL/6J mice to chronic treatment with corticosterone (CORT; 5 mg/kg/day), which mimics chronic stress and induces several negative valence behaviors and bilaterally injected AAV-CaMKIIa-hM3-Gq-DREADD into the mPFC. We hypothesized that excitatory neuronal activation in the mPFC would ameliorate the negative valence behaviors induced by chronic CORT administration. We found that acute chemogenetic activation of mPFC excitatory neurons reduced both latency to eat in novelty suppressed feeding and immobility in the forced swim test, while not impacting overall locomotor activity. Taken together, excitatory neuronal activation of the mPFC reverses the behavioral effects of chronic CORT administration, a well-validated chronic stress paradigm. These data suggest that mPFC excitatory neurons are a potential therapeutic target for antidepressant development.

Disclosures: **A. Dieterich:** None. **K. Stech:** None. **B.A. Samuels:** None.

Poster

776. Mood Disorders: Molecular Mechanisms and Approaches

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 776.12/V43

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: NIH

Title: Inhibition of NRG1-ErbB4 signaling in midbrain dopamine neurons attenuated chronic social defeat-induced depressive phenotypes

Authors: *H. WANG[1], W. CUI[1], W. CHEN[1], Z. DONG[1], F. LIU[2], W.-C. XIONG[1], L. MEI[1]; [1]Dept. of Neurosciences, Case Western Reserve Univ., Cleveland, OH; [2]DNRM, Augusta Univ., Augusta, GA

Abstract: Genetic studies including genome wide association studies (GWAS) suggest the involvement of NRG1-ErbB4 signaling in major depressive disorder (MDD), but the underlying mechanism is not known. Mesolimbic dopaminergic system plays a crucial role in chronic stress-induced depression in animal studies. ErbB4 is expressed in midbrain dopaminergic neurons and NRG1-ErbB4 signaling was suggested to promote dopaminergic transmission. We investigated whether and how impaired NRG1-ErbB4 signaling in midbrain dopamine (DA) neurons contributes to depression. ErbB4 deletion from DA neurons caused resilience to depression in a chronic social defeat model. AAV-Cre virus-mediated local deletion of ErbB4 in VTA or local pharmacological inhibition of ErbB4 kinase recapitulated the resilience phenotype. Mechanism

study with in vivo fast scan cyclic voltammetry (FSCV) or ex vivo electrophysiological recording showed NRG1-ErbB4 signaling at soma of VTA DA neurons increases DA neurons' excitability and promotes both DA and BDNF release in nucleus accumbens (NAc), perhaps through MAPK/ERK-mediated phosphorylation of K+ channels and suppressed I_A current. Interestingly, selective inhibition of ErbB4 kinase with 1NMPP1 infusion after development of depression attenuated depressive phenotypes. Similar antidepressant effects were observed with Afatinib, an inhibitor of ErbB4. These results suggest ErbB4 in midbrain DA neurons mediates susceptibility to social defeat stress-induced depression-like phenotypes and might be a potential treatment target of MDD.

Disclosures: H. Wang: None. **W. Cui:** None. **W. Chen:** None. **Z. Dong:** None. **F. Liu:** None. **W. Xiong:** None. **L. Mei:** None.

Poster

776. Mood Disorders: Molecular Mechanisms and Approaches

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 776.13/V44

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: MOST, Taiwan

Title: Blm-s, a BCL-2 family member, functions in mood control

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Abstract: Mood disorders such as depression and anxiety are common public health problems and both together rank among the top ten causes of disability. Mood disorders are heterogeneous diseases, involving multiple factors including neural circuits, neuromodulators, immune function, and genetic factors. Although highly penetrant genetic variants that cause depression and anxiety have not yet been reported, past studies clearly indicate that mutations in certain 'risk genes' enhance the probability to develop mood disorders, pointing to a genetic component in the etiology of mental illnesses. In line with such view, we recently uncover that deficit of a BCL-2 pro-apoptotic family member- BLM-s (BCL-2 like molecule, small form) causes *Blm*-s-null mice with increased susceptibility to depression- and anxiety-like behaviors, as probed by elevated plus maze, open field, forced swim, and tail suspension tests. However, *Blm-s*$^{-/-}$mice have no alteration in learning and memory as assessed by Morris water maze and novel object recognition test. Using immunohistochemistry and RNA *in situ* hybridization, we found that BLM-s is expressed in cells located close to the subgranular zone (SGZ) of hippocampal dentate

gyrus, in which adult hippocampal neural stem/progenitor cells proliferate and differentiate into functionally integrated dentate granule neurons. To test whether BLM-s regulates adult hippocampal neurogenesis, BrdU-labeling and Ki-67 immunohistochemistry were used to quantify neurogenesis in the SGZ. *Blm-s*$^{-/-}$mice examined at age of 2- and 5-month show much decreased number of BrdU- or Ki-67-labeled cells in close proximity to the SGZ. Further, via Golgi stain, the granule neurons in the DG of the *Blm-s*$^{-/-}$mice demonstrate reduced spine density and reduced complexity of the dendrites evident by decreased number of dendritic node, end, segment, and spine density.Electron microscopic analysis of the synapses over the dendrites of the granule neurons in the DG revealed reduced number and size of excitatory synapse.The decreased branching complexity of dendrites with reduced spine density in granular cells of DG implicates physically altered circuit connectivity in *Blm-s*$^{-/-}$mice, which could provide long-lasting traces underlying depression and anxiety.

Disclosures: T. Yang: None. **C. Chou:** None. **P. Huang:** None.

Poster

776. Mood Disorders: Molecular Mechanisms and Approaches

Location: Hall A

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Program #/Poster #: 776.14/V45

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: Hacettepe University Scientific Research Projects Coordination Unit (Project number THD-2018-17350)

Title: Molecular players of depressogenic phenotype induced by hippocampal FGF-AS overexpression identified with proteomic analysis

Authors: *B. UZAY, T. DALKARA, E. EREN-KOCAK;
Neurosci., Hacettepe Univ. Inst. of Neurolog. Sci. and Psychiatry, Ankara, Turkey

Abstract: Background: FGF-antisense (FGF-AS), the natural antisense transcript of fibroblast growth factor-2 (FGF2) is indicated in the regulation of FGF2 expression. Hippocampal overexpression of FGF-AS increased depression-like behaviors and, impaired learning and memory without changing FGF2 expression. Clarifying the molecular mechanisms underlying the depressogenic effects of FGF-AS will help to better understand the pathophysiology of affective disorders. We aimed to determine the proteins, whose expressions were changed by hippocampal FGF-AS overexpression.
Methods: FGF-AS expressing AAV (FGF-AS-AAV) (n=5) or blank AAV (n=6) was injected bilaterally into the hippocampi of male Sprague-Dawley rats. Rats were sacrificed 8 weeks later. Hippocampal protein was analyzed using Liquid Chromatography Tandem Mass Spectrometry. Raw data was processed and compared between groups; proteins with significant expression

differences were determined by principal component analysis. To further delineate possible interacting proteins, network and pathway analyses were performed. The activated or inhibited proteins were determined by their relative activation z-scores.
Results: Proteomic analyses revealed 34 proteins, whose expressions were different between groups. Out of 34 proteins, 31 were upregulated and 3 were downregulated by hippocampal overexpression of FGF-AS when compared to the controls ($p<0.05$). Interestingly S100 calcium binding protein A9 (S100A9) increased 32-fold while chloride intracellular channel 6 (CLIC6) protein increased 46-fold in the FGF-AS-AAV group. Pathway and interaction analyses identified possible involvement of 4 pathways, namely inflammation, growth and proliferation, injury and abnormalities and mitochondrial dysfunction. S100A9 was found to be linked to other inflammatory molecules, including NF-KB, on the other hand, CLIC6 was linked to various hub proteins namely NFkB, CREB, Akt, TP53 and ERK1/2. Interaction analyses revealed activation of IL-6 and MeCP2, and inhibition of PP2A. Other proteins with possible change in the activity in response to FGF-AS overexpression were TGFB1, TNF, HNF4A, PPARG, EGF, STAT3, PRDM1, SMARCA4 and PP2A.
Conclusion: The depressogenic effects of FGF-AS in the hippocampus may be mediated by proteins involved in growth factor and inflammatory signaling, and in mitochondrial function, which is in line with both neurotropic and inflammatory hypotheses of depression. Further molecular analysis is necessary to provide evidence for the players of the aforementioned pathways as the downstream effectors of FGF-AS in the development of depression-like behavior in rats.

Disclosures: B. Uzay: None. **T. Dalkara:** None. **E. Eren-Kocak:** None.

Poster

776. Mood Disorders: Molecular Mechanisms and Approaches

Location: Hall A

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Program #/Poster #: 776.15/V46

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: NRF-2018M3C7A1024150
NRF-2017R1A2B4012237

Title: Integrative analysis of Gata1 associated transcriptome and epigenome in the cortical neuron

Authors: *K. CHOI, J. PARK, H. KANG;
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Abstract: Gata1, a member of the GATA transcription factor family, has been considered as an important factor in the hematopoietic system. As a transcriptional regulator, Gata1 has a crucial

role in blood cell differentiation such as erythrocytes, megakaryocytes, eosinophils, and dendritic cells. Recently, a novel function of Gata1 in the central nervous system was demonstrated. Gata1 showed increased expression in the dorsolateral prefrontal cortex (dlPFC) of patients with depression and functioned as a transcriptional repressor of synapse-related genes. In this study, we examined the global alteration in gene expression by Gata1 overexpression of using Chromatin immunoprecipitation followed by sequencing (ChIPseq), mRNAseq, and smallRNAseq. From the result of ChIPseq for histone marks H3K4me3 and H3K27me3, we have identified 1127 and 4881 unique peaks marking H3K4me3 and H3K27me3 in the gene promoter region, respectively, in the cultured cortical neuron overexpressed with Gata1 compared to control. Gene ontology analysis revealed that Gata1 might be involved in transcriptional activation of genes related to development, differentiation, and immune-related functions. On the other hands, it might act as a transcriptional repressor of genes related to macromolecule processing, synapse-related functions, and signal transduction. In addition, we identified 113 differentially expressed genes and 82 miRNAs in cultured neuron transfected with Gata1 through the mRNAseq and smallRNAseq analysis. Among the differentially expressed genes, down-regulated genes showed a higher correlation with the ChIPseq result than the upregulated genes. Subsequently, we performed target prediction for differentially expressed miRNAs using several online databases. Gene ontology analysis indicated that predicted target genes of up-regulated miRNAs in cultured neuron overexpressed Gata1 associated with synapse-related function, development, and regulation of gene expression. Interestingly, target genes, which are predicted to be decreased in expression by up-regulated miRNAs showed a higher correlation with the ChIPseq result. These results will provide a further understanding that Gata1 can act as a transcriptional regulator that affects the pathophysiological condition such as depression.

Disclosures: **K. Choi:** None. **J. Park:** None. **H. Kang:** None.

Poster

776. Mood Disorders: Molecular Mechanisms and Approaches

Location: Hall A

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Program #/Poster #: 776.16/W1

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: MH 113899
VA 01 BX000559

Title: Mechanisms contributing to the sustained antidepressant-like response of L-655,708

Authors: *F. R. CARRENO[1], V. BUGAY[1], A. FRAZER[1,2], D. J. LODGE[1], R. BRENNER[1]; [1]UT Hlth. San Antonio, San Antonio, TX; [2]South Texas Veterans Hlth. Care Syst., San Antonio, TX

Abstract: Selective modulation of hippocampal transmission by systemic administration of α5-GABAA receptor negative allosteric modulator, namely L-655,708, is capable of producing a sustained antidepressant-like effect in the absence of any psychotomimetic or abuse-related effects. We utilized conventional pharmacological, electrophysiological (whole-cell, patch clamp), and behavioral approaches to examine the mechanisms by which L-655,708 produces plasticity within the hippocampus to account for its sustained antidepressant-like effect. We found that unlike ketamine, L-655,708 did not cause an increase in the phosphorylation of TrkB in the ventral hippocampus (vHipp) 30 or 60 min after its administration nor did vHipp administration of TrkB inhibitor, K252a, block the sustained antidepressant-like effect of L-655,708. Moreover, acute L-655,708 activation of CamKII does not mediate its sustained antidepressant-like effects, as vHipp administration of KN-93, a CamKII inhibitor, did not block the sustained antidepressant-like effect of L-655,708. Recording of vHipp CA1 pyramidal cells 24h after a single administration of L-655,708 revealed a significant increase of input resistance, which resulted in an approximately two fold increase in action potential frequency. In addition, we found a reduced IPSC half-width. These results are consistent with reduced tonic and evoked chloride currents in ventral CA1 neurons as a consequence of L-655,708, indicating that the sustained antidepressant-like effects of L-655,708 may be mediated by changes in GABA receptor gating properties, with resultant enduring changes in ventral CA1 neuronal excitability. By identifying the mechanisms by which systemic administration of α5-GABAA receptors negative allosteric modulators recapitulate the therapeutic effects of ketamine without its psychotomimetic and abuse-related effects, it should be possible to provide novel, safe, and effective approaches for treating patients suffering from refractory depression.

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Poster

776. Mood Disorders: Molecular Mechanisms and Approaches

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Program #/Poster #: 776.17/W2

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: NSERC

Title: Fast acting antidepressant potential of reelin in a preclinical animal model of depression: Mechanisms and avenues for future research

Authors: *K. J. BRYMER[1], J. J. BOTTERILL[2], R. ROMAY-TALLON[3], J. T. ALLEN[3], H. J. CARUNCHO[3], L. E. KALYNCHUK[3];
[1]Psychology, Univ. of Saskatchewan, Saskatoon, SK, Canada; [2]Ctr. for Dementia Res., Nathan Kline Inst., Orangeburg, NY; [3]Div. of Med. Sci., Univ. of Victoria, Victoria, BC, Canada

Abstract: Reelin is an extracellular matrix protein involved in the regulation of synaptogenesis, learning and memory, promoting contacts onto dendritic spines, and hippocampal neurogenesis. Work by our lab and others have shown that repeated injections of the stress hormone corticosterone (CORT) decreases hippocampal reelin expression, and this decrease is accompanied by the development of depressive-like behavior. This led us to hypothesize that reelin supplementation would produce an antidepressant effect in a preclinical rodent model of depression. We set out to test this hypothesis through a series of experiments. First, we conducted stereotaxic surgery on male rats to implant an indwelling cannula into the left dorsal hippocampus. A subset of rats received either a single intrahippocampal reelin infusion or repeated intrahippocampal reelin infusions during 21 days of CORT injections. We then assessed depressive-like behavior using the forced-swim test (FST), hippocampal-dependent memory using the object-location memory test (OBL), and examined hippocampal neurogenesis and markers of GABA and glutamate activity. In the second experiment, we tested the involvement of AMPA in the fast-acting antidepressant effects of reelin by infusing the AMPA antagonist CNQX after a single intrahippocampal reelin infusion during CORT treatment in male rats. We then assessed depressive-like behavior using the FST, and examined hippocampal neurogenesis. CORT injections increased time spent immobile on the FST and impaired performance on the OBL, and reelin infusions restored these measures to control levels. A single intrahippocampal CNQX infusion blocked reelin's antidepressant effects on the FST. CORT decreased hippocampal neurogenesis, and reelin infusions restored this back to control levels. CNQX did not block reelin's effects on hippocampal neurogenesis. These novel results demonstrate that reelin has antidepressant effects, and that part of the mechanism behind this effect may be AMPA receptor signaling. Future directions can explore the potential of reelin to reverse depressive-like behavior when infused into regions other than the hippocampus (amygdala and medial prefrontal cortex)

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Poster

776. Mood Disorders: Molecular Mechanisms and Approaches

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Program #/Poster #: 776.18/W3

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: P50MH096890
Hope for Depression Research Foundation

Title: Epigenetic mediated paternal transmission of stress phenotypes

Authors: *A. M. CUNNINGHAM[1], D. M. WALKER[1], M. A. DOYLE[2], R. C. BAGOT[3], D. BUREK[4], E. J. HARRIGAN[5], G. E. HODES[6], A. RAMAKRISHNAN[1], E. S. CALIPARI[7], H. M. CATES[1], O. ISSLER[1], M. E. CAHILL[1], B. LABONTÉ[8], E. A. HELLER[9], J. FENG[10], C. J. PENA[11], E. A. RIBEIRO[1], O. ENGMANN[1], Z. S. LORSCH[1], P. J. HAMILTON[12], S. J. RUSSO[1], L. SHEN[1], E. J. NESTLER[1];
[1]Nash Family Dept. of Neurosci. and Friedman Brain Inst., Icahn Sch. of Med. at Mount Sinai, New York, NY; [2]Neurosci. Program, Michigan State Univ., East Lansing, MI; [3]Dept. of Psychology, McGill Univ., Montreal, QC, Canada; [4]Washington Univ. Sch. of Med., Saint Louis, MO; [5]SUNY Downstate Col. of Med., Brooklyn, NY; [6]Neurosci., Virginia Tech., Blacksburg, VA; [7]Pharmacol., Vanderbilt Univ. Sch. of Med., Nashville, TN; [8]Neurosci. and Psychiatry, Laval Univ., Quebec, QC, Canada; [9]Dept. of Systems Pharmacol. and Translational Therapeut., Univ. of Pennsylvania, Philadelphia, PA; [10]Dept. of Biol. Sci., Florida State Univ., Tallahassee, FL; [11]Princeton Neurosci. Inst., Princeton Univ., Princeton, NJ; [12]Neurosci., Virginia Commonwealth Univ. Hlth. Syst., Richmond, VA

Abstract: Depression risk is determined by both genetic and environmental factors. Recently, it has been proposed that epigenetic mechanisms may also be a contributing factor. Studies show that the offspring of male mice that have been exposed to stress show anxiety- and depression-like phenotypes. We tested the hypothesis that epigenetic alterations in sperm during chronic social defeat stress (CSDS) transmit increased susceptibility to stress phenotypes to both F1 and F2 generations. Male C57BL/6J mice were exposed to 10 days of CSDS and subjected to social interaction testing to assess paternal phenotype. Males classified as resilient or susceptible to CSDS and control F0 males were allowed to mate with non-stressed females 30 days after the stress, to allow the sperm exposed to the stress to mature. One week following natural mating, those same F0 males were euthanized and their sperm was collected for artificial insemination. At ~P60, 1 male and 1 female from each litter was exposed to sub-threshold unpredictable stress and depression- and anxiety-like behaviors were assessed. Each animal was compared to an unstressed littermate of the same sex to control for litter effects. Preliminary evidence suggests that F1 offspring of defeated fathers produced by natural mating or by artificial insemination display altered phenotypes, with reverse effects seen in male and female offspring. Paternal stress enhances stress susceptibility of F1 males, while diminishing it in F1 females. These data suggest that there are changes in sperm during CSDS that encode altered depressive- and anxiety-like phenotypes in their offspring. To identify the molecular mechanisms of this paternal transmission, RNA sequencing was conducted for the sperm of a separate cohort of F0 susceptible and resilient males. Two sperm samples were collected from each animal: 1) ~10 days prior to and 2) 30 days post-CSDS to determine how RNA profiles within the sperm might change due to stress exposure in susceptible and resilient males. Preliminary data suggest that substantial changes in the transcriptomic profiles occur after exposure to stress in susceptible and resilient mice. Current studies are focused on exploring if similar transcriptomic differences are maintained in various tissues of offspring mice.

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Poster

776. Mood Disorders: Molecular Mechanisms and Approaches

Location: Hall A

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Program #/Poster #: 776.19/W4

Topic: F.04. Stress and the Brain

Support: R01MH086828

Title: Taking the fun out of psilocybin: Can psilocybin's rapid antidepressant action be preserved in the absence of hallucinations?

Authors: *N. HESSELGRAVE[1], J. M. FISCHELL[2], S. M. THOMPSON[2];
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Abstract: Major depression is a debilitating illness and one of the leading causes of disability world-wide. First line pharmacotherapies targeting the serotonin system, such as selective serotonin reuptake inhibitors (SSRIs) like fluoxetine, are effective in ~60% of patients. Typically, patients must take SSRIs for 4-8 weeks to experience relief of depressive symptoms. More effective and faster acting medications are needed. Recently, psilocybin, a hallucinogenic plant-derived pan-serotonergic agonist, was shown to produce a rapid antidepressant response in humans with treatment resistant depression. However, the hallucinations pose a significant barrier to its widespread use. Antagonists of serotonin2A receptor (5-HT2AR), such as ketanserin, can be used to block hallucinations in humans. Can a combination of psilocybin plus ketanserin provide rapid relief of depressive symptoms without hallucinations? In rodents, chronic administration of fluoxetine reverses anhedonic deficits in reward behavior produced by chronic multimodal stress (CMS). Fluoxetine also restores the strength of temporoammonic (TA) - CA1 synapses in the hippocampus. Here, we test the hypothesis that psilocybin can exert a rapid anti-anhedonic effect in rodents subjected to CMS and ask whether this effect is independent of 5-HT2ARs. Using 10-21 days of CMS, we induced an anhedonic phenotype in rodents, as assessed by loss of sucrose preference. Sucrose preference was restored within 48 hours of a single acute dose of psilocybin (1mg/kg). Experiments with psilocybin and ketanserin are in progress. Ketanserin did not impair the ability of fluoxetine to restore sucrose preference and to strengthen TA-CA1 synapses, suggesting that psilocybin’s antidepressant effect may also be independent of 5-HT2ARs. Blocking the hallucinogenic side effect of psilocybin, but not the rapid acting antidepressant effect, by co-administering psilocybin and ketanserin could provide a novel and viable approach for safe and effective rapid relief of depression.

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Poster

776. Mood Disorders: Molecular Mechanisms and Approaches

Location: Hall A

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Program #/Poster #: 776.20/W5

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: NIMH R01 086828

Title: The $GABA_AR$ α5 subunit is required for the fast antidepressant-like actions of MRK-016 on stress-induced anhedonia and weakened synaptic function

Authors: *T. TROPPOLI[1], P. ZANOS[2], P. GEORGIOU[2], U. RUDOLPH[3], T. D. GOULD[4], S. M. THOMPSON[1];
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Abstract: Major depression is a common debilitating psychological disorder. Current clinical treatment options primarily involve reuptake inhibition of monoamine neurotransmitters, but these therapeutics are only effective in half of patients and have a delayed onset of therapeutic action. Negative allosteric modulators of $GABA_A$ receptors containing α5 subunits (GABA-NAMs), such as MRK-016, exhibit rapid antidepressant-like properties in preclinical models of stress-induced anhedonia and restore stress-weakened glutamatergic excitation at hippocampal temporoammonic-CA1 synapses (TA-CA1). These behavioral outcomes are dependent on the activity of the benzodiazepine site of the $GABA_A$ as they can be blocked via pretreatment with the selective $GABA_A$ competitive antagonist flumazenil. Here we test the prediction that the anti-anhedonic and synaptic responses to these compounds specifically require the $GABA_AR$ α5 subunit. Eight-week old, male C57BL/6J mice were subjected to a 10-day chronic multimodal stress paradigm, sufficient to induce anhedonia, as measured with sucrose and female urine sniffing preference tests. Strength of TA-CA1 synaptic transmission was compared between $GABA_AR$ α5 KO and wild-type animals treated with either MRK-016 or vehicle, as quantified via fEPSP AMPA:NMDA ratios. Additionally, we posit that an increase in cortical quantitative electroencephalogram (qEEG) gamma-power is associated with the persistent antidepressant-like activity of rapid-acting antidepressants. A single IP injection of MRK-016 (3 mg/kg) significantly reversed deficits in these reward behaviors in wild-type animals with intact $GABA_A$ α5 subunits. C57BL/6J mice lacking the α5 subunit ($GABA_AR$ α5 KO) showed no significant improvement in post-stress anhedonic state following MRK-016 treatment. MRK-016 induced significant increases in gamma-power in wild-type, but not in $GABA_AR$ α5 KO animals. Significant increases in gamma-power over baseline were achieved in both strains of animals

following a single IP injection of 10 mg/kg (*R,S*) ketamine, confirming that the absence of the $GABA_A$ α5 subunit does not preclude increases in gamma-power in response to a different rapid-acting antidepressant. We conclude that GABA-NAMs act via the benzodiazepine binding site of α5-containing $GABA_A$Rs to produce a transient increase in correlated neuronal discharge at gamma frequencies, thereby inducing intrinsic activity-dependent synaptic strengthening in critical reward circuits, which may be responsible for its anti-anhedonic actions. α5 selective GABA-NAMs thus have potential as novel, fast-acting antidepressants.

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Poster

776. Mood Disorders: Molecular Mechanisms and Approaches

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 776.21/W6

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: P50MH096890
R01MH051399

Title: Blood microRNAs as biomarkers for stress susceptibility or resiliency and treatment response

Authors: *Y. Y. VAN DER ZEE[1], O. ISSLER[2], D. M. WALKER[3], A. TORRES-BERRÍO[4], E. M. PARISE[5], A. RAMAKRISHNAN[6], J. W. MURROUGH[6], B. P. RUTTEN[7], E. J. NESTLER[8]; [1]Maastricht Univ., Maastricht University, Netherlands; [3]Neurosci., [2]Icahn Sch. of Med. at Mount Sinai, New York, NY; [4]Neurosci., Icahn Sch. of Med. At Mount Sinai, New York, NY; [5]Dept. of Neurosci., Ichan Sch. of Med. At Mount Sinai, New York, NY; [6]Icahn Sch. of Med., New York, NY; [7]Maastricht Univ. Med. Ctr., Maastricht, Netherlands; [8]Icahn Sch. Med. at Mount Sinai, New York, NY

Abstract: Major depressive disorder (MDD) is an episodic form of mental illness that is characterized by mood disturbances, anhedonia, and alterations in cognitive function. There is a great need for objective biological indicators for the diagnosis of MDD, for prediction of treatment response and for assessment of treatment efficacy. In recent years, small noncoding RNAs known as microRNAs (miRNAs) have been acknowledged as key actors in numerous diseases including mental disorders such as MDD. These molecules act as potent epigenetic post-transcriptional regulators of gene expression. Interestingly, miRNAs can be detected in the circulation and there is evidence for correlations between specific circulating miRNA levels and disease states, suggesting a potential use for these molecules as biomarkers. The present study explored the potential use of miRNAs as biomarkers for MDD and for prediction and assessment

of treatment response. To that end, we performed Nanostring analysis on miRNAs from whole blood of mice that was collected before and after exposure to the chronic social defeat stress (CSDS), as well as after antidepressant treatment (*i.e.*, imipramine or ketamine). This allowed us to profile the expression levels of approximately 600 circulating miRNAs and explore whether they can predict behavioral response to CSDS or antidepressant treatment. Our results demonstrate widespread changes in miRNA expression after stress and antidepressant treatment. Both resilient and susceptible mice demonstrate strong regulatory changes in miRNA expression levels directly after CSDS when compared to control mice. Interestingly, more miRNAs are regulated in susceptible mice treated with ketamine as opposed to mice treated with imipramine. As a result, we have identified a subset of miRNAs that might serve as candidate biomarkers to aid diagnosis and predict treatment response. To probe the involvement of these miRNAs in human drug response, we are conducting qRT-PCR on the blood of treatment resistant depressed patients compared to controls before and after treatment with ketamine. Taken together, this study enhances our understanding of epigenetics changes in response to stress and provides a potentially actionable set of biomarkers for use in clinical settings.

Disclosures: **Y.Y. van der Zee:** None. **O. Issler:** None. **D.M. Walker:** None. **A. Torres-Berrío:** None. **E.M. Parise:** None. **A. Ramakrishnan:** None. **J.W. Murrough:** None. **B.P. Rutten:** None. **E.J. Nestler:** None.

Poster

776. Mood Disorders: Molecular Mechanisms and Approaches

Location: Hall A

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Program #/Poster #: 776.22/W7

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: National Natural Science Foundation of China (No. 81402910)

Title: Genetic and pharmacological inhibition of two-pore domain potassium channel TREK-1 alters depression-related behaviors and neuronal plasticity in the hippocampus in mice

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Abstract: The two-pore domain potassium channel TREK-1 is a member of background K^+ channels that are thought to provide baseline regulation of membrane excitability. Recent studies have highlighted the putative role of TREK-1 in the action of antidepressants, and its antagonists might be potential effective antidepressants. However, the mechanisms underlying the actions of TREK-1 are not yet fully understood. Here, we demonstrated that chronic unpredictable mild stress (CUMS) increased TREK-1 expression in the mouse hippocampus. Knockdown of TREK-

1 in hippocampal neurons significantly attenuated depressive-like behaviors and prevented the decrease of CUMS-induced synaptic proteins and dendritic spines in mice. Further examination indicated that neuron-specific knockdown of TREK-1 in the hippocampus prevented stress-induced impairment of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid-mediated synaptic transmission in the CA1 region. Moreover, chronic TREK-1 inhibition protected against CUMS-induced depressive-like behaviors and impairment of synaptogenesis in the hippocampus. Taken together, our results indicate a role for TREK-1 in the modulation of synaptic plasticity in a mouse model of depression. These findings will provide insight into the pathological mechanism of depression and further evidence for a novel target for antidepressant treatment.

Disclosures: F. Wu: None. **Z. Zhang:** None.

Poster

776. Mood Disorders: Molecular Mechanisms and Approaches

Location: Hall A

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Program #/Poster #: 776.23/W8

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: NIMH P50MH096890
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Hope for Depression Research Foundation

Title: Astrocyte-specific expression of the extracellular matrix gene Htra1 regulates susceptibility to stress in a sex specific manner

Authors: *E. M. PARISE[1], A. TORRES-BERRÍO[1], C. J. BROWNE[1], T. M. GYLES[2], L. F. PARISE[1], Y. VAN DER ZEE[1], Z. S. LORSCH[1], P. J. HAMILTON[3], B. LABONTÉ[4], S. J. RUSSO[1], E. J. NESTLER[1];
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Abstract: Major Depressive Disorder (MDD) is a highly debilitating and costly mental disorder affecting more than 300 million people worldwide. While the underlying pathophysiology is poorly understood, convergent evidence from pre-clinical and clinical research supports the idea that MDD is related to impaired structural plasticity in key limbic brain areas. However, how these structural brain abnormalities contribute to MDD pathology is unknown. The extracellular matrix (ECM) of the brain represents a novel avenue for study and potential therapeutics as it not only provides structural support but is intimately involved in regulating synaptic plasticity and remodeling. We hypothesized that alterations to this complex network of proteins surrounding

neurons and glial cells could regulate morphological processes that may be involved in MDD. To that end, 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 that exhibit depression-like behavioral abnormalities after exposure to chronic variable stress (CVS). A large number of ECM-specific genes were identified as being differentially expressed, however, only those that were similarly dysregulated across species were selected for downstream manipulations. In particular, we identified *Htra1*, an astrocyte-enriched secreted serine protease, as being significantly and consistently down-regulated in males and significantly up-regulated in females in both species. Using a combination of viral and transgenic tools, we show that selective manipulation of the *Htra1* gene in astrocytes within the mouse NAc increases susceptibility to stress in a sex-specific manner. Taken together, 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.

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Poster

776. Mood Disorders: Molecular Mechanisms and Approaches

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Program #/Poster #: 776.24/W9

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: P50MH096890
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Hope for Depression Research Foundation

Title: Transcriptional signatures of treatment resistant depression in mouse models

Authors: *A. TORRES-BERRIO[1], E. M. PARISE[2], T. GYLES[3], F. J. MARTINEZ[4], C. J. BROWNE[5], E. J. NESTLER[6];
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Abstract: Major Depressive Disorder (MDD) is the most prevalent psychiatric disorder in the world, representing a high level of global economic burden. Despite decades of research, the treatments for MDD remain inadequately effective for roughly half of patients due to the heterogeneity of depressive symptoms and our limited understanding of the molecular

mechanisms associated with treatment response. Fluoxetine (FLX), a selective serotonin reuptake inhibitor (SSRI), has been widely used to treat MDD; however, a majority of patients do not achieve full remission. As an alternative, ketamine (KET), an antagonist of the glutamate N-methyl-D-aspartate (NMDA) receptor among other actions, induces a rapid antidepressant response thus providing a novel therapeutic approach. Importantly, KET has been shown to be effective in ~50% of patients who fail to show full responses to FLX or other SSRI antidepressants. However, the molecular mechanisms underlying this effect are poorly understood. This study was aimed at characterizing the transcriptional profile of successful response to KET in FLX-treatment resistant mice. We exposed adult male mice to chronic social defeat stress (CSDS), a validated mouse model for the study of depression that differentiates between resilient and susceptible mouse populations based on a social interaction test (SIT). Mice exhibiting reduced social interaction were classified as susceptible and underwent antidepressant treatment with FLX in their drinking water for 28 days. After FLX treatment, we identified a subset of mice that continued to show reduced social interaction despite treatment (non-responders). FLX non-responder mice were subsequently given a single injection of KET and assessed in the SIT. We found that FLX treatment primed successful antidepressant response to a single KET injection in comparison to non-responder mice treated with water. We present RNA-seq transcriptional profiling of key neural circuits implicated in MDD, including the prefrontal cortex, nucleus accumbens, ventral hippocampus, and ventral tegmental area of responder and non-responder mice to FLX and KET treatments.

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Poster

777. Mood Disorders: Depression and Bipolar Disorders: Animal Studies

Location: Hall A

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Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: National Center of Competence in Research (NCCR) Synapsy
The Préfargier Foundation
King Abdullah University of Science and Technology (KAUST)

Title: Role of adult hippocampal neurogenesis in the antidepressant effects of lactate

Authors: *A. CARRARD[1], F. CASSÉ[1], S. BURLET-GODINOT[1], N. TONI[1], P. J. MAGISTRETTI[2], J.-L. MARTIN[1];
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Abstract: Astrocytes are key players in energy metabolism and glutamate transport. In particular, astrocytes respond to glutamate by increasing the rate of glucose utilization and the release of lactate (Magistretti and Allaman, Nat Rev Neurosci. 2018). Growing evidence indicates that astrocytes are also involved in the pathophysiology and treatment of depression. For instance, SSRIs stimulate lactate release from cortical astrocytes. Recently, we showed that acute lactate administration increased lactate concentration in the hippocampus and reduced immobility in the forced swim test (Carrard et al, Mol Psychiatry 2018). We further investigated the antidepressant-like behavioral effects of lactate in two animal models of depression that respond to chronic antidepressant treatment; the corticosterone model of depression and the open-space forced swim model of depression. We found that chronic administration of lactate improved depressive-like behavior (Carrard et al, Mol Psychiatry 2018). In particular, chronic lactate injection reversed the corticosterone-induced anhedonia-like behavior and partially restored mobility in the open-space forced swim model of depression, in a manner similar to desipramine. The antidepressant effects of lactate are associated with changes in the expression of specific target genes of which Hes5 is involved in adult hippocampal neurogenesis. These findings led us to investigate the role of adult hippocampal neurogenesis in the antidepressant effects of lactate.The involvement of hippocampal neurogenesis in the antidepressant effects of lactate was assessed in the corticosterone model of depression. We found that chronic peripheral injections of lactate counteracted the decreased neural progenitor proliferation and survival induced by chronic corticosterone treatment. In contrast, chronic administration of pyruvate did not produce antidepressant effects and did not prevent the inhibition of neural progenitor proliferation and survival induced by chronic corticosterone injections. Furthermore, depletion of adult hippocampal neurogenesis by administration of the antimitotic drug temozolomide suppressed the antidepressant-like effects of lactate in the chronic corticosterone paradigm. Collectively, these data emphasize the importance of adult hippocampal neurogenesis in the antidepressant effects of lactate.

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Poster

777. Mood Disorders: Depression and Bipolar Disorders: Animal Studies

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 777.02/W11

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Title: Subcutaneous administration of beta-hydroxybutyrate produces antidepressant like effects in a rodent model of depression caused by interferon-α

Authors: *R. MATSUO, M. IWATA, N. KAJITANI, T. YAMANASHI, K. TSUNETOMI, M. SHIBUSHITA, A. MIURA, T. NISHIGUCHI, K. KANEKO;
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Abstract: Interferon-α (IFN-α) is a potent pro-inflammatory cytokine, which is used for the treatment of chronic hepatitis C and some types of leukemia or cancer. While there are many beneficial aspects, IFN-α therapy causes numerous side effects such as fever, fatigue, anorexia, and depression. Amongst the various side effects of IFN-α, depression is a severe side effect which may result in the termination of IFN-α therapy. Although it is unclear how IFN-α causes depression, recent studies demonstrate a role for the involvement of intracerebral inflammation, including evidence that the interleukin-1β (IL-1β) causes depressive behavior. Previously we had reported that stress increases ATP, which activates the Nucleotide-binding protein, Leucine-rich repeat, Pyrin domain containing 3 (NLRP3) inflammasome, which in turn promotes the formation of mature IL-1β in the rat brain. Also, it is well known that IFN-α induces pro-inflammatory cytokines such as IL-1β and tumor necrosis factor α (TNF-α). Thus, we propose a hypothesis that the inhibition of the NLRP3 inflammasome will produce an antidepressant effect by preventing IL-1β production caused by IFN-α therapy. Recently, it has been reported that beta hydroxybutyrate (BHB), a ketone body that supports mammalian cell metabolism during states of energy deficiency, such as fasting or exercise, reduces NLRP3 inflammasome mediated production of IL-1β. We have found that peripheral BHB administration suppressed NLRP3 activation and reduced pro-inflammatory cytokines such as IL-1β and TNF-α, which improved anxious and depressive behaviors in a rodent chronic unpredictable stress (CUS) model of depression. In this study, we aimed to evaluate the possible beneficial effects of BHB in rat depression model caused by IFN-α. The model was made administrating IFN-α daily for seven days, as other groups have already published. Here we show that BHB administration twice a day for fourteen days after making depression model produces antidepressant effects in evaluated elevated plus maze (EPM) test and forced swim test (FST). These findings suggest that BHB may be a therapeutic candidate for the treatment of depression caused by IFN-α.

Disclosures: R. Matsuo: None. **M. Iwata:** None. **N. Kajitani:** None. **T. Yamanashi:** None. **K. Tsunetomi:** None. **M. Shibushita:** None. **A. Miura:** None. **T. Nishiguchi:** None. **K. Kaneko:** None.

Poster

777. Mood Disorders: Depression and Bipolar Disorders: Animal Studies

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 777.03/W12

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: FR AR 17_333

Title: Acoustic range electromagnetic stimulation reduces anxiety degree in depressed rats

Authors: *N. BUKIA[1], L. MACHAVARIANI[1], M. SVANIDZE[1], M. BUTSKHRIKIDZE[1], N. JOJUA[2];
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Abstract: Depression is one of the most common disorders. Despite the fact that it is possible to treat depression using pharmacological substances, about 35-40% of the patients are resistant to such treatment. The electric-magnetic stimulation (EMS) is a noninvasive treatment method, it is used as a complementary to the drugs, for treating different neurodegenerative diseases. Neonatal administration of clomipramine (25 mg/kg) produces physiological, neuroendocrinal and behavioral abnormalities in rats which are similar to those observed in animal models of depression. So, the goal of this study was to explore the impact of EMS on the ECoG activity and anxiety degree in clomipramine -induced depressed rats. Parameters of EMS which full or partially depressed EEG and behavior manifestation of depression, were established during pilot experiments. The forced swim test (FST) and open field test were chose. Experimental group of rats received EMS before testing. Data reliability was assessed using parametric and non-parametric techniques, with the use of one- way layout of factorial analysis. We have obtained the optimal parameters of repeated EMS (10000 -15000 Hz frequency, 1,5 m/Tesla, during 15 min, 10 days), which full or partially Inhibited depressive-like behavior in rats. In depressed rats domination of delta-wave were registrated. Besides, separate, low amplitude beta waves were recorded. Predominance of delta-waves were in positive correlation with the level of rat immobilization in the FST and open field test. On the background of EMS restoration of Beta waves and reduction of the Delta-waves were detected. The EMS reduced immobility time in the FST ($p < 0.05$) in depressed rats compared to nonstimulated one's. Besides, the EMS increased struggling behavior ($p < 0.05$) and swimming in the FST ($p < 0.05$). EMS have no effect on time spent under the water. On the background of EMS in depressed rats, the number of crossed squares ($P \leq 0.01$), hole reflex ($P \leq 0.01$) and head lifts ($P \leq 0.05$) were increased in the Open field test. The number of vertical stands ($P \leq 0.05$), duration ($P \leq 0.05$) and the number of grooming episodes ($P \leq 0.01$), as well as the number of fecal boluses and the frequency of urination were decreased. The present study identified a positive effects of EMS on the treatment of depression-like activity in rats. The acoustic range EMS decreases fear and anxiety degree and consequently, increases the escape activity in FST and exploratory activity in open field test. Therefore, findings of this study will promote the development of new approaches to the treatment of depression.

Disclosures: **N. Bukia:** None. **L. Machavariani:** None. **M. Svanidze:** None. **M. Butskhrikidze:** None. **N. Jojua:** None.

Poster

777. Mood Disorders: Depression and Bipolar Disorders: Animal Studies

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Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: MRC Grant MR/L011212/1
BBSRC Grant BB/L009137/1
University of Bristol Research Postgraduate Studentship

Title: The affective bias test: A refined and translational method for assessment of novel antidepressants

Authors: *J. K. HINCHCLIFFE, E. S. J. ROBINSON;
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Abstract: For more than 40 years the pre-clinical methods for research into antidepressants has been the forced swim test and tail suspension test. Whilst these assays have been very useful in the development of many of the antidepressant treatments used today, it is now becoming apparent that they only really work for drugs acting through a specific neurochemical system and they show a much poorer ability to predict clinical outcomes. We sought to develop an alternative method to study depression-related biology in rodents which would also avoid the need to use aversive methods and have better translational validity. The affective bias test (ABT) is a bowl digging task based on associative learning and memory. Translated from clinical observations in patients with mood disorders and evidence that they experience impairments in reward-related learning and memory, the task requires animals to learn two independent cue-reward associations (digging in specific substrate to obtain food reward). The value of each experience is the same but affective state can be manipulated prior to one of the experiences. Using a choice test the animal is then 'asked' which do you prefer? We have been able to establish that treatments which cause depression in humans will induce negative biases in this task i.e. the animal is less likely to choose the cue-reward association learnt following treatment. The opposite is seen with treatments which are antidepressant with animals showing a positive bias towards these cue-reward associations. Because the absolute value of the reward is kept constant, these biases can be attributed to the animal's affective state at the time of learning. We have shown that delayed vs rapid onset antidepressants differentially modulate biases in this assay and that animals exposed to early life adversity show increased vulnerability to negative biases. We suggest that the ABT demonstrates face, predictive, construct and translational validity. The ABT has a medium to large effect sizes across different rodent strains and is effective in males and females.

Disclosures: J.K. Hinchcliffe: None. **E.S.J. Robinson:** None.

Poster

777. Mood Disorders: Depression and Bipolar Disorders: Animal Studies

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Program #/Poster #: 777.05/W14

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: Spanish Ministry of Economy SAF2016-79008-P
PPIT.UMA.B1.2017/17

Title: The effect of Galanin N-terminal fragment (1-15) in anhedonia: Involvement of the dopaminergic mesolimbic system

Authors: *C. MILLÓN[1], A. FLORES-BURGESS[1], B. GAGO[1], L. GARCÍA-DURÁN[1], N. CANTERO-GARCÍA[1], F. ALÉN[2], L. ORIO[2], J. NARVÁEZ[1], K. FUXE[3], L. SANTÍN[4], Z. DÍAZ-CABIALE[1];
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Abstract: The Galanin N-terminal fragment (1-15) [GAL(1-15)] induces depressant- and anxiogenic-like actions in behavioral tests and these effects were significantly stronger than the ones induced by Galanin. Since anhedonia is a core feature of depression, we have analyzed GAL(1-15) actions in two anhedonic-like behavior tests: saccharin Self-administration and Sucrose Preference test (SPT). In order to investigate whether the effect of GAL(1-15) was associated with the reward circuit, we have studied the GAL(1-15) actions over the mesolimbic system by the expression of the C-Fos, Dat, Vmat2 and Dopamine and GAL receptors genes in VTA and NAc. Three sets of experiments were conducted in the saccharin Self-administration test. In the first, a dose-response curve of GAL(1-15) 1nmol, 3nmol or vehicle was performed. We have also compared the effects in the number of saccharine reinforcements of GAL 3nmol and GAL(1-15) 3nmol. In the last experiments, rats received i.c.v. GAL(1-15) 3nmol and the GALR2 antagonist M871 3nmol. In SPT, we have analyzed the effects of GAL(1-15) 3nmol in the sucrose intake and preference after 2, 8 and 24 h. In the qPCR experiments, groups of rats were killed 1h after i.c.v. GAL(1-15) 3nmol or vehicle. The VTA and NAc were dissected and the mRNA expression of C-Fos, Dat, Vmat2 and D1, D2, D3, D5, GALR1, and GALR2 receptors were measured. GAL(1-15) 3nmol significantly decreased the number of reinforcement of saccharin self-administer ($p<0.01$), while 1nmol lacked effect. GAL(1-15) also significantly reduced the number of reinforcement ($p<0.01$) compared with GAL. The GALR2 antagonist M871 significantly blocked ($p<0.05$) the decrease in the number of saccharin reinforcements induced by GAL(1-15). In the SPT, GAL(1-15) decreased the sucrose intake 8 ($p<0.05$) and 24 hours ($p<0.01$) after administration. GAL(1-15) at a dose of 3 nmol produced a significant

decrease in the mRNA levels of Dat and Vmat2 ($p<0.05$) and an increase in the D3 receptor ($p<0.05$) in VTA. In the NAc, GAL(1-15) induced a significant decrease in the expression of C-Fos ($p<0.05$) mRNA and a significantly increased the mRNA expression of D1 ($p<0.05$), D2 ($p<0.05$) and D3 ($p<0.05$). In the current study, we described for the first time that GAL(1-15) induced a strong anhedonia-like phenotype in several behavioral tests, confirming an important role of this neuropeptide in anhedonia, moreover, the dopaminergic mesolimbic system was described as a key region in GAL(1-15)-mediated action on anhedonia. These results may give the basis for the development of novel therapeutic strategies using GAL(1-15) for treatment of depression and reward-related diseases.

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Poster

777. Mood Disorders: Depression and Bipolar Disorders: Animal Studies

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Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

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Fondation de France (00081244)
EURIDOL Graduate School of Pain

Title: Role of amygdalo-cingulate pathway in major depressive disorder

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Abstract: Major Depressive Disorder (MDD) is a chronic and debilitating disease with poor treatment outcomes. Although significant achievements have been yielded in the field, there is

still a need for identifying mechanisms underlying MDD. Compelling evidence from animal models and human studies suggest a crucial role of the anterior cingulate cortex (ACC) and the anterior part of the basolateral amygdaloid nucleus (BLA) in the development of MDD. Moreover, track-tracing analysis conducted by our team, highlighted a strong reciprocal connection between areas 24a/24b of the ACC and the BLA, making this pathway a good candidate to begin the dissection of the ACC connectome in mood disorders. In order to manipulate the BLA-ACC pathway in C57BL/6J naive mice we used an optogenetic approach. An AAV5 coding for the channelrhodopsine was injected in the BLA and repeated blue light pulses were delivered in areas24a/24b of the ACC to activate the pathway. Using a battery of behavioural tests we showed that chronic activation of the BLA-ACC pathway induced depressive but not anxiety-like behaviours. The need for repeated stimulation strongly suggests the setting up of plasticity mechanisms.In parallel we also assessed the impact of BLA-ACC pathway activation on whole brain connectivity using resting-state functional magnetic resonance imaging. We observed altered connectivity between ACC and amygdala and mesolimbic pathway as well as between BLA and brain structures coding aversive states. Thus, BLA-ACC activation seems to alter global brain connectivity and mimic some of the changes observed in other animal model of depression and patients.To go further, we tested if the inhibition of the BLA-ACC connection could alleviate the anxiodepressive-like behaviours in a chronic pain-induced depression model. A polyethylene cuff was inserted around the principal branch of the sciatic nerve to induce an immediate and long-lasting allodynia, along with anxiodepressive-like behaviours emerging 6 weeks after the surgery. We injected an AAV5 coding for the archaerhodopsine in the BLA and delivered green light in the ACC during behavioral testing to inhibit the BLA-ACC connection. This manipulation resulted in an improvement of the depressive but not anxiety-like behaviour without affecting the mechanical allodynia, consistent with data obtained when activating this pathway in naive mice.Altogether these data reveal the importance of the BLA-ACC pathway in emotional regulation and highlight the need of dissecting circuits rather than single structure to deepen our understanding of mechanisms underlying mood disorders.

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Poster

777. Mood Disorders: Depression and Bipolar Disorders: Animal Studies

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 777.07/W16

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: Hacettepe University Scientific Research Projects Coordination Unit (Project number THD-2016-11687)

Title: FGF-AS overexpression in medial prefrontal cortex is depressogenic

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Abstract: Background: The natural antisense transcripts (NATs) are widespread in a great range of organisms, from prokaryotes and viruses to humans. NATs are shown to regulate protein synthesis in prokaryotes and viruses, however, their role in eukaryotes is poorly understood. Most NATs are not translated into a protein and are thought to control their sense partners' expression. Fibroblast growth factor antisense (FGF-AS) is a NAT, transcribed from the opposite strand of fibroblast growth factor 2 (FGF2) gene. We previously showed the role of hippocampal FGF-AS on depression- and anxiety-like behaviors in rats. We also reported that FGF-AS overexpression in medial prefrontal cortex (mPFC), a region known to be involved in the pathophysiology of the affective disorders, increased anxiety-like behavior. In this study we aimed to investigate the effects of increased expression of FGF-AS in mPFC on depression-like behavior.
Methods: FGF-AS expressing adeno-associated virus 2 (AAV2) (n=16) or a blank control AAV2 (n=13) was injected into both prelimbic and infralimbic regions in mPFC of 8-10 week-old male wild type Sprague Dawley rats. Four weeks later, sucrose preference test (SPT) and forced swim test (FST) were performed to evaluate depression-like behavior, anhedonia and behavioral despair, respectively. Depending on the distribution of the data, Student T-test or Mann Whitney U test was used to compare groups.
Results: FGF-AS overexpression did not change the preference of rats for sucrose ($p=0.694$) but it increased time spent immobile ($p= 0.095$) and decreased time spent swimming in FST ($p= 0.093$).
Conclusion: We reported an increase in behavioral despair by FGF-AS overexpression in mPFC, in parallel with its previously reported anxiogenic effects. Our findings indicate the role of medial prefrontal FGF-AS in some but not in all depressogenic behaviors. Since SPT and FST model different symptomatic aspects of depression, which may be mediated by different brain networks, effects of manipulations of FGF-AS expression in other brain regions on different symptomatic aspects of depression should be studied further.

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Poster

777. Mood Disorders: Depression and Bipolar Disorders: Animal Studies

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Title: Characterization of a novel rare missense variant of the D-amino acid oxidase gene as a penetrant cause of psychosis

Authors: *N. HASIN[1], L. M. RIGGS[2,3], T. SHEKHTMAN[6], J. BADNER[7], D. W. CRAIG[8], J. I. NURNBERGER[9], E. GERSHON[10], J. R. KELSOE[6], J. C. ROACH[11], T. G. GOULD[2,4,5,12], S. AMENT[1,2];
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Abstract: Despite the familial prevalence of adult-onset psychiatric disorders, only a handful of genetic variants have been shown to dramatically increase the risk for these conditions. Previously, we conducted linkage analyses of 972 multiply affected pedigrees with bipolar disorder and found evidence that large-effect variants may exist in a subset of these pedigrees. However, causal variants have yet to be identified. To address this, we conducted whole-genome sequencing in 40 of the 972 pedigrees to identify pedigree-specific large-effect risk variants. By analyzing these genomes together with exome and genome sequences from an additional 2,536 psychiatric cases and 198,840 controls, including population reference datasets, we identified an ultra-rare nonsynonymous variant (G131V) in the *DAO* gene that co-segregated with bipolar disorder in a four-generation pedigree and was significantly associated with risk for psychotic disorders across the combined dataset (p-value = 4.5×10^{-14}). *DAO* encodes D-amino acid oxidase, which has been shown previously to modulate anxiety-like behavior in mice via degradation of the *N*-methyl-D-aspartate receptor (NMDAR) co-agonist, D-serine. Convergent evidence supports a role for aberrant NMDAR neurotransmission in psychiatric disease. In

addition, structural modeling predictions indicate that the G131V substitution could destabilize DAO protein. Thus, we hypothesized that impaired function of DAO via the G131V mutation confers risk for the onset of bipolar disorder. To test this hypothesis, we used site-directed mutagenesis to introduce the DAO G131V variant into HEK293T cells *in vitro.* We found that DAO G131V led to a ~50% reduction in DAO protein levels. Moreover, DAO enzymatic activity was essentially ablated due to the G131V mutation. To further characterize DAO G131V, we generated a new knock-in mouse, using Cas9 genome editing to introduce the precise mutation observed in patients at the endogenous *Dao* locus. Ongoing studies are characterizing the molecular, cellular, and behavioral changes that are associated with the DAO G131V variant in the mouse line *in vivo*.

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Poster

777. Mood Disorders: Depression and Bipolar Disorders: Animal Studies

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 777.09/W18

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: FAPESP 2014/18929-9
CAPES Finance code 001

Title: Ginkgo biloba extract reduces oxidative stress and inflammation while restores 5-HT_{1A} serotonin receptor levels in hippocampus of ovariectomized rats

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Abstract: Menopause is associated with the development of physical and psychological alterations related to reduction of estrogen levels. In cerebral structures involved in cognition and memory such as the hippocampus, hypoestrogenism may impair synaptic signaling, contributing to the emergence of cognitive disturbances. Furthermore, cognitive impairment is also associated with the accumulation of oxidative damages to different cells compounds. *Ginkgo biloba* extract (GbE), a widely used herbal supplement, is recognized as an antioxidant and anti-inflammatory agent. We previously demonstrated a stimulatory effect of GbE on the hypothalamic serotonergic system of ovariectomized rats. Therefore, the aim of this study was to evaluate GbE action on oxidative stress, inflammation and 5-HT receptors levels in hippocampus of ovariectomized rats.

Two-month-old female Wistar rats were ovariectomized (OVX) or not (SHAM). Sixty days after surgery, OVX rats were given 500mg/kg of GbE (OVX+GbE) daily by intragastric gavage, while SHAM and OVX groups received saline 0.9% (vehicle) for 14 days. After treatment, rats were euthanized and their hippocampi were removed. Both 5-HT_{1A} (-52.4%; $p<0.001$) and 5-HT_{1B} (-43.8%; $p=0.044$) levels were significantly reduced in OVX rats in comparison to SHAM rats, while GbE partially reversed the effect of OVX on 5-HT_{1A} (38.8%; $p=0.013$). Superoxide dismutase activity was 98% higher in OVX rats in relation to SHAM rats ($p=0.027$), while no differences were observed between SHAM and OVX+GbE groups. Additionally, OVX+GbE rats also presented a significant reduction in phospho-NF-κBp50 levels in comparison to SHAM (-29%; $p=0.006$) and OVX groups (-24%; $p=0.025$), as well as a reduction of 36% phospho-ERK/ERK ratio in comparison to SHAM group ($p=0.034$). In summary, the present data shows that GbE improves oxidative stress and inflammation markers and restores 5-HT_{1A} levels in hippocampus of OVX rats. Since the development of psychological diseases are common features of estrogen depletion, these findings indicate a promising therapeutic use of GbE for menopausal women.

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Poster

777. Mood Disorders: Depression and Bipolar Disorders: Animal Studies

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Support: NIH Grant R01MH104261
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Hope for Depression Research Foundation
Pritzker Neuropsychiatric Research Consortium
NIDA Grant U01DA043098

Title: The role of developmental and environmental factors in a mouse model of high emotional reactivity

Authors: *D. MURRA, K. L. HILDE, Q. WEI, L. ZHANG, E. K. HEBDA-BAUER, Z. FREEMAN, S. J. WATSON, Jr., H. AKIL;
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Abstract: Early life adversity and genetic factors both influence the development and expression of mood disorders and future emotional reactivities to stress. Although numerous studies have sought to describe individual factors that predispose adults to depression, anxiety, and

other psychiatric disorders, the interplay and hierarchy of these individual factors and their combinations are not fully understood. In this study, we sought to incorporate a genetic mouse model of predisposition to emotional lability, multiple environmental stress models, and various behavioral outcomes to untangle the many factors that influence the propensity of developing adult anxiety and depression-like behavior. Genetically, we have previously shown that constitutive overexpression of the glucocorticoid receptor (GRov) in the forebrain during only the first 3 weeks of life resulted in long-lasting gene-expression changes and increased anxiety-like behavior in adulthood. Because of their role in the transduction of the stress responses, glucocorticoid hormones and their receptors serve as both genetic factors and mediators environmental influences, and thus the extent of emotional reactivity. Moreover, we compared two models of early life stress: maternal separation and developmental enrichment to ask what environmental manipulations change the genetic and control susceptibility to subsequent adulthood anxiety-like behavior. We used those individual factors and their combinations, that when expressed during a critical period of development(P1-P21), to induce future vulnerability or resilience to anxiety-like behavior. Moreover, we were able to further manipulate those factors in adulthood with group and single housing to test the stability of each factor to carry on its behavioral phenotype. Finally, this then allowed us to create a hierarchy model of environmental and genetic interactions that influence emotional reactivity.

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Poster

777. Mood Disorders: Depression and Bipolar Disorders: Animal Studies

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Program #/Poster #: 777.11/W20

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: P50MH096890
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Hope for Depression Research Foundation

Title: Sex-specific role for long non-coding RNAs in depression: Focus on linc00473 as a female-specific effector of CREB signaling

Authors: *O. ISSLER[1], Y. Y. VAN DER ZEE[1], A. RAMAKRISHNAN[1], Y.-H. E. LOH[1], I. PURUSHOTHAMAN[1], J. WANG[2], C. TAN[3], D. M. WALKER[1], Z. S. LORSCH[1], P. J. HAMILTON[1], C. J. PENA[4], B. J. HARTLEY[1], E. FLAHERTY[1], A. TORRES BERRÍO[1], E. M. PARISE[1], H. KRONMAN[1], E. S. CALIPARI[5], B. LABONTÉ[6], C. A. TAMMINGA[7], K. J. BRENNAND[1], Y. DONG[2], L. SHEN[1], E. J. NESTLER[1];
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Abstract: Depression is a common, chronic and debilitating disorder. Women are twice as likely to suffer from depression as men, yet the molecular mechanisms contributing to this sex difference remain poorly understood. Long non-coding RNAs (lncRNAs) are a recently discovered class of regulatory transcripts which represent a substantial portion of the human genome. To explore the role of lncRNAs in depression we utilized a comprehensive genome-wide profile of RNAs in six brain regions from both male and female post-mortem depressed and control human subjects. Overall, lncRNAs represent about one-third of the differentially expressed genes in depressed subjects compared to controls, and displayed complex region- and sex-specific patterns of regulation. Furthermore, we identified specific targets lncRNAs with potential sex-specific roles in depression. One of these targets is the neuronal gene linc00473, which is downregulated in prefrontal cortex (PFC) and several other brain regions in depressed females, but not males. To explore the causal role for linc00473 in depression, we virally expressed it in mouse PFC neurons. This approach mirrored the human sex-specific phenotype, as expressing linc00473 consequently induced stress resilience in females only. Furthermore, electrophysiological recordings from PFC pyramidal neurons expressing linc00473 compared to control indicated changes in synaptic properties in female mice only. To analyze the molecular mechanism of action of this lncRNA, we performed RNA sequencing on PFC infected with the linc00473 or control viruses either at baseline or following exposure to chronic stress. We found that expressing the linc00473 blunted the normal transcriptional changes in response to stress that was observed in control mice. Furthermore, CREB and cAMP signaling were predicted as upstream regulators of the genes whose levels were altered in mice expressing linc00473. Finally, we utilized Chromatin Isolation by RNA Purification (ChIRP) assay to identify direct DNA biding sites of linc00473 in human neuroblastoma cells either at baseline or following treatment with forskolin, an activator of adenylyl cyclase. Notably, in the forskolin group linc00473 bound genes enriched for those implicated in brain activity in general, and in anxiety and depression in particular. Taken together our studies identify linc00473 as a female pro-resilient effector of CREB signaling that is aberrant in female depression. These studies provide a fundamentally new view of molecular adaptations in brain that contribute to sex-specific stress resilience and may lead to the identification of novel targets for treatment.

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Poster

777. Mood Disorders: Depression and Bipolar Disorders: Animal Studies

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Program #/Poster #: 777.12/W21

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: 511-6/17-8017; BUAP-PTC-550

Title: Cannabinoid CB1 receptors blockade, decreases food intake and anxiety events in rats with metabolic syndrome

Authors: *M. MUNOZ ARENAS, B. VÁZQUEZ-GONZÁLEZ, A. DÍAZ;
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Abstract: Metabolic syndrome (MS) is characterized by insulin resistance, hyperglycemia, hypertension etc. Insulin resistance consist in a poor activation of insulin receptor and this event decreases glucose uptake and storage; in compensation, beta pancreatic cells increase production and secretion of insulin. It has been demonstrated that CB1 receptor activation, produce an increment in glucose concentration in blood, while blocked of these receptors decrease the zoometric measure and the insulin resistance in diabetic rats. The objective of this work was to evaluate the anxiety and depression behavior in rats with metabolic syndrome and to evaluate oxidative stress in brain areas implicated in anxiety. 32 wistar male rats were divided in two groups: Normocaloric (n= 16) and Hypercaloric/hyperglycemic diet (n= 16). Rats were alimented during 90 days for to stablish MS. After to induce MS, rats were divided again in four groups: SSI (1 mL/kg), ACEA (0.25 mg/kg), AM251 (0.1 mg/kg) and ACEA+AM251. All drugs were administrated intraperitoneally during 15 days. We evaluated anxiety in the open field test and the depression in the tail suspension test. CB1 receptors activation increase hyperglycemia and increase depression in rats with MS, while antagonism of these receptors produce contrary effect but increase anxiety in the rats. Diary administration of AM251decreases insulin concentration and food intake. We propose that blocked of CB1 receptors could be an important terapy in the treatment of metabolic syndrome.

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Poster

777. Mood Disorders: Depression and Bipolar Disorders: Animal Studies

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Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: Whitworth University Strategic Initiative Fund internal grant

Title: Hypervigilant responses to a novel environment in a rodent model of epilepsy and depression comorbidity

Authors: *S. A. EPPS, S. D. HUGHES, F. N. MARTIN, A. E. KELLY, R. B. KREGER, E. L. RANSOM, S. K. RYAN-COATS;
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Abstract: A strong bi-directional comorbidity between epilepsy and depression exists in the clinical population. Both conditions have interacting relationships with stress and are comorbid with anxiety; thus, an understanding of the effects of stress on this comorbidity may provide important insights for treatment and quality of life.
The SwLo rat is a valid animal model of comorbid depression and epilepsy. These rats are selectively bred for low activity in the Porsolt Swim Test, reflective of depression-related behaviors. Additionally, they demonstrate enhanced susceptibility to chemically- and electrically-induced seizures and pilocarpine-induced epileptogenesis. Their counterpart, the SwHi rat, is selectively bred for high activity in Porsolt Swim Test and is resistant to seizures and epileptogenesis.
The current study therefore hypothesized that SwLo rats would show increased anxiety-like behaviors in a novel environment compared to their depression- and epilepsy-resistant counterparts, the SwHi rat. SwLo and SwHi rats (n=12-13 rats per group, equal numbers of males and females) were tested for anxiety-related behaviors in the open field test (OFT), elevated plus maze (EPM) and light-dark chamber (LD). SwLo rats showed a significant increase in number of entries into the inner ($F(1,23)=26.201$, $p<0.0001$) and outer ($F(1,23)=13.189$, $p=0.001$) squares of the OFT compared to SwHi rats. They also showed a significant increase in rearing behaviors when in the inner area of the OFT ($F(1,23)=10.876$, $p=0.003$), the closed arms of the EPM ($F(1,23)=6.64$, $p=0.017$), and the dark area of the LD chamber ($F(1,20)=11.793$, $p=0.003$) compared to SwHi rats. When in the LD box, SwLo rats spent significantly more time in the light compartment of the LD box than SwHi rats ($F(1,20)=4.863$, $p=0.039$). Ongoing studies are assessing the response of these behaviors to a mild restraint stress prior to novel environment exposure.
Contrary to our original hypothesis, SwLo rats exhibited increased locomotor responses and rearing behaviors during novel environment tests when compared to SwHi rats. This may best be

interpreted as either stress-related hypervigilance or attention-deficit hyperactivity (ADHD)-related behavior. Rearing has been associated with hypervigilant information gathering, which could suggest stress-related associations. Alternatively, the increase in exploratory behaviors may be associated with ADHD-related behaviors, suggesting the utility of SwLo rats for assessing underlying mechanisms and treatment possibilities for this comorbidity as well.

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Poster

777. Mood Disorders: Depression and Bipolar Disorders: Animal Studies

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Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: Thomas F. and Kate Miller Jeffress Memorial Trust, Bank of America

Title: A detailed analysis of voluntary wheel running in OBX mice reveals multiple behavioral changes

Authors: *R. P. WATERS[1], A. M. RINKO[1], W. D. STAHLMAN[2], D. M. COPPOLA[3]; [1]Biol., [2]Psychological Sci., Univ. of Mary Washington, Fredericksburg, VA; [3]Randolph-Macon Col., Ashland, VA

Abstract: Bulbectomized mice are a leading model of human major depressive disorder. A primary characteristic of bulbectomy is hyperactivity, which is robustly displayed when bulbectomized mice are housed with a running wheel. Reports of this behavioral phenotype demonstrate a positive effect of bulbectomy on wheel running activity. We performed a detailed analysis of individual voluntary wheel running activity in bulbectomized mice living in social colonies. We incorporated radio frequency identification (RFID) tags to assign wheel running activity to individual mice and to limit access of animals to the running wheel. Our data suggest that olfactory bulbectomy increases wheel running with free access to the wheel; however, delaying access to the running wheel reduces voluntary wheel running. Bulbectomy may also decrease the rewarding properties of running on the wheel. Finally, this surgical procedure disrupts the circadian pattern that is typically observed with voluntary wheel running. These data further characterize this premier model of major depressive disorder, which allows us to better understand the etiology of the disorder.

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Poster

777. Mood Disorders: Depression and Bipolar Disorders: Animal Studies

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Program #/Poster #: 777.15/W24

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: CONACYT BI 15-007

Title: Fetal programming of the brain structure in the development of behaviors like to depression-anhedonia

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Abstract: Exposure to selective nutritional formula during development programs behavioral changes in later stages of life, an event known as fetal programming. Anhedonia-like behavior integrates a macro and microstructural deficit of the mesocorticolimbic circuit including the medial prefrontal cortex (mPFC), hippocampus (Hpp) and the nucleus accumbens (NAc) and defective glutamatergic plasticity. However, it is unknown if nutritional programming contributes to the anhedonia-like behavior phenotype by promoting aberrant macro and micro glutamatergic plasticity of the mesocorticolimbic circuit in the offspring. Here, we characterized macro and microstructural plasticity changes of the mesocorticolimbic circuit in the offspring induced by maternal caloric food exposure, and if these changes reproduce the anhedonia-like behavior phenotype. We use female Wistar rats exposed to a cafeteria diet (high in fat-sugar) for 9 weeks including pre-pregnancy, pregnancy and lactation, a protocol known as fetal programming. Motivating behavior to obtain natural rewards was characterized in male offspring (n= 93) as follow: Operational Conditioning (protocols in the Skinner box), preference to sucrose, open field and novel suppressed feeding. Changes in macro and microstructural plasticity were identified by Magnetic Resonance Imaging (MRI), Western blot (NMDA and AMPA receptor markers) and immunohistochemistry (synaptophysin and Glial fibrillary acidic protein (GFAP)), respectively. We found that the offspring of mothers exposed to cafeteria diet shows less motivation to obtain natural rewards, evidenced by: decrease in the protocols FR1, FR5 and PR, decrease in preference to sucrose, and longer time in the suppressed feeding test. MRI analyzes showed volume decrease in regions including the NAc, Hpp and mPFC. On the other hand, the microstructural analysis reveals anatomical changes in the regions of the Hpp and

NAc, which correlates with an increase in the GluR2 subunit of the AMPA receptor in the Hpp and a decrease in the NAc. Also, offspring exposed to cafeteria show positive hippocampal astrogliosis evidenced by an increase in the GFAP marker when compare with control. Our findings reveal that programming to mothers by caloric diet leads to anhedonia-like behavior phenotype in the offspring, which correlates with macrostructural defects and defective glutamatergic plasticity, and astrogliosis in the mesocorticolimbic circuit.

Disclosures: L.A. Trujillo Villarreal: None. **V. Romero-Díaz:** None. **I.A. Marino Martínez:** None. **L. Fuentes Mera:** None. **A. Camacho:** None. **M. Chakravarty:** None. **E. Garza-Villarreal:** None.

Poster

777. Mood Disorders: Depression and Bipolar Disorders: Animal Studies

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 777.16/W25

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: NRF grant NRF-2017M3C7A1079696

Title: 3-dimensional analysis of mice habenula in lipopolysaccharide depression model

Authors: *E. YANG, J. KIM, S. YANG, H. LEE, H. KIM;
Korea Univ., Seoul, Korea, Republic of

Abstract: Habenula is known to act as a central mechanism of depression related monoamine neuronal circuit in the brain, hence, it has become an important target for the treatment of depression. The the expression of few markers has been reported in tissue sections of habenula and several volumetric or three-dimensional (3D) analysis of human Hb have been performed. But three-dimensional analysis of mice habenula is still not to be conducted.
In this study, we set up 3D reconstruction methods for mice habenula, and performed volumetric analysis and gene expression analysis of LPS depression model habenula. As a results, we found that LPS injected mice showed smaller habenula volume than vehicle injected control mice. Interestingly, this volume reduction was prominent in MHb(medial habenula) but not in LHb(lateral habenula). Furthermore, the expression of Tac1 (dMHb specific marker) was decreased in all parts of dMHb, ChAT (vMHb specific marker) was decreased in rostral and middle part of vMHb, and Tacr1 (Hb marker) was decreased in rostral and middle part of MHb and LHb.
These results suggest that medial habenula plays important role in LPS depression model and our three-dimensional analysis method (volumetry and gene expression) for habenula will be useful for further investigation of the role of habenula in pathophysiology of depression.

Disclosures: **E. Yang:** None. **J. Kim:** None. **S. Yang:** None. **H. Lee:** None. **H. Kim:** None.

Poster

777. Mood Disorders: Depression and Bipolar Disorders: Animal Studies

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 777.17/W26

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: NRF grant NRF-2017M3C7A1079696
NRF grant NRF-2017R1D1A1B06032730

Title: The CAPS2 (calcium-dependent secretion activator 2) knock-down in the medial habenula induces despair-like behavior

Authors: *H. YOO, J. KIM, S. YANG, E. YANG, K. SONG, H. PARK, H. LEE, H. KIM; Korea Univ., Seoul, Korea, Republic of

Abstract: In the central nervous system, calcium-dependent secretion activator 2 (CAPS2 also known as CADPS2) regulates trafficking and exocytosis of large dense core vesicles (LDCV), which is essential in releasing neuropeptides. The medial habenula (MHb) in epithalamus is an important structure related to various neuropsychiatric diseases including anxiety, nicotine withdrawal, addiction, and depression.
In this study, we characterized CAPS2 cell in MHb by *in situ* hybridization and analyzed habenular CAPS2 mRNA level with qPCR in depression animal models. To test the relationship of CAPS2 and depression, we performed depression-related behavior tests and immunohistochemistry after knocking down CAPS2 in MHb by stereotaxic injection of AAV-sh-CAPS2 virus.
In situ hybridization showed that CAPS2 is highly expressed in MHb, both in the substance P-ergic neurons of dorsal MHb (MHbD) and the cholinergic neurons of ventral MHb (MHbV). The mRNA level of CAPS2 in MHb is decreased in rat chronic depression stress (CRS) model and learned helplessness (LH) model, implicating that CAPS2 would play a role in MHb mediated depressive symptoms. CAPS2 knockdown in mouse MHb resulted in despair-like behavior in tail suspension test (TST) and forced swim test (FST), but not anhedonia-like behavior in sucrose preference test (SPT). In the open field test (OFT), the latency to center area was increased, but the frequency and the duration in the center were not changed. The CAPS2 knockdown showed increased p-ERK expression in the interpeduncular nucleus (IPN) and decreased c-fos expression in the ventral tegmental area (VTA).
The results suggest that the reduced CAPS2 expression would have changed neuronal activity in IPN and VTA, leading to induction of despair-like behavior, and the MHb CAPS2 is related to depression.

Disclosures: **H. Yoo:** None. **J. Kim:** None. **S. Yang:** None. **E. Yang:** None. **K. Song:** None. **H. Park:** None. **H. Lee:** None. **H. Kim:** None.

Poster

777. Mood Disorders: Depression and Bipolar Disorders: Animal Studies

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 777.18/W27

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: US Department of Defense-USAMRAA
JPB Foundation
Black Family Foundation
Ministry of Health & Welfare

Title: Ahnak modulates depression-like behavior

Authors: ***J. JIN**[1], D. L. BHATTI[2], K.-W. LEE[2], L. MEDRIHAN[2], J. CHENG[3], C. SONG[2], J. E. GRESACK[2], P. GREENGARD[2], Y. KIM[2];
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Abstract: Genetic polymorphisms of the L-type voltage-gated calcium channel (VGCC) are associated with psychiatric disorders including major depressive disorder. Alterations of S100A10 (p11) level are also implicated in the etiology of major depressive disorder. However, the existence of an endogenous regulator in the brain regulating p11, L-type VGCC, and depressive behavior has not been known. Here we report that Ahnak, whose function in the brain has been obscure, stabilizes p11 and Anxa2 proteins in the hippocampus and prefrontal cortex in the rodent brain. Protein levels of Ahnak, p11, and Anxa2 are highly and positively correlated in the brain. Together these data suggest the existence of an Ahnak/p11/Anxa2 protein complex. Ahnak is expressed in p11-positive as well as p11-negative neurons. Ahnak, through its N-terminal region, scaffolds the L-type pore-forming α1 subunit and, through its C-terminal region, scaffolds the β subunit of VGCC and the p11/Anxa2 complex. Cell surface expression of the α1 subunits and L-type calcium current are significantly reduced in primary cultures of Ahnak knockout (KO) neurons compared to wild-type controls. A decrease in the L-type calcium influx is observed in both glutamatergic neurons and parvalbumin (PV) GABAergic interneurons of Ahnak KO mice. Constitutive Ahnak KO mice or forebrain glutamatergic neuron-selective Ahnak KO mice display a depression-like behavioral phenotype similar to that of constitutive p11 KO mice. In contrast, PV interneuron-selective Ahnak KO mice display an antidepressant like behavioral phenotype. Our results demonstrate L-type VGCC as an effector of the Ahnak/p11/Anxa2 complex, revealing a novel molecular connection involved in the control of depressive behavior.

Disclosures: **J. Jin:** None. **D.L. Bhatti:** None. **K. Lee:** None. **L. Medrihan:** None. **J. Cheng:** None. **C. Song:** None. **J.E. Gresack:** None. **P. Greengard:** None. **Y. Kim:** None.

Poster

777. Mood Disorders: Depression and Bipolar Disorders: Animal Studies

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 777.19/W28

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Title: Hyper-excitable neurons produce hypo-functional neuronal networks that predict psychiatric disease: Evidence from modeling CRMP2 in bipolar disorder

Authors: *C. D. PERNIA[1], Y. GOSHIMA[3], E. Y. SNYDER[2];
[2]Stem Cell and Regenerative Biol. Program, [1]Sanford Burnham Prebys Med. Discovery Inst., La Jolla, CA; [3]Yokohama City Univ. Sch. Med., Yokohama, Japan

Abstract: Bipolar disorder (BPD) is a neuropsychiatric disease in 2.6% of the adult population, and is characterized by oscillations in depressive and manic behavior. BPD is the most fatal psychiatric disease due to a high suicide rate, and little is known regarding its underlying pathology. Currently there is no reliably safe or predictably efficacious therapy for treating BPD. Recently, through a combinatorial approach taking advantage of hiPSC-derived neurons, animal models and human tissues, we demonstrated that the “lithium-response pathway” in BPD governs the phosphorylation and activation of collapsin response mediator protein 2 (CRMP2), a key cytoskeleton regulator, particularly for dendrites and dendritic spines. How CRMP2 mediates BPD has yet to be determined. Comparing transgenic mice with endogenous, absent, and constitutively active CRMP2, we have discovered CRMP2 activity impacts neuronal signaling kinetics and neurite proteomics. Specifically, BD-like transgenic CRMP2 neurons have hyperactive calcium activity, while having hypofunctional neuronal-network signaling, implying BPD is a disorder more of "neurodevelopment" than "mood", as was previously categorized in the DSM-IV. Furthermore, a machine learning classifier trained on BPD neuronal calcium data can successfully diagnose if an individual has BPD, and can determine if they will respond clinically to lithium. Collectively, this work illuminates long sought-after findings in BPD pathology, insights into brain function at large, novel targets for future neuropsychiatric therapeutics, and the first ever *in vitro* diagnostic BPD assay.

Disclosures: **C.D. Pernia:** None. **Y. Goshima:** None. **E.Y. Snyder:** None.

Poster

777. Mood Disorders: Depression and Bipolar Disorders: Animal Studies

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 777.20/W29

Topic: G.06. Post-traumatic Stress Disorder

Support: DOD W81XWH-16-1-0016

Title: Intranasal delivery to rats of [D^{26}His]NPY prevents traumatic stress triggered prolonged anxiety and depressive-like symptoms

Authors: *E. L. SABBAN, C. NWOKAFOR, L. I. SEROVA;
Biochem. and Mol. Biol., New York Med. Col., Valhalla, NY

Abstract: Considerable evidence from animal and human studies indicates that in the brain, neuropeptide Y (NPY) can attenuate the response to stress, and has therapeutic potential to prevent stress-triggered impairments such as PTSD, depression etc. We have shown that intranasal infusion of NPY to rats leads to widespread delivery to the brain without significantly changing plasma NPY concentrations. The biological effects of NPY are mediated by at least four G-protein coupled receptor subtypes: Y1R, Y2R, Y4R, Y5R. The anxiolytic effects of NPY are proposed to involve Y1R and possibly also Y2R and Y5R. Most studies have used [Leu^{31}Pro^{34}]NPY as a Y1 preferred agonist that also can activate Y5R. [D^{26}-His] NPY is reported to reduce development of anxiety. However, it was delivered by ICV injection and anxiety was reduced one hour later. Long term effects were not examined.
Here we examined the long-term effectiveness of intranasal administration of NPY and Y1R agonists. In a series of experiments, Sprague Dawley male rats were exposed to the single prolonged stress (SPS) model of PTSD. While still under the influence of ether (the last SPS stressor) they were given intranasal infusion of NPY or Y1R agonists [Leu^{31}-Pro^{34}]NPY, or [D^{26}His]NPY. One or two weeks later they were tested for anxiety on the Elevated Plus Maze (EPM) or depressive/despair behavior on the Forced Swim Test (FST). SPS led to anxiolytic behavior on the EPM. The vehicle infused animals (SPS/V) had less entries into the open arms and higher anxiety index than the unstressed controls, or the NPY infused rats (SPS/NPY). The Y1R agonist [D^{26}His]NPY was exceptionally effective to prevent development of anxiety, while [Leu^{31}-Pro^{34}]NPY was not. SPS also led to greater immobility time in the FST and this was reduced with NPY or [Leu^{31}-Pro^{34}]NPY. [D^{26}His]NPY was significantly more effective than NPY to prevent development of the immobility on the FST.
To study the ability to reverse the anxiety and depressive-like symptoms, SPS treated rats were given intranasal NPY, one or two weeks after the traumatic stress. A high concentration of NPY was able to reverse symptoms of anxiety, depressive-like behavior and hyperarousal. However, when [D^{26}His]NPY was given at the same concentration, in contrast to NPY, it was not effective

to reverse the behavioral impairments.
These data demonstrate therapeutic potential of Y1R agonists, such as[D^{26}His]NPY as early intervention to prevent development of PTSD associated behavioral impairments. It indicates that activation of the Y1R is sufficient to prevent the traumatic stress elicited impairments in anxiety and depressive behaviors, while NPY is able to also reverse these effects.

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Poster

777. Mood Disorders: Depression and Bipolar Disorders: Animal Studies

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 777.21/W30

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: NIH R01 MH108562
NIH 1P50MH096972

Title: Developmental photoperiod alters TREK-1 and SK currents in dorsal raphe serotonergic neurons

Authors: *M. A. GIANNONI GUZMÁN[1], T. N. MALIK[2], J. K. SIEMANN[1], D. G. MCMAHON[1];
[1]Dept. of Biol. Sci., [2]Neurosci. Training Program Vanderbilt Univ., Vanderbilt Univ., Nashville, TN

Abstract: Environmental factors can have profound effects on development and physiology. Seasonal changes in circadian day length during fetal development have been linked with the prevalence of mood disorders in adulthood. Among the different depression disorders, seasonal affective disorder manifests in people around the same time every year, most commonly in the winter months when light exposure is lowest during the year. Our laboratory has shown that developmental exposure to seasonal photoperiods has enduring effects on the excitability of dorsal raphe serotonergic neurons, their response to noradrenergic stimulation, intrinsic electrical properties, as well as on depression and anxiety-related behaviors. Here we extend this work by focusing on the twin-pore K+ channels TREK-1 and TASK-1, and the small conductance calcium-activated K+ channels (SK) as possible ionic mechanisms that underlie photoperiodic changes in the DRN. Using multielectrode array recordings, we examined the effects of pharmacological inhibition of these channels on the spike rate of serotonergic neurons in DR slices from mice exposed to different photoperiods. TREK-1, but not TASK-1 currents were modulated by photoperiod. In equinox slices, inhibition of TREK-1 via two independent

inhibitors, low dose amlodipine, and spadin, increased spike rate in a dose-dependent manner, however, in long and short slices TREK-1 inhibition had no effect on spike rate. In contrast, inhibition of TASK-1 resulted in increases in firing rate across all photoperiods. SK channel inhibition with apamin increased spike rates of short neurons, but not equinox or long. These results suggest a combinatorial mechanism in which the high spike rates of long neurons are mediated by reductions in both TREK-1 and SK currents, while the lower spike rates of short neurons are due to increased SK current, and the lower spike rates of equinox are due to increased TREK-1 current. Consistent with this, preliminary RT-PCR data, reveals significant reductions in the expression of TREK-1 expression in both long and short vs. equinox. This data provides evidence of how circadian light input during early life results in enduring changes in neural function.

Disclosures: **M.A. Giannoni Guzmán:** None. **T.N. Malik:** None. **J.K. Siemann:** None. **D.G. McMahon:** None.

Poster

777. Mood Disorders: Depression and Bipolar Disorders: Animal Studies

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 777.22/W31

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: NIH R01 MH108562
Silvio O. Conte Center for Neuroscience Research Vanderbilt University
1P50MH096972

Title: Determining the impact of photoperiod during sensitive pre & postnatal developmental periods for dorsal raphe serotonin neuronal physiology and serotonergic signaling

Authors: *J. K. SIEMANN[1], D. G. MCMAHON[2];
[2]Dept of Biol. Sci., [1]Vanderbilt Univ., Nashville, TN

Abstract: Early life experiences during sensitive developmental periods have been linked to increased risk for neuropsychiatric disorders later in life. The serotonin system is implicated in mood disorders and is impacted by the duration of daylight or photoperiod. Human epidemiological work has now demonstrated that high magnitude photoperiodic changes during the second trimester of gestation result in a decreased risk for depression in the adult offspring. Recently, we found that, in mice, Long photoperiods program dorsal raphe (DRN) serotonin (5-HT) neuronal firing rate *prenatally*, resembling the firing rate of animals maintained under Long photoperiods throughout development. We also observed that Long summer-like photoperiod exposure during postnatal development results in elevated monoamine content along with reduced mood-related behavior compared to mice exposed to Short winter-like photoperiods. We

are now systematically investigating when during *prenatal* development do Long photoperiods impact DRN 5-HT neuronal firing rate and identifying the sensitive periods in postnatal development responsible for changes to midbrain monoamine signaling and mood-related behaviors. For our prenatal experiments, we switched mice from either Long to Short or Short to Long photoperiods at E14.5 as this is after 5-HT neuronal gestation, when 5-HT switches from a maternal to a fetal source, and represents the approximate equivalent of second trimester human brain development. Surprisingly, we found that mice exposed only to Long photoperiods before E14.5 demonstrated 5-HT neuronal firing rates (1.13 ± 0.12 Hz) similar to animals exposed to Long photoperiods during the entirety of prenatal development (1.18 ± 0.08 Hz) as well as mice maintained under Long photoperiods throughout prenatal and postnatal development (1.24 ± 0.10 Hz). Interestingly, we observed that mice exposed to Long photoperiods after E14.5 demonstrated adult 5-HT firing rates (1.69 ± 0.17 Hz) similar to mice exposed to these conditions throughout the entirety of prenatal development and measured in early adolescence (1.86 ± 0.19 Hz), potentially representing a juvenile state. For our postnatal experiments, we measured midbrain monoamine content in mice developed continuously under either Long or Short photoperiods at P8, P18, and P35. We found elevated levels of 5-HT ($p = 0.0001$), 5-HIAA ($p = 0.0001$), DA ($p = 0.0060$) and DOPAC ($p = 0.0120$) content for Long compared to Short photoperiod mice arising at P18 and P35. We are continuing to investigate developmental sensitive periods impacted by photoperiod with the goal that this may lead to novel insights into the etiology for mood disorders.

Disclosures: J.K. Siemann: None. **D.G. McMahon:** None.

Poster

777. Mood Disorders: Depression and Bipolar Disorders: Animal Studies

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 777.23/W32

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: F32-MH110128 (MRC)
MH101180 (AAG)

Title: Social context modulates depressive-like behavior and dopamine deficit induced by early pup removal in late postpartum rats

Authors: *M. RINCÓN-CORTÉS[1], A. A. GRACE[2];
[1]Neurosci., [2]Neuroscience, Psychology, Psychiatry, Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Maternal mood during the postpartum can be dependent on offspring exposure (Feldman et al. 1999). In humans, the loss of a child can lead to severe grief and depression in mothers (Badenhorst and Hughes, 2006). In rodents, repeated long separations from pups impair

maternal behavior and alter emotionality in late postpartum rats (Boccia and Pedersen, 2001). Both repeated long separations and pup removal shortly (<24-hours) after birth increase immobility duration in the forced swim test (FST) in rat dams, which is interpreted as increased depressive-like behavior (Pawluski et al., 2009; Boccia et al., 2007). However, the use of the FST as a measure of depressive-like behavior has recently been questioned (Molendjik and de Kloet, 2019); and, other measures of depressive-like behavior in rat dams following pup removal remain unexplored. Here we evaluated long-lasting effects of pup removal and social context on maternal affect and dopamine (DA) activity. 3 groups: i) dams with pups, ii) dams with no pups, single-housed, iii) dams with pups removed and co-housed with another dam, underwent a behavioral test battery including: sucrose consumption, forced swim, elevated plus maze, and social approach tests during postpartum days (PD) 21-23. In vivo electrophysiological recordings of ventral tegmental area (VTA) DA neurons were performed (PD22-23) in subset of animals used for behavioral testing (EPM, social approach) to measure 3 parameters: number of spontaneously active DA neurons (i.e. population activity), firing rate, and firing pattern (i.e. burst firing). Dams that underwent pup removal and postpartum single-housing exhibited increased depression-like phenotypes (i.e. reduced sucrose intake, increased FST immobility, decreased social motivation) compared with co-housed dams or control dams kept with pups (one-way ANOVA: $p < 0.05$; n=8-10). Furthermore, single-housed dams that underwent pup removal exhibited an attenuation in VTA DA activity (i.e. reduced number of active DA cells) compared with dams that were co-housed or control dams kept with pups (one-way ANOVA: $p < 0.05$; n=7-9). These data indicate that disruption of social relationships during the postpartum period induces long-lasting alterations in depression-related behaviors and decreased VTA DA activity.

Disclosures: M. Rincón-Cortés: None. **A.A. Grace:** F. Consulting Fees (e.g., advisory boards); Dr. Grace received consultant fees from Lundbeck, Pfizer, Otsuka, Asubio, Autofony, and Janssen, and is on the advisory board for Alkermes, Newron and Takeda..

Poster

777. Mood Disorders: Depression and Bipolar Disorders: Animal Studies

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 777.24/W33

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: CT Institute for the Brain and Cognitive Sciences, University of Connecticut

Title: Low effort bias induced by the dopamine depleting agent tetrabenazine in an effort-related decision making task using mouse touchscreen procedures

Authors: *J.-H. YANG[1], A. SHAH[1], T. QUILES[1], R. PRESBY[1], R. A. ROTOLO[1], R. FITCH[1], M. CORREA[2], J. D. SALAMONE[1];
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Abstract: Tetrabenazine (TBZ) is a vesicular monoamine transport type-2 inhibitor that blocks striatal dopamine (DA) storage and depletes DA. TBZ is used to treat Huntington's disease, but studies report that TBZ induces side effects such as motivation dysfunction and depression. In animal research, effort-based decision making has emerged as a commonly used experimental approach for evaluating activational aspects of motivation. Typically, effort-related choice tasks offer the organism the option of choosing between a preferred reinforcer that requires high effort to obtain vs. a concurrently available but less preferred food. TBZ has been shown to reliably induce a low-effort bias in rats, characterized as a shift of preference from choosing high effort/high reward option toward low effort/low reward one. While the neural mechanisms of effort-based choice have been widely studied in rats, fewer studies have been performed in mice. The present studies used previously established touchscreen procedures to assess the effort-related effects of TBZ in C57BL6 mice. Mice were trained to choose either rearing up to press an elevated lit panel on the touchscreen in order to receive Ensure strawberry milkshake as the reinforcer, or approaching and consuming a concurrently available but less preferred choice food pellets (Bio-serv). C57BL6 mice were tested on a fixed ratio 1/choice schedule, and injections of the DA depleting agent TBZ (2.0 - 8.0 mg/kg IP) produced a dose-related decrease in panel pressing but an increase in the choice food pellet intake. In contrast, reinforcer devaluation by pre-feeding substantially decreased both panel pressing and pellet intake. In free-feeding choice tests, mice strongly preferred the Ensure vs. the pellets, and TBZ had no effect on milkshake intake or preference, suggesting that the TBZ-induced low effort bias is not due to change in primary food motivation or preference. This work provides cross-species evidence of the ability of the DA depleting agent TBZ to induce motivational dysfunction in mice, and it may have clinical relevance for assessing novel drug targets for their potential use as therapeutic agents in patients with motivation impairments.

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Poster

777. Mood Disorders: Depression and Bipolar Disorders: Animal Studies

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 777.25/W34

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: University of Connecticut Research Foundation
Connecticut Institute for Brain and Cognitive Sciences

Summer Undergraduate Research Fund at the University of Connecticut
University of Connecticut Psychological Sciences Department

Title: Novel atypical dopamine transport inhibitors and chemogenetic activation of mesolimbic dopamine neurons induce effort-related motivational changes in rats

Authors: *R. A. ROTOLO[1], R. SCHWARTZ[1], S. SAMELS[1], E. M. ROBERTSON[1], R. E. PRESBY[1], J.-H. YANG[1], V. DRAGACEVIC[2], P. KALABA[2], M. PISTIS[3], M. A. DE LUCA[3], F. CARIA[3], M. CORREA[4], G. LUBEC[2], J. D. SALAMONE[1];
[1]Psychological Sci., Univ. of Connecticut, Storrs, CT; [2]Neuroproteomics, Paracelsus Med. Univ., Salzburg, Austria; [3]Biomed. Sci., Univ. of Cagliari, Italy, Italy; [4]Àrea de Psicobiologia, Univ. Jaume I, Castelló, Spain

Abstract: Individuals diagnosed with depression and other psychiatric disorders often suffer from fatigue, anergia, and motivational dysfunctions, which are among the most difficult symptoms to treat. Animal studies have been developed to measure effort-related decision making, offering animals a choice between high effort instrumental actions leading to highly valued reinforcers, or low effort/low reward options. Previous studies have shown that dopamine (DA) transport inhibitors, including GBR12909, lisdexamfetamine, methylphenidate, and PRX-14040, can reverse the effort-related effects of the vesicular monoamine transport inhibitor tetrabenazine. Because many drugs that block DA transport (DAT) act as major stimulants and produce a number of undesirable side effects, there is a need to develop and characterize novel atypical DAT inhibitors with unique and selective binding profiles. A recently synthesized analog of modafinil, (S)-CE-123, is highly selective for DAT, with biochemical characteristics of atypical DAT blockers. Studies from our lab have shown that (S)-CE-123 (24.0 mg/kg) significantly but partially reverses the effort-related effects of tetrabenazine (1.0 mg/kg) when co-administered during a fixed ratio 5/chow feeding choice test, and significantly increases lever pressing on a progressive ratio (PROG)/chow feeding choice test. Microdialysis results indicate a significant increase in nucleus accumbens core DA, which remains stable 40 to 180-minutes after injection. Additional studies have examined a newly synthesized and more potent compound, CE-158 (3.0-8.0 mg/kg), which is being assessed for its ability to reverse the effort-related effects of tetrabenazine, and to increase lever pressing in a high-effort task when administered alone. Increases in high-effort responding induced by selective DAT inhibitors are consistent with the behavioral effects of chemogenetic stimulation of mesolimbic DA neurons observed in our lab. TH-Cre rats were trained on the PROG/chow feeding choice task and injected with pAAV-hSyn-DIO-hM3D(Gq)-mCherry into the ventral tegmental area (VTA). Activation of mesolimbic DA neurons in the VTA significantly increased selection of PROG lever pressing in male and female rats, supported by clear immunohistochemical visualization of mCherry in the VTA. In summary, enhancement of DA transmission by (S)-CE-123 and CE-158, and by chemogenetic activation of DA neurons, is able to reverse the effort-related effects of tetrabenazine and/or increase high-effort responding. It is possible that atypical DAT blockers could be useful as treatments for effort-related motivational dysfunction in humans.

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Poster

777. Mood Disorders: Depression and Bipolar Disorders: Animal Studies

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 777.26/W35

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: MINECO PSI2015-68497-R. Spain
Min. Ciencia RTI2018-101424-B-I00. Spain

Title: Behavioral and dopaminergic correlates of individual differences in the selection of effortful and vigorous behaviors in rodents

Authors: *M. CORREA[1], A. MARTINEZ-VERDU[1], P. IBANEZ-MARIN[1], C. CARRATALA-ROS[1], S. PORRU[1], E. ARIAS-SANDOVAL[1], P. MATAS-NAVARRO[1], J. HIDALGO-CORTES[1], J. SALAMONE[2];
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Abstract: Nucleus Accumbens (NAcb) dopamine (DA), plays an important role in effort-related processes and behavioral activation, and individual differences in effort-based decision-making are related to DA activity markers in NAcb. In the present studies, individual differences in the selection of effortful and vigorous behavioral options were studied in rats and mice, as well as their relation to markers of DA activity in the Nacb. Sprague Dawley adult male rats were assessed using an operant progressive ratio task (PROG) in which animals can either lever press on a PROG schedule for a preferred high-sucrose concentrated (5%) solution, or approach and consume a less-preferred (0.3%) solution that is freely available. Before operant training started, animals were tested for anxiety in the Dark and Light box, novelty-induced exploration in the Open Field, voluntary locomotion in running wheel (RW), and free sucrose preference (0.3% vs 5%). Using the two extreme quartiles in PROG performance, animals were divided into high-responders (HR), and low-responders (LR). HR rats had higher voluntary RW locomotion, but were not different in sucrose preference, anxiety, or locomotion compared to LR. DARPP-32 expression was also different between groups. In CD1 male mice we evaluated the relationship between individual differences in running on a voluntary wheel (RW), and the selection of reinforcers with different vigor requirements. Mice were allowed to run in a RW for two hours a day, 5 days a week, for 4 weeks. Using the two extreme quartiles of RW activity, animals were separated into high (HR) and low (LR) runners. Before training, mice were tested for anxiety, sociability, sucrose consumption and general exploration. After training, mice were evaluated in a T-maze where they interacted freely with 3 reinforcers: a RW, sucrose pellets, or a neutral smell. HR showed higher relative preference for the RW compared to LR, and spent less time

eating and sniffing. HR explored less the T-maze, and were also less sociable, although they did not show differences in anxiety or sucrose consumption. Phosphorylation of the DARPP-32-Thr34 protein was lower among HR. Identifying behavioral and neural correlates of individual differences in effort-based decision-making and selection of vigorous behavioral options could promote an understanding of the factors underlying vulnerability to symptoms such as anergia and fatigue common in many neurological and psychiatric disorders.

Disclosures: M. Correa: None. **A. Martinez-Verdu:** None. **P. Ibanez-Marin:** None. **C. Carratala-Ros:** None. **S. Porru:** None. **E. Arias-Sandoval:** None. **P. Matas-Navarro:** None. **J. Hidalgo-Cortes:** None. **J. Salamone:** None.

Poster

777. Mood Disorders: Depression and Bipolar Disorders: Animal Studies

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 777.27/W36

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: SPAIN PSI2015-68497-R

Title: Bupropion reverses the effort-related and depression-like effects of the VMAT-2 inhibitor tetrabenazine and increases selection of high-effort running wheel activity in mice

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Abstract: Vigor, persistence, and work output are fundamental features of normal motivation. Nucleus Accumbens (Nacb) dopamine (DA) regulates behavioral activation and effort-related decision-making in motivated behavior, and DA depletion has been shown to induce anergia and fatigue in effort-based decision tasks in animals. These motivational symptoms are seen in pathologies such as depression and are highly resistant to treatment. In the present work, we evaluated the antidepressant effect of the catecholamine uptake blocker bupropion (BUP) on its own and also its impact after the administration of tetrabenazine (TBZ), a VMAT2 blocker that has been reported to induce depression in humans, and to deplete DA. The effect of these drugs was assessed on a new 3-choice-T-maze task developed to assess preference between a reinforcer that requires voluntary behavioral activation (running wheel, RW), and other more sedentary reinforcers (sweet food pellets and a neutral non-social odor) in male CD1 mice. We also studied the effects of BUP and TBZ on the forced swim test (FST), which measures behavioral activation in a stressful setting. In addition, anxiety was also studied after the administration of these drugs in the dark-light box (DL), and in the elevated plus maze (EPM). In

the T-maze, BUP alone increased selection of RW activity in animals tested on the T-maze as well as time spent climbing in the FST. TBZ reduced time running, but increased time-consuming sucrose, indicating an induction of fatigue but not an effect on primary sucrose reinforcement. In the FST, TBZ decreased time performing the most active behavior (climbing) and increased passive behaviors (immobility). TBZ did not affect anxiety-related behavior in any of the tests. BUP reversed the effects of TBZ in mice tested on the FST and on the T-maze, and also attenuated the effects of TBZ on pDARPP32-Thr34 expression in Nacb as assessed with immunohistochemistry. These results indicate that BUP shows antidepressant properties in traditional test of depression like the FST, and also in the T-maze task, which could be useful for assessing preferences based on effort requirements. The T-maze task could be a suitable test for the evaluation of antidepressant effects of drugs under non-stressful conditions.

Disclosures: J.D. Salamone: None. **C. Carratalá-Ros:** None. **A. Martinez-Verdu:** None. **E. Arias-Sandoval:** None. **M. Correa:** None.

Poster

777. Mood Disorders: Depression and Bipolar Disorders: Animal Studies

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 777.28/W37

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: Department of Veterans Affairs grant numbers BX002085, IO1 BX001804 and 1IS 1BX003556 (LPR)
Office of the Vice President for Research at USC (LPR)
National Science Foundation grant number IOS-1656626 (CAG)

Title: Hippocampal-specific insulin resistance elicits depressive-like behavior

Authors: *C. A. GRILLO[1,2], F. Z. LOYO-ROSADO[1], J. L. WOODRUFF[1,2], H. B. COWAN[1], N. D. MAXWELL[1], L. P. REAGAN[1,2];
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Abstract: In the central nervous system (CNS), insulin plays a critical role in the formation of neural circuits and synaptic connections from the earliest stages of development and facilitates and promotes neuroplasticity in the adult brain. Conversely, CNS insulin resistance contributes to the neurological complications of metabolic disorders, including decreases in cognitive function. Indeed, we have previously reported that induction of hippocampal-specific insulin resistance elicits neuroplasticity deficits in the rat hippocampus that include reduction of stimulus-evoked long term potentiation, granule neuron dendritic atrophy and deficits in spatial learning and memory. Since clinical and preclinical studies demonstrate that patients with

metabolic disorders that include insulin resistance have an increased risk of developing neuropsychiatric disorders like depressive illness, the goal of the current study was to determine whether rats with hippocampal-specific insulin resistance exhibit depressive-like behaviors. In agreement with our previous studies, rats with hippocampal-specific insulin resistance did not exhibit significant differences in body weight or body composition compared to control rats. In the sucrose preference test, rats with hippocampal-specific insulin resistance did not exhibit anhedonia as they consumed similar amounts of sucrose compared to control rats. In the forced swim test, rats with hippocampal-specific insulin resistance exhibited similar immobility, swimming and climbing behaviors as control rats. However, rats with hippocampal-specific insulin resistance exhibited significant decreases in the latency to float in the forced swim test, illustrating that these rats are exhibiting behavioral despair. These behavioral differences observed in rats with hippocampal-specific insulin resistance were accompanied by decreases in plasma BDNF levels. Collectively, these data demonstrate that hippocampal-specific insulin resistance elicits depressive-like behaviors and provide insight into the mechanistic basis for comorbid depressive illness in insulin resistance states like type 2 diabetes, obesity and Alzheimer's disease.

Disclosures: C.A. Grillo: None. **F.Z. Loyo-Rosado:** None. **J.L. Woodruff:** None. **H.B. Cowan:** None. **N.D. Maxwell:** None. **L.P. Reagan:** None.

Poster

777. Mood Disorders: Depression and Bipolar Disorders: Animal Studies

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 777.29/W38

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: NIH T32 GM008798
Hope for Depression Research Foundation
NIH Grant # MH068542

Title: Role of the mu opioid receptor in the antidepressant action of tianeptine

Authors: *J. HAN[1], V. ANDREU[1], J. E. PINTAR[3], B. L. KIEFFER[4], A. HARRIS[1], R. HEN[2], K. M. NAUTIYAL[5];
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Abstract: Depression is widely thought to arise from an imbalance of monoamine neurotransmitters, particularly serotonin. However, this hypothesis cannot fully explain the

pathophysiology of the disease: most depressed patients do not have reduced monoamine levels, and only a fraction achieve remission with monoaminergic drugs such as selective serotonin reuptake inhibitors (SSRIs). The discovery that the atypical antidepressant tianeptine is a mu opioid receptor (MOR) agonist has provided a potential avenue for expanding our understanding of depression beyond the monoamine hypothesis. Thus, our studies aim to understand the neural circuits underlying tianeptine's antidepressant effects. By administering tianeptine to MOR KO mice, we showed that MOR is required for the antidepressant behavioral effects of tianeptine, following both acute (forced swim test) and chronic (novelty suppressed feeding) administration. Using tissue-specific MOR knockout (via a floxed MOR mouse) we further show that MOR expression on GABAergic cells is necessary for the acute antidepressant response. Preliminary evidence suggests that this can be localized to SST+ neurons. Moreover, we were able to show a double dissociation of the antidepressant phenotype from other opioid-like phenotypes resulting from acute tianpetine administration. Specifically, while mice lacking MOR expression on GABAergic neurons failed to show the antidepressant-like effect, these mice still showed acute hyperlocomotion, analgesia, and conditioned place preference. Furthermore, knockdown of MOR expression on other neuronal subsets resulted in an absence of typical opioid-like phenotypes, with an intact antidepressant phenotype. Finally, using two different stress-induced depression paradigms, we showed that tianeptine also has MOR-dependent chronic antidepressant effects. Notably, these behavioral effects are present after just one week of treatment, suggesting that tianeptine may be more rapid-acting than SSRIs. Taken together, these results suggest a novel entry point for understanding what circuit dysregulations occur in depression, and possible targets for the development of new classes of antidepressant drugs.

Disclosures: J. Han: None. **V. Andreu:** None. **J.E. Pintar:** None. **B.L. Kieffer:** None. **A. Harris:** None. **R. Hen:** None. **K.M. Nautiyal:** None.

Poster

778. Depression and Bipolar Disorders: Treatment Strategies in Animal Studies

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 778.01/W39

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: Gayle & Ben Batey Neuroscience Fund
MARC U STAR NIH 5T34GM118212

Title: Is a high fat diet always bad and a low fat diet always good? The effects of a low and high fat diet and the selective serotonin reuptake inhibitor, fluoxetine (prozac), in an animal model of depression

Authors: *I. C. SUMAYA, M. MUSQUEZ, A. ALVARADO, L. HERRERA, I. CABANILLAS;
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Abstract: The overwhelming consensus in both human and animal studies is that high fat intake leads to negative outcomes and a risk factor for many health concerns including diabetes, heart disease, and stroke. Counterintuitive, there is emerging preclinical evidence that a high fat diet may not always have negative consequences in the context of the psychological domain. Recently it was reported that feeding rats a high fat diet (32% fat, isocaloric) served to decrease immobility in the Forced Swim Test thus showing anti-depressive effects. The aim of the present study was to further investigate the previously reported anti-depressive effects of a high fat diet and to provide an animal model of food intake more closely mimicking that found in humans, a 45% non-isocaloric fat diet (Western Diet). Additionally, previous work used as a control diet, standard chow containing unmatched amounts of major macronutrients. To rule out the effects of the major macronutrients, protein and sugar, used in the current experiment was a low-fat diet (10% fat) and a the high-fat diet (45%) with similar amounts of protein and sugar. Also, rats (male, Sprague Dawley) were treated with the selective serotonin reuptake inhibitor, fluoxetine (10 mg/kg ip). Results showed no significant differences in weight between the low (n = 17) and high fat (n = 18) groups or differences in muscle strength as measured by the hanging wire test after a 7 day food regime. In the groups not treated with fluoxetine, the rats fed the high fat diet (45%) showed the least amount of depressive-like symptom (n = 9, immobility: 17.95 $\pm$ 4.79 sec) as compared to their low fat controls (n = 9, immobility: 37.98 $\pm$ 14.64 sec). For the rats treated with fluoxetine, the same pattern was found. Rats on the high fat diet treated with fluoxetine experienced greater antidepressive-like effects (n = 9, immobility: 55.15, $\pm$ 10.96 sec) as compared to their low fat counterparts (n = 8, immobility: 84.09 $\pm$ 16.05 sec). These data provide support for an antidepressive-like effect of the high fat Western Diet (45%) as reported previously in a lower fat content diet (32% fat, isocaloric). Unexpected, and providing first time data, low fat had a depressive-like effect in this animal model of depression.

Disclosures: I.C. Sumaya: None. **M. Musquez:** None. **A. Alvarado:** None. **L. Herrera:** None. **I. Cabanillas:** None.

Poster

778. Depression and Bipolar Disorders: Treatment Strategies in Animal Studies

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 778.02/W40

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: Spanish Ministry of Economy SAF2016-79008-P
Spanish Ministry of Economy PSI2017-82604-R

Grant BES-2014-068426

Title: Galanin(1-15) reverses the impaired long-term memory effect of fluoxetine in the novel object recognition test. Role of 5-HT1A receptor in medial prefrontal cortex

Authors: A. FLORES-BURGESS[1], C. MILLÓN[1], B. GAGO[1], L. GARCÍA-DURÁN[1], N. CANTERO-GARCÍA[1], R. COVEÑAS[2], J. NARVÁEZ[1], K. FUXE[3], L. SANTÍN[1], ***Z. DIAZ-CABIALE**[1];
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Abstract: Galanin(1-15) [GAL(1-15)] enhances the antidepressant effects induced by Fluoxetine (FLX) in the forced swimming test through an interaction between GALR1-GALR2 and 5-HT1A receptors in the hippocampus. In this work, we have studied the effects of GAL(1-15) on FLX-mediated effects on the Novel Object Recognition (NOR) and the Object Location Memory (OLM), two tasks where FLX treatment impaired long-term memories 24h post-training. Since the medial prefrontal cortex (mPFC) is a core region for the interaction between emotional processing and cognition with a high density of 5-HT1AR and GALR1 and GALR2, we have also analyzed the binding characteristics and mRNA levels of 5-HT1AR in the mPFC after GAL(1-15)-FLX administration in rats. Groups of male rats (n=5-6) received three injections of FLX(10mg/Kg) between the training and test phases of the NOR and OLM tasks, and a single intracerebroventricular (icv) injection of a threshold dose of GAL(1-15)(1nmol) alone or in combination with the GALR2 antagonist M871(3nmol) 15´ before the test phase. A discrimination index (DI) was calculated as: DI=(N-F)/(N+F), and represent the difference in exploration time expressed as a proportion of the total time spent exploring the two objects. To analyze the binding characteristics and mRNA levels of 5-HT1AR, group of animals (n=6) were injected with FLX(10mg/kg) and GAL(1-15)(1nmol) alone or in combination and coronal sections of the mPFC were obtained to perform a quantitative autoradiography and in situ hybridization experiments In the NOR task, GAL(1-15)+FLX reversed the impairment memory effect induced by FLX(10mg/Kg) ($p<0.05$). This effect was blocked by the GALR2 antagonist M871. On the contrary, GAL(1-15) did not reverse the effect of FLX in the OLM task. In the autoradiographic experiments, GAL(1-15)+FLX increased the Kd ($p<0.01$) and the Bmax ($p<0.05$) values of the agonist radioligand [3H]-8-OH-DPAT compared with FLX in the mPFC. The coadministration also increased the 5-HT1AR mRNA levels ($p<0.01$) compared with the FLX group. Our results describe an interactions between GAL(1-15) and FLX in the mPFC involving interactions at the 5-HT1AR receptor level with implications also at functional level. The GALR1-GALR2-5-HT1A heteroreceptor could be used to reverse some of the adverse effects of FLX on memory processes.

Disclosures: **A. Flores-Burgess:** None. **C. Millón:** None. **B. Gago:** None. **L. García-Durán:** None. **N. Cantero-García:** None. **R. Coveñas:** None. **J. Narváez:** None. **K. Fuxe:** None. **L. Santín:** None. **Z. Diaz-Cabiale:** None.

Poster

778. Depression and Bipolar Disorders: Treatment Strategies in Animal Studies

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 778.03/W41

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: CONACYT 243, 247
CONACYT 243, 333
BUAP-CA-288
CONACYT 885936

Title: Evaluation of fluoxetine effects in depressive-like behavior in high and low yawning rats

Authors: *D. BRAVO DURÁN[1], J. EGUIBAR[2], C. CORTES[3], A. FERNÁNDEZ-GUASTI[4]; [1]Inst. de Fisiología, Benemerita Univ. Autonoma De Puebla, Puebla, Mexico; [2]Benemerita Univ. Autonoma De Puebla, Puebla, Pue., Mexico; [3]B. Univ. Autonoma de Puebla, Puebla, Mexico; [4]CINVESTAV SUR, Mexico D.F, Mexico

Abstract: In our laboratory, we selectively inbred two sublines from Sprague-Dawley (SD) rats, the high-yawning (HY) with 22 yawns/h and low-yawning (LY) with just 2 yawns/h. These sublines have shown different behaviors in anxiety and stress-related tests where the LY rats are more emotional reactive than HY and SD subjects (Ss). High levels of stress have been linked to more susceptibility to develop anxiety and depression. The aim of this study is to evaluate the depression-like behavior in the forced swimming test (FST) of HY, LY and SD and the effects of FLUO (2.5, 5 and 10 mg/Kg). Adult HY, LY and SD male rats (n = 6 per dose), were housed in standard room conditions with free access to rodent pellets and water. We used an acrylic cylinder filled with warm water (24 ± 1°C) for the FST. All Ss had two swim sessions in two consecutive days, the first 15 min and, 24 h later, a second session of 5 min test. The Ss received, at 23.5, 5 and 1 h before the second test, three i.p. injections of FLUO with 2.5, 5 or 10 mg/Kg or vehicle. We scored the following behaviors: immobility, swimming, climbing and diving. With a fluoxetine 10 mg/Kg dose there was a significantly enhanced swimming and decreased immobility duration in all three groups of rats ($P<0.05$). Importantly, the HY had stronger effects under FLUO with respect to LY and SD rats. We conclude that LY rats exhibit more depressive-like behavior and FLUO is less effective, supporting as a model with higher susceptibility and HY being resilient.

Disclosures: D. Bravo Durán: None. **J. Eguibar:** None. **C. Cortes:** None. **A. Fernández-Guasti:** None.

Poster

778. Depression and Bipolar Disorders: Treatment Strategies in Animal Studies

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 778.04/W42

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Title: The effects of thyroid hormone manipulation on performance in the saccharin preference test, the elevated plus maze, and novel object placement task in male C57BL/6J mice

Authors: H. OVADIA, *A. L. PEHRSON;
Psychology, Montclair State Univ., Montclair, NJ

Abstract: There is abundant evidence suggesting that Major Depressive Disorder (MDD) is related to thyroid hormone (TH) function, but the exact nature of this relationship is poorly defined in the literature. The present study examined whether hypothyroidism could viably model symptoms of MDD in mice using established behavioral paradigms to measure anhedonia, anxiety, and spatial memory. We hypothesized that hypothyroidism would produce anhedonia-like behavior in the saccharin preference test, elevated anxiety-like behavior in the elevated plus maze, and impaired spatial memory, as assessed in the novel object placement task. 45 male C57BL/6J mice were randomly assigned to one of three groups, which received either control diet, diet infused with 6-propyl-2-thiouracil (hypothyroid group), or 6-propyl-2-thiouracil and thyroxine (hyperthyroid group). Each group had ad libitum access to their food for four weeks prior to behavioral assessment. Contrary to our hypothesis, hypothyroid mice did not exhibit anhedonia-like behavior or spatial memory impairments compared to controls. However, they did spend a significantly lower percentage of time in the open arms of the elevated plus-maze compared to both the control and hyperthyroid groups. These data suggest that hypothyroidism may be related to anxiety, but is not clearly related to anhedonia or spatial memory impairment. Hypothyroid mice also had a lower travel distance in the elevated plus maze, which may be consistent with the fatigue, slowed metabolism, or lower body temperature associated with hypothyroidism in humans. Additionally, the hyperthyroid mice had a greater preference for sweetened water than the other groups in the saccharin preference test, and consumed more liquid volume overall. TH over-stimulation therefore induced behaviors in opposition to a depression-like phenotype. These findings suggest a complex relationship between TH function and mood, and contributing to a large body of research aiming to elucidate the disorder's underlying mechanisms.

Disclosures: H. Ovadia: None. **A.L. Pehrson:** None.

Poster

778. Depression and Bipolar Disorders: Treatment Strategies in Animal Studies

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 778.05/W43

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Title: Selective serotonin reuptake inhibitor dosing and receptor occupancy: A systematic review and analysis of the mouse forced swim task

Authors: *D. T. ROBERTS, A. FOMIN, L. SANTOS, A. L. PEHRSON;
Dept. of Psychology, Montclair State Univ., Montclair, NJ

Abstract: Traditional approaches used in preclinical behavioral pharmacology studies dictate the administration of increasingly high doses until a behavioral effect is observed. Historically, this practice was used due to methodological constraints, including an inability to empirically estimate occupancy of a drug's mechanistic targets. Recent technological advances allow empirical target occupancy determinations, obviating the need for blind dosing methods, but these techniques are seldom used in preclinical research to determine mechanistically-relevant doses. This may result in the use of inappropriately low or high doses, limiting our ability to draw accurate mechanistic conclusions based on available data. We conducted a systematic review and meta-analysis of preclinical studies testing selective serotonin reuptake inhibitors (SSRIs) in the mouse forced swim test (FST). A random effects model examined the effect of SSRI administration on FST immobility time. Paroxetine and fluoxetine administration had significant, medium to large effects on immobility time compared to placebo. Evidence of publication bias and high heterogeneity were observed. SERT occupancy was estimated for each SSRI using ex vivo autoradiography. Clinically-relevant doses were calculated based on clinical target occupancy data, which indicate that 80% SERT occupancy is required for clinical SSRI efficacy. A metaregression revealed that heterogeneity was only partly explained by SERT occupancy. We found substantial variation in dosing practice across drugs. Fluoxetine doses were generally close to clinical relevance, while the majority of paroxetine study arms used supra-mechanistic doses 20 or more times the clinically-relevant dose. These data suggest that acute SSRIs administration is effective in FST, but acute SSRI administration shows little evidence of antidepressant efficacy in humans. Furthermore, supra-mechanistic doses are commonly used in preclinical studies, which may skew mechanistic interpretations of data. Thus, these data call into question the validity of some common preclinical methodologies and suggests that a lack of access to dose-target occupancy data is a critical weakness in neuropharmacology methods.

Disclosures: D.T. Roberts: None. **A. Fomin:** None. **L. Santos:** None. **A.L. Pehrson:** None.

Poster

778. Depression and Bipolar Disorders: Treatment Strategies in Animal Studies

Location: Hall A

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Program #/Poster #: 778.06/W44

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: One Mind Bipolar Disorder Translational Research Award (PMJ)
Heinz C. Prechter Bipolar Research program and Richard Tam Foundation (PMJ)
Michigan Predoctoral Training in Genetics (T32GM007544) (ADN)

Title: Lithium partially restores presynaptic GABAergic signaling deficits in the Ank3 W1989R mouse model

Authors: *R. N. CABALLERO[1], A. D. NELSON[1], J. PHILIPPE[3], P. M. JENKINS[2];
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Abstract: Multiple genome-wide association studies (GWAS) have shown that the *ANK3* gene is one of the most significant risk loci for bipolar disorder (BD). The *ANK3*gene encodes ankyrin-G, an adaptor protein that is involved in the formation of the axon initial segment (AIS), nodes of Ranvier, and GABAergic synapses. Recently, we have generated a mouse model with a W1989R mutation in *Ank3,* which abolishes the interaction between ankyrin-G and GABARAP necessary for ankyrin-G-¬dependent stabilization of postsynaptic $GABA_A$ receptors. We have shown that the *Ank3* W1989R mice have striking reductions in inhibitory currents in cortex and hippocampus compared to control mice resulting in increases in the intrinsic excitability of pyramidal neurons. Importantly alterations in inhibitory signaling have also been seen in BD patients. Consistent with this idea, we recently identified a BD family carrying the *ANK3* W1989R variant in our patient cohort in the Heinz C. Prechter Bipolar Research Program at the University of Michigan. The proband is a Caucasian male with type I BD characterized by recurrent mania and depression with a successful treatment with lithium. In these studies, we have treated *Ank3* W1989R mice for 21 days with chow containing lithium carbonate until serum levels reach the therapeutic range and used voltage clamp and current clamp whole cell electrophysiology recordings to measure inhibitory postsynaptic currents in cortical and hippocampal pyramidal neurons. Our results showed a 21 day lithium treatment partially reverses the defect in spontaneous inhibitory post-synaptic current (sIPSC) frequency, while not significantly affecting sIPSC amplitude. Since sIPSC frequency is a measure of presynaptic GABA release probability, we hypothesize that lithium is increasing activity of parvalbumin-positive GABAergic interneurons. In summary, these results suggest that the *ANK3* has an important role in the control of cortical and hippocampal neuronal excitability and dysfunction of this pathway may contribute to the imbalance of circuits seen in BD patients. In addition, our

work suggests that lithium may act to increase the presynaptic GABA release in our model, perhaps resulting from increased excitability of parvalbumin-positive interneurons.

Disclosures: R.N. Caballero: None. **P.M. Jenkins:** None. **A.D. Nelson:** None. **J. Philippe:** None.

Poster

778. Depression and Bipolar Disorders: Treatment Strategies in Animal Studies

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 778.07/X1

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: W81XWH-14-0130
W81XWH-14-0390

Title: Roles of p11 and serotonin in depression and antidepressant action

Authors: *Y. SAGI[1], L. MEDRIHAN[4], J. CHENG[2], G. UMSCHWEIF[3], P. GREENGARD[2]; [1]Lab. of Mol. and Cell. Neurosci., [3]Lab. for Mol. and Cell. Neurosci., [2]Rockefeller Univ., New York, NY; [4]The Rockefeller Univ., New York, NY

Abstract: Major depressive disorder is a debilitating disease affecting millions of people worldwide. A role for the protein p11, a member of the s100a family of calcium sensors, has been established in attenuating depressive-like behaviors as well as in mediating the action of antidepressants. We elucidated the cellular and molecular functions of p11 in three classes of neurons: GABAergic cholecystokinin (CCK)-expressing neurons of the dentate gyrus, GABAergic parvalbumin-expressing neurons of the dentate gyrus, and cholinergic neurons of the nucleus accumbens. In these neuronal populations, p11 regulates ion channels and serotonergic receptors in a cell-type specific manner. p11 regulates basal cell activity, cellular response to serotonin (5-HT), and adaptation in cell activity in response to chronic antidepressant treatment. The mechanisms underlying these functions include regulation of transcription and regulation of endocytosis. The different roles of p11 in preventing depressive-like behavior or in mediating the action of antidepressants will be discussed.

Disclosures: Y. Sagi: None. **L. Medrihan:** None. **J. Cheng:** None. **G. Umschweif:** None. **P. Greengard:** None.

Poster

778. Depression and Bipolar Disorders: Treatment Strategies in Animal Studies

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 778.08/X2

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Title: Fluoxetine effect on chronic unpredictable stress into a depression-epilepsy comorbidity model

Authors: *J. GONZALEZ-GOMEZ, I. ROMERO-ELIZALDE, C. GARCIA-CABALLERO, A. VALDES-CRUZ, S. ALMAZAN-ALVARADO, D. MARTINEZ-VARGAS;
Inst. Nacional De Psiquiatria Ramon De La Fuente, Mexico City, Mexico

Abstract: Chronic unpredictable stress (CUS) and electrical amygdala kindling (EAK) subsequently applied may be a depression-epilepsy comorbidity model, present in a high incidence in the population. The aim was to analyze the effect of the fluoxetine (FLX) on CUS and the seizures induced by the EAK. Nineteen adult male Wistar rats were used; CUS was made with 9 different stressful stimuli during 21 days. The FLX (10 mg/kg) was applied subcutaneously every 24 h in the course of CUS. In all animals, a tripolar stainless steel electrode was placed stereotaxically in the left temporal lobe amygdala (AM), and both prefrontal cortex (PFC). The EEG coherence was recorded and analyzed with an analogical-digital system (ADQCH8). EAK was performed as follow: Daily electrical stimulations of 60 Hz monophasic square-wave pulses, 1 ms width pulses, with a current intensity between 150-300 μA. When the animals exhibited three consecutive stage 5 seizures according to Racine's scale, they were regarded as fully kindled, 24 h later a seizure susceptibility test was performed. Animals were submitted to forced swim test 5 minutes duration to assess the depressive-like behaviors before to start EAK and after the seizure susceptibility test, animals were divided in three groups: CUS+FLX+EAK (n = 7), CUS+EAK (n = 6), and EAK(n = 6). The results showed that CUS+FLX+EAK group had a less frequency of spikes during generalized seizures, a depressive-like behaviors (immobility) diminution after the seizure susceptibility test, and a decrease of the EEG coherence power was observed. Higher susceptibility to evoked focal seizures was observed in CUS+EAK group. Results suggest that the FLX could induce a decrease of propensity to generate focal seizures, as well as, temporal lobule generalized seizures severity into the depression-epilepsy comorbidity, with no effects on antidepressant efficacy. These changes may be associated to decrease of the EEG coherence.

Disclosures: J. Gonzalez-Gomez: None. **I. Romero-Elizalde:** None. **C. Garcia-Caballero:** None. **A. Valdes-Cruz:** None. **S. Almazan-Alvarado:** None. **D. Martinez-Vargas:** None.

Poster

778. Depression and Bipolar Disorders: Treatment Strategies in Animal Studies

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 778.09/X3

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Title: Effect of unpredictable chronic stress and fluoxetine on pentyneletetrazole induced seizures in rats

Authors: *J. ROMERO-ELIZALDE, J. GONZALEZ-GOMEZ, A. VALDÉS-CRUZ;
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Abstract: The chronic unpredictable stress (CUS) model of depression, in this model, rats or mice are exposed chronically to a constant bombardment of unpredictable micro-stressors, resulting in the development of a plethora of behavioural changes, including decreased response to rewards, a behavioural correlate of the clinical core symptom of depression. The fluoxetine (FLX) is a selective serotonin reuptake inhibitor used for the treatment of depression. Despite of the efficacy of FLX in depressive disorders, its effect on epilepsy remains controversial. Experimental models have shown that FLX affects excitability in short time scales which may lead to changes in epilepsy severity. Pentylenetetrazol (PTZ) is a $GABA_A$ receptor antagonist commonly used as a convulsing drug in experimental studies. The aim of the study was to analyze the effect of the FLX administration on epileptic seizures induced with PTZ in rats submitted to CUS. Experiments were performed using 26 Wistar male rats, with electrodes stereotaxically implanted in dorsal hippocampus (dentate gyrus) bilaterally and epidural electrodes in both prefrontal cortices for EEG recording. The rats were classified as follows: ECI-PTZ, ECI-FLX-PTZ, FLX and PTZ. ECI was applied for 21 days, using 9 different stressors stimuli. FLX (10 mg/kg in 2 ml 0.9% NaCl), was applied every 24 h during the ECI. One day after CUS was ended, animals were submitted to forced swimming test (FST) 5 minutes duration to quantify depressive-like behavior. Induction of convulsive seizures activity was done 24 h after to FST, this was performed as follow: Initial PTZ 20 mg/Kg dose, followed by subsequent PTZ 10 mg/Kg doses every 10 minutes, until status epilepticus was observed. The EEG recording was done during all experiment. The results were showed a depressive-like behaviors decrease in FLX-PTZ group. In the same group also was observed an increase in accumulated and average duration of the seizures, as well as a reduction in the number of seizures. ECI-PTZ group was showed a decrease of accumulated duration and number of seizures. In ECI-FLX-PTZ was observed an increase in the acumulative duration of the seizures. Altought, that FLX administration in patients with comorbid depression-epilepsy has been common and considered safe, our results suggest that its use should be careful due to differential effects on seizures in some kinds of epilepsy.

Disclosures: **J. Romero-Elizalde:** None. **J. Gonzalez-Gomez:** None. **A. Valdés-Cruz:** None.

Poster

778. Depression and Bipolar Disorders: Treatment Strategies in Animal Studies

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 778.10/X4

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: NIH Grant 1R03MH112984-01
University of Connecticut
Arnold and Mabel Beckman Foundation

Title: Motivational dysfunction induced by the SSRI fluoxetine (Prozac) in rats: Possible involvement of 5-HT1B receptors

Authors: *S. M. FERRIGNO[1], R. A. ROTOLO[1], R. PRESBY[1], J.-H. YANG[1], M. CORREA[2], J. D. SALAMONE[1];
[1]Psychological Sci., Univ. of Connecticut, Storrs, CT; [2]Psicobiologia. Univ. Jaume I, Castello, Spain

Abstract: Selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine (Prozac) are the most commonly prescribed treatments for depression. Although efficacious for many symptoms of depression, motivational impairments such as psychomotor retardation, anergia, fatigue and amotivation are relatively resistant to SSRI treatment. Furthermore, in clinical studies SSRIs have been reported to exacerbate these deficits in some people. In order to study motivational dysfunctions in animal models, procedures have been developed to measure effort-related decision making, which offer animals a choice between high effort instrumental actions leading to highly valued reinforcers, or low effort/low reward options. Fluoxetine fails to reverse the effort-related effects of the VMAT-2 inhibitor tetrabenazine in rodent studies, and also has been shown to suppress high effort activities such as wheel running and lever pressing on fixed ratio or progressive ratio choice tasks. Because fluoxetine blocks 5-HT uptake, it is likely that fluoxetine-induced motivational dysfunctions are due to overstimulation of one or more 5-HT receptors. Several experiments have been conducted to characterize the 5-HT receptors that may be associated with the fluoxetine-induced suppression of lever pressing. Co-administration of antagonists of either the 5-HT_{2A} or 5-HT_{2C} receptor have failed to reverse the effects of fluoxetine. Recent studies have focused on the 5-HT_{1B} receptor. For these experiments, the selective 5-HT_{1B} receptor antagonist, NAS-181, was co-administered with fluoxetine to determine if suppression of high effort behavior could be attenuated. There were considerable individual differences in the suppression of fixed ratio 5 lever pressing induced by fluoxetine. Thus, animals were divided into two groups (i.e., high suppression and low suppression). NAS-181 partially reversed the effects of fluoxetine in rats that showed a higher fluoxetine-induced

suppression of lever pressing, with moderate doses of NAS-181 increasing lever pressing in fluoxetine-treated rats. Future directions involve intracranial administration and investigation of the potential role of other 5-HT receptors on effort-related behaviors.

Disclosures: S.M. Ferrigno: None. **R.A. Rotolo:** None. **R. Presby:** None. **J. Yang:** None. **M. Correa:** None. **J.D. Salamone:** None.

Poster

778. Depression and Bipolar Disorders: Treatment Strategies in Animal Studies

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 778.11/X5

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: NIH/NIMH R03MH112984

Title: Modeling selection of voluntary physical activity in psychiatric disorders: Effects of the SSRI fluoxetine in rodents

Authors: *R. E. PRESBY[1], F. KUPERWASSER[2], E. ZORDA[2], O. DIMARCO[2], R. A. ROTOLO[1], J.-H. YANG[1], C. CARRATALÁ-ROS[4], M. CORREA[5], J. D. SALAMONE[3]; [1]Psychological Sci., [2]Univ. of Connecticut, Storrs, CT; [3]Dept Psychological Sci., Univ. of Connecticut, Storrs Mansfield, CT; [4]Univ. Jaume I, Castellon DE LA Plana/Castello DE LA Pla, Spain; [5]Psicobiologia. Univ. Jaume I, Castello, Spain

Abstract: It is important to characterize the factors that influence physical activities such as voluntary exercise in people with psychiatric disorders. Depressed people, on average, show reduced levels of locomotor activity, and it has been suggested that increased physical activity could be a useful therapeutic intervention for some people. Furthermore, many people with major depressive disorder show motivational/psychomotor symptoms such as psychomotor retardation, fatigue, and anergia. Drugs that inhibit the serotonin transporter (SERT inhibitors, also known as SSRIs) are the most commonly used class of antidepressants, however, these drugs have been reported to be relatively poor at treating motivational/psychomotor symptoms, and in some people they can induce or worsen fatigue. In view of this, it is important to develop animal models that assess the factors regulating the selection of voluntary physical activities. The present studies focused on the development of a novel choice procedure that allows animals to choose between physical activity (running in a running wheel; RW) vs. intake of food (standard laboratory chow). Male and female Sprague Dawley rats were placed in the task daily for 30 minutes and were able to go back and forth between the two options. Results show a significant difference between the amount of RW activity and chow intake between the two sexes, with the females running more and consuming less, and males showing the opposite. When examining the effects of the SSRI fluoxetine (Prozac), a common treatment for depression that also reduces

appetite, a drug-induced reduction in both RW activity and chow intake in both sexes was observed. These results are similar to those obtained from mouse studies showing that fluoxetine also suppresses selection of running wheel activity. It is possible that this line of research will contribute to an understanding of the neurochemical factors regulating selection of voluntary physical activity vs. sedentary behaviors, which could be relevant for understanding the role of physical activity in psychiatric disorders.

Disclosures: **R.E. Presby:** None. **F. Kuperwasser:** None. **E. Zorda:** None. **O. DiMarco:** None. **R.A. Rotolo:** None. **J. Yang:** None. **C. Carratalá-Ros:** None. **M. Correa:** None. **J.D. Salamone:** None.

Poster

778. Depression and Bipolar Disorders: Treatment Strategies in Animal Studies

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 778.12/X6

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: Progetti di Ricerca di Ateneo, PRA 2018

Title: Fluoxetine induces morphological rearrangements of serotonergic fibers in the hippocampus

Authors: S. NAZZI, G. MADDALONI, M. PRATELLI, ***M. PASQUALETTI**;
Univ. of Pisa, Pisa, Italy

Abstract: Serotonin (5-HT)-releasing fibers show substantial structural plasticity in response to genetically-induced changes in 5-HT content. However, whether 5-HT fibers appear malleable also following clinically-relevant variations of 5-HT levels that may occur throughout an individual's life has not been investigated. Here, using confocal imaging and 3D modeling analysis in *Tph2*^{GFP} knock-in mice, we show that chronic administration of the antidepressant fluoxetine dramatically affects the morphology of 5-HT fibers innervating the hippocampus resulting in a reduced density of fibers. Importantly, GFP fluorescence levels appeared unaffected in the somata of both dorsal and median *raphe* 5-HT neurons, arguing against potential fluoxetine-mediated down-regulation of the *Tph2* promoter driving GFP expression in the *Tph2*^{GFP} mouse model. In keeping this notion, mice bearing the pan-serotonergic driver *Pet1-Cre* partnered with a Cre-responsive tdTomato allele also showed similar morphological alterations in hippocampal 5-HT circuitry following chronic fluoxetine treatment. Moreover 5-HT fibers innervating the cortex showed proper density and no overt morphological disorganization, indicating that the reported fluoxetine-induced rearrangements were hippocampus specific. On the whole, these data suggest that 5-HT fibers are shaped in response

to subtle changes of 5-HT homeostasis, and may provide a structural basis by which antidepressants exert their therapeutic effect.

Disclosures: **M. Pasqualetti:** None. **S. Nazzi:** None. **G. Maddaloni:** None. **M. Pratelli:** None.

Poster

778. Depression and Bipolar Disorders: Treatment Strategies in Animal Studies

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 778.13/X7

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: National Natural Science Foundation of China (31771170 and 31400942)
Project funded by China Postdoctoral Science Foundation(2018M643369)

Title: A visual circuit related to habenula underlies the antidepressive effects of light therapy

Authors: ***H. LU**[1], Y. XI[1], X. HUANG[1], F. XU[2], T. XUE[3], M. LUO[4], K.-F. KWOK-FAI SO[1], C. REN[1];
[1]Jinan Univ., GuangZhou, China; [2]Wuhan Inst. of Physics and Mathematics, Chinese Acad. of Sci., Wu Han, China; [3]Univ. of Sci. and Technol. of China, He Fei, China; [4]Natl. Inst. of Biol. Sci., Bei Jin, China

Abstract: Light stimulation of the retina is a powerful modulator of non-visual functions such as affective behavior. Clinical evidence supports an anti-depressive effect of light therapy. However, the precise circuits that mediate the impact of light on depressive-like behaviors remain elusive. In the present study, by combining conventional neurotracer and transneuronal virus tracing techniques, we identified a di-synaptic visual circuit connecting the retina and lateral habenula (LHb) in the mouse. We show that a subset of M4-type retinal ganglion cells (RGCs) innervate GABA neurons in the ventral lateral geniculate nucleus and intergeniculate leaflet (vLGN/IGL), which in turn inhibit the neural activity of the LHb. Specific activation of LHb-projecting vLGN/IGL neurons, activation of LHb-projecting vLGN/IGL neurons, or inhibition of postsynaptic LHb neurons is sufficient to decrease the depressive-like behaviors and reduce the aberrant LHb neuronal activity evoked by long-term exposure to aversive stimuli or chronic social defeat stress. Furthermore, we demonstrate that the anti-depressive effects of bright light therapy are dependent on the activation of the retina-vLGN/IGL-LHb pathway. These results reveal a dedicated subcortical visual circuit that regulates depressive-like behaviors and may shed light on our current understanding of the mechanisms of light therapy.

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Poster

778. Depression and Bipolar Disorders: Treatment Strategies in Animal Studies

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 778.14/X8

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: FR AR 17_333

Title: Effect of low frequency electromagnetic stimulation on the blood quantitative indices in clomipramine-induced depressed rats

Authors: *M. J. SVANIDZE[1], M. BUTSKHRIKIDZE[1], N. JOJUA[2], N. BUKIA[1], L. MACHAVARIANI[1];
[1]Neurophysiol., LEPL Ivane Beritashvili Ctr. of Exptl. Bio, Tbilisi, Georgia; [2]Biochem., European Univ., Tbilisi, Georgia

Abstract: Depression is a common medical illness that negatively effects on living organism. Despite the fact that it is possible to treat depression using pharmacological substances, about 30-40% of the patients are resistant to such treatment and so, their recovery is impossible. In 2008 repetitive electromagnetic stimulation (EMS), was approved by the FDA for the treatment of moderate depression. The content of blood can be changed as a result of depression and also as a repeated exposure of EMS. So, the goal of this investigation was to study the quantitative characteristics of blood cells in depressed and intact albino rats on the background of EMS. In implementation of the project the depressed rats and albino intact rats (250-450 g) were used (n=20). For each task two groups of animal were conducted: experimental group (with EMS) and control group (without EMS). For repetitive (10-days) EMS, the following parameters were used: 10000 -15000 Hz frequency, 1,5 m/Tesla, during 15 min. An animal model of depression was received by subcutaneous injection of Clomipramine from 8 to 21 days of neonatal development. The control group received saline injection in the same period of life. The determination of depression and anxiety reaction of rats were performed 2 months later after clomipramine injection. For hematological analysis of blood HumaCount 30 TS were used. This analyzer allows to quantify the number of red blood cells, leukocytes, platelets, hemoglobin, the hematocrit in 1 ml blood of rats. Determination of these parameters is very important because of EMS affected whole body, including the bone marrow, which is main place blood cells genesis. The blood was collected from the tail lateral vein. Hematological analysis was performed 2 weeks later after EMS. The EMS did not change the main characteristics of blood content during two weeks. In depressed rat's important changes of blood cells was detected. Particularly, the amount of monocytes and mean platelet volume (MPV) was increased, the number of Platelets was decreased. low platelet counts and a high MPV level, suggested that the bone marrow is rapidly producing platelets. This may be because older platelets are being destroyed, so the bone

marrow is trying to compensate. In depressed rats on the background of EMS, the number of monocytes and MPV decreased, but its level was remained high. The number of platelets was increased. In depressive rats, the content of erythrocytes increased. We suggested, that EMS might effected on bone marrow and potentiate erythropoiesis. EMS is non-invasive treatment method without side effects on the blood cell count. In depressed rats the EMS can restore the blood cells imbalance.

Disclosures: M.J. Svanidze: None. **M. Butskhrikidze:** None. **N. Jojua:** None. **N. Bukia:** None. **L. Machavariani:** None.

Poster

778. Depression and Bipolar Disorders: Treatment Strategies in Animal Studies

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 778.15/X9

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Title: TRH and TRH-like peptides participate in the therapeutic effects of metformin

Authors: *A. E. PEKARY[1], A. SATTIN[2];
[1]Res., VA Greater Los Angeles Hlthcare Syst, Los Angeles, CA; [2]Res., VA Greater Los Angeles Hlth., Los Angeles, CA

Abstract: Major depression, heart disease, obesity, and type 2 diabetes are increasingly common comorbidities in aging populations due, in part, to the adoption of Western diets which alter the gut microbiome. Co-administration of metformin (MF) and ascorbic acid (AA) have recently been reported to effectively treat these disorders. The present studies explore the acute, chronic and withdrawal effects of oral MF, which binds copper, to explore how it perturbs the rate-limiting, copper- and ascorbate-dependent processes controlling the expression of the neuro- and gut-protective TRH and TRH-like peptides. These endogenous tripeptides, like MF, have beneficial metabolic, gastrointestinal, cardiac, and neuroprotective effects which may counter some of the pathophysiological effects of Western culture and aging. Sixteen young, adult, male Sprague-Dawley rats, were divided into 4 equal groups. Controls received only tap water. The acute group was provided with tap water for 9 days and then 6 mg MF/ml tap water for 1 day. Chronic animals received MF in tap water for 10 days. The withdrawal rats drank MF-containing water for 8 days and then regular tap water for 2 days. TRH and TRH-like peptide levels were measured in 12 brain and 7 peripheral tissues. The pattern of acute, chronic and withdrawal effects of MF on the expression of each TRH and TRH-like peptide in brain and peripheral tissues tended to increase (↑), or decrease (↓), monotonically in proportion to the total time of exposure to MF. The withdrawal of MF appeared to be too short a period for a return toward control levels to be detected for any peptide. MF-induced acute, chronic, and withdrawal changes in TRH and TRH-like peptide levels, in decreasing order of number of significant changes were:

frontal cortex (21↓), hippocampus (18↓), nucleus accumbens (2↑,14↓), striatum (3↑,12↓), medulla oblongata (2↑,9↓), piriform cortex (2↑,9↓), hypothalamus (2↑,7↓), entorhinal cortex (7↓), amygdala (1↑,6↓), cerebellum (2↑,4↓), posterior cingulate (1↑,3↓), anterior cingulate (2↑,2↓), testis (19↑), adrenals (15↓). Metformin mimics the effects of caloric restriction (CR) which increases health and life spans. CR suppresses central TRH activity resulting in bradycardia and suppression of energy expenditure. The observed persistence of MF effects on TRH and TRH-like peptide levels in the brain and peripheral tissues during MF withdrawal is consistent with a lag in the return of the gut microbiome to its pretreatment composition. We conclude that TRH and TRH-like peptides participate in the therapeutic effects of MF primarily via its sustained alterations in the gut microbiome.

Disclosures: **A.E. Pekary:** None. **A. Sattin:** None.

Poster

778. Depression and Bipolar Disorders: Treatment Strategies in Animal Studies

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 778.16/X10

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Title: SUVN-D4010, a 5-HT4 receptor partial agonist with antidepressant properties: Behavioral and neurochemical studies in mice and rats

Authors: A. MOHAMMED, N. BOGARAJU, R. PALACHARLA, *S. DARIPELLI, S. GANDIPUDI, P. JAYARAJAN, R. NIROGI;
Suven Life Sci. Ltd., Hyderabad, India

Abstract: SUVN-D4010 is a potent, selective and orally bioavailable 5-HT_4 receptor partial agonist. SUVN-D4010 is a phase-2 ready clinical candidate. Literature indicates involvement of 5-HT_4 receptor in behavioral features of depression, since the deletion of or pharmacological blockade of 5-HT_4 receptor results in depressive and anxiety-like behaviors in rodents. Based on this, potential antidepressant-like properties of SUVN-D4010 were investigated in animal models of depression. Compound was evaluated in dominant submissive model in Wistar rats where the dominance and submissive level was scored for 5 minutes daily for 5 days in a week, 1 hour after the treatment SUVN-D4010. Compared to the control group, the dominance levels of SUVN-D4010 treated group decreased significantly, thus confirming its anti-depressant activity. Additionally, SUVN-D4010 in combination with serotonin re-uptake inhibitor (SSRI) paroxetine produced synergistic effects on serotonin levels in ventral hippocampus of Wistar rats. Results from these preclinical studies provide strong evidence for SUVN-D4010 in alleviating depressive symptoms by complementary mechanism with existing anti-depressants.

Disclosures: **A. Mohammed:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **N. Bogaraju:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **R. Palacharla:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **S. Daripelli:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **S. Gandipudi:** 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

778. Depression and Bipolar Disorders: Treatment Strategies in Animal Studies

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 778.17/X11

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: Janeway Foundation Research Grant
CIHR
NSERC

Title: The use of transcranial direct current stimulation and paroxetine to treat depressive-like behaviours in olfactory bulbectomized adolescent rats

Authors: *S. WAYE[1], F. BAMBICO[1,2], J. NOBREGA[2], R. RAYMOND[2];
[1]Mem. Univ. of Newfoundland, St. John's, NL, Canada; [2]Ctr. for Addiction and Mental Hlth., Toronto, ON, Canada

Abstract: Adolescent depression is a complex condition that proves difficult to treat, as current treatments have been shown to produce paradoxical effects that worsen depressive symptoms, such as suicidality risk or anxiety. Therefore, we tested if a non-invasive brain stimulation technique known as transcranial direct current stimulation (tDCS) could be used either by itself or in combination with selective serotonin reuptake inhibitor (SSRI) drug therapy to safely and effectively treat adolescent depression. We induced a depressive-like phenotype in adolescent Sprague-Dawley rats (PND 28, n= 90) using olfactory bulbectomy (OBX), a rodent model of depression that results in behavioural and neurochemical changes that are reversed by antidepressant treatment. We examined if two weeks of tDCS treatment (50 μA, 15 minute sessions) was sufficient to reverse OBX-induced depressive-like behavioural symptoms, including hyperlocomotion in an open field chamber, immobility in a forced swim test, and deceased sucrose consumption. We tested if these effects were achievable with tDCS alone or with adjunct Paroxetine treatment (20mg/kg, IP). We found that tDCS, but not Paroxetine, was able to successfully reverse the OBX-induced hyperlocomotion in the open field test, however there were no significant differences in swimming behaviour in the forced swim test. Additionally, acute administration of Paroxetine caused a significant reduction in sucrose

preference, an effect that was completely blocked by concurrent tDCS stimulation. Sucrose preference was normalized after chronic treatment of Paroxetine, with no additional benefit of concurrent tDCS at this point. These findings support the idea that SSRI treatment results in the worsening of depressive symptoms, particularly at the start of treatment. They also suggest that tDCS is an effective intervention for adolescent depression and can be used to treat the disorder in place of, or in addition to, SSRI administration.

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Poster

778. Depression and Bipolar Disorders: Treatment Strategies in Animal Studies

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 778.18/X12

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: LAU SRDC grant

Title: Nicotine mediates the positive effects of water pipe tobacco smoking on resilience to chronic social defeat stress by increasing hippocampal BDNF levels, but does not mediate its negative effects on anxiety

Authors: *S. SLEIMAN[1], M. KHALIFEH[2], R. HOBEIKA[2], J. S. STEPHAN[3], R. KHNAYZER[2], C. KHALIL[2];
[1]LAU Sch. of Arts and Sci., Byblos, Lebanon; [3]Sch. of Med., [2]Lebanese American Univ., Byblos, Lebanon

Abstract: The main purpose of this study was to investigate the effects of waterpipe tobacco smoking (WTS) and nicotine on depression and anxiety-like behaviors associated with chronic social defeat stress (CSDS). Male C57BL/6 were exposed to WTS for thirty days, then subjected to CSDS for ten days. Twenty-four hours after the last defeat session, the social interaction test was used to assess social avoidance behavior associated with CSDS and to classify animals as resilient or susceptible to stress. The open-field test was used to evaluate the anxiety-like behavior of the mice. After behavioral testing, the mice continued to be exposed to WTS or were subjected to WTS withdrawal and their behavior was reexamined using the social interaction and open-field tests after ten days. Nicotine (1 mg/kg), Nicotine+Ana-12 (a TRKB inhibitor) or saline were given intraperitoneally after each defeat session for the duration of the CSDS experiments and behavioral testing was also performed. We found that WTS promotes resilience to chronic stress, as well as rescues social avoidance and anxiety-like behaviors associated with CSDS. We also found that continued exposure to WTS after CSDS increases resilience to stress and promotes social interaction, whereas smoking withdrawal did not have significant effects. Interestingly, even though exposure to WTS initially rescued anxiety-like behaviors, prolonged

exposure after the completion of the CSDS paradigm significantly enhanced anxiety-like behaviors. Finally, we showed that nicotine mediates the effects of WTS on resilience to stress, and social interaction behaviors by increasing hippocampal BDNF levels and signaling. Our results show that WTS and nicotine have positive effects on social behavior after CSDS by activating hippocampal BDNF signaling. Furthermore, they also suggest that even though WTS is initially anxiolytic, prolonged exposure to WTS promotes anxiety-like behaviors. Interestingly, nicotine does not modulate anxiety-like behavior suggesting that the effects of WTS on anxiety is mediated by other components of the waterpipe tobacco.

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Poster

778. Depression and Bipolar Disorders: Treatment Strategies in Animal Studies

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 778.19/X13

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: NRF funded by Ministry of Science, Information and Communication Technologies (2017R1D1A1B03035649)

Title: Electroconvulsive seizure alleviates MPTP-induced motor deficits and promotes AMPK-related autophagy signaling in mice

Authors: *Y. KIM[1], S. KIM[2], H. YU[2];
[1]Dongguk Univ. Med. Sch., Goyang-Si, Gyeonggi-Do, Korea, Republic of; [2]Seoul Natl. Univ. Hosp., Seoul, Korea, Republic of

Abstract: Electroconvulsive seizure (ECS) is an animal model of electroconvulsive therapy (ECT), which has been used in the treatment of psychiatric disorders, including depression, bipolar disorder, and schizophrenia, as well as Parkinson's disease. The clinical beneficial effect of ECT on Parkinson's disease has been demonstrated, however, underlying mechanisms of ECS on Parkinson's disease have not been studied yet. In this study, the effects of repeated ECS treatments on a mouse model of Parkinson's disease (PD) induced by neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) on behavioral and neurochemical aspects have been investigated. Firstly, the stimulation protocol of ECS for C57Bl/6J mice has been confirmed, and, for repeated treatments, ECS was applied three times per week during two weeks (total 6 times; E6X). E6X treatments significantly ameliorated the MPTP-induced motor deficits of mice as measuring rotarod and pole test, which were normalized to control level. In mice frontal cortex and striatum, AMP-activated protein kinase (AMPK) and related autophagy signaling molecules were examined. E6x increased the phosphorylation level of AMPKalpha at Thr172,

and phosphorylation of its down-stream molecules, including unc-51-like kinase (ULK1) (Ser317) and Beclin1 (Ser93), was increased concurrently. In MPTP-treated mice, the phosphorylation of AMPK, ULK1, and Beclin1 was reduced in frontal cortex and that of AMPK and ULK1 was decreased in striatum, which were all normalized to the control level by E6X treatments. At the same time, E6X treatments increased the immunoreactivity of LC3-II and ATG5-ATG12 conjugate indicating the activation of autophagy signaling, and E6X restored the MPTP-induced decrease in the level of LC3-II and ATG5-ATG12 conjugate. Taken together, our results show that repeated treatments of ECS activated AMPK-related autophagy signaling which could mediate the beneficial effects of ECS on the mouse model of Parkinson's disease induced by MPTP.

Disclosures: **Y. Kim:** None. **S. Kim:** None. **H. Yu:** None.

Poster

778. Depression and Bipolar Disorders: Treatment Strategies in Animal Studies

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 778.20/X14

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: PAPIIT, DGAPA IN:214017 (scholarship to J Arroyo-Pérez)

Title: Differential effects of low and high frequencies of rTMS on depressive and anxiety-like behaviors in chronic unpredictable mild stress rat model

Authors: *J. ARROYO-PÉREZ[1], B. L. GARCÍA-QUINTERO[1], E. RUIZ-HERNÁNDEZ[2], D. ELÍAS-VIÑAS[2], L. VERDUGO-DIAZ[1];
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Abstract: Repetitive Transcranial Magnetic Stimulation (rTMS), has proven to be an effective alternative for treatment-resistant depression. A variety of frequencies ranging from 1Hz to 25Hz have been used on animal and human research. It’s urgent to clarify each frequency efficacy not only to have a reliable method for treating patients, but also to bring about specific treatment designs suitable for each patient. The objective of the current study was to differentiate behavioral effects using low (1Hz) and high (10 Hz) frequencies on a Chronic Umpredictable Mild Stress (CUMS) induced rat depression model. To apply rTMS we used an In-House Electronic System (EMAGPRO 12). This system was designed and developed by engineers at the Center of Research and Advanced Studies, IPN (Mexico City). The rTMS system consisted of a figure-eight coil and the frequency could range from 1 to 10Hz. We applied 10 minute sessions of 1 and 10Hz rTMS for 15 days on Wistar male rats (n=30) that were exposed to CUMS 20 days before rTMS and 15 days during treatment. We used different measures to

evaluate locomotor activity, anxiety and depressive-like behaviors. Forced Swim Test (FST) was used before and after rTMS treatment to assess the extent of 1 and 10 Hz antidepressant effect. Anxiety was assessed by duration and frequency of entries through closed and open arms of an elevated plus maze (EPM). Locomotor activity as well as other depressive and anxiety related measures (e.g. time spent grooming, rearing and immobility) were assessed using an open field test (OFT). Control rats differed in weight and sucrose consumption from CUMS, CUMS+1 Hz rTMS and CUMS+10 Hz rTMS. Compared to control and SHAM animals, CUMS, CUMS+1 Hz rTMS and CUMS+10 Hz rTMS animals showed significant differences in time spent on close arms of EPM, distance traveled in OPF center and time of immobility in FST. Further research is required to measure other frequencies effects and neurobiochemical markers are still needed to correlate with behavioral outcomes.

Disclosures: J. Arroyo-Pérez: None. **B.L. García-Quintero:** None. **E. Ruiz-Hernández:** None. **D. Elías-Viñas:** None. **L. Verdugo-Diaz:** None.

Poster

778. Depression and Bipolar Disorders: Treatment Strategies in Animal Studies

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 778.21/X15

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: NIMH Grant 4UH3MH109334-03

Title: The effects of modafinil on behavioral and neurophysiological indices of cognitive control in a touchscreen-based rodent Flanker Task

Authors: *M. A. ROBBLE[1], H. SCHRODER[1], M. BRANHAM[1], L. WOOLDRIDGE[1], M. BREIGER[1], B. D. KANGAS[1], J. BERGMAN[1], W. A. CARLEZON, Jr[2], D. A. PIZZAGALLI[3]; [1]McLean Hospital, Harvard Med. Sch., Belmont, MA; [2]Dept Psychiat, Harvard Med. Sch./Mclean Hosp., Belmont, MA; [3]McLean Hosp., Belmont, MA

Abstract: Dysregulation of cognitive function, including deficits in reward sensitivity and cognitive control, is a common feature of virtually all neuropsychiatric disorders. While perturbations in cognitive control have been studied extensively in humans, it has been challenging to examine these complex processes in laboratory animals. In turn, stagnation in the development of translationally-relevant tasks to assess these processes in laboratory animals and humans has impeded the development of innovative treatments for neuropsychiatric disorders. As part of an NIMH initiative to create reliable and valid cross-species assays of cognitive function, we have developed a touchscreen-based version of the Eriksen Flanker Task to assess cognitive control in rats. Here we examine the effect of modafinil on behavioral performance, as well as event-related potentials (ERPs) and oscillations in the Flanker Task.

Using fading and correction procedures combined with touch-sensitive response technology, we trained male and female Long-Evans rats to discriminate between detailed photographic stimuli (green leaf/violet flower). Discrimination was deemed successful when the criterion of 70% response accuracy during the session was recorded on two consecutive days. Following training, rats underwent stereotaxic surgery for implantation of surface and depth electrodes for neurophysiology data collection. Using a within-subjects design, five 300-trial Flanker Task test sessions subsequently were conducted during which rats received saline, vehicle (100% DMSO), or modafinil (16, 32, and 64 mg/kg IP, 30-minute pretreatment time); continuous EEG and LFP data were collected throughout test sessions.
Early data indicate no effect of modafinil treatment on overall or post-error accuracy. However, preliminary analyses suggest that modafinil decreases the magnitude of the difference between incorrect and correct responses on incongruent trial types, a negative deflection that shares qualitative features with the human error-related negativity (ERN) component of the ERP. These data raise the possibility that modafinil reduces the impact of incorrect responses, which can affect performance in people with psychiatric illness. The analysis of data from additional subjects will aid in evaluating the reliability of this effect and, also, modafinil's possible modulation of expected, task-specific changes in spectral power. Comparing results from rats and human subjects in the same task will indicate whether modafinil-induced changes in behavior and/or neurophysiology are consistent across species.

Disclosures: M.A. Robble: None. **H. Schroder:** None. **M. Branham:** None. **L. Wooldridge:** None. **M. Breiger:** None. **B.D. Kangas:** None. **J. Bergman:** None. **W.A. Carlezon:** None. **D.A. Pizzagalli:** None.

Poster

778. Depression and Bipolar Disorders: Treatment Strategies in Animal Studies

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 778.22/X16

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: U.S. Department of Veterans Affairs Biomedical Laboratory Research and Development Program Merit Award 1I01BX003512
William and Ella Owens Medical Research Foundation

Title: Antidepressant effects of fear extinction, an animal model of exposure therapy

Authors: *J. LIU[1], A. D. RIGODANZO[1], D. A. MORILAK[2];
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Abstract: Depression is a serious mental disorder and the leading cause of disability worldwide. Current treatment includes antidepressant drugs, psychotherapy, or a combination of both. Unfortunately, treatment-resistance and relapse are still high. In recent years, exposure-based therapies, which are among the most effective treatments for anxiety and trauma-related disorders (e.g., PTSD), have been used in the context of depression, by adding principles of exposure and emotional processing to improve cognitive-behavioral therapies for treating depression. In clinical studies, exposure-based therapy has been demonstrated to be associated with significant reductions in depressive symptoms, which is comparable with other cognitive behavioral therapies. Recently, our lab established a model of cognitive behavioral intervention in rats, namely extinction therapy, which resembles exposure-based therapy in the clinic. We found that extinction therapy ameliorated chronic unpredictable stress (CUS)-induced deficits in cognitive flexibility and active coping behavior that mimic symptom dimensions of cognitive inflexibility and avoidance behavior shared by PTSD and depression. In the current study, the potential antidepressant effects of extinction therapy are examined. We found that extinction therapy reduced immobility and increased active coping behaviors in the forced swim test (FST), a widely used animal model to screen for potential antidepressant efficacy. The antidepressant effects of extinction therapy were further demonstrated in reversing CUS-induced anhedonia, a core symptom of depression. Since medial prefrontal cortex (mPFC) is involved in extinction learning in rats, the inhibitory Gi-coupled designer receptor exclusively activated by designer drug CaMKIIα-hM4Di was expressed in vmPFC. vmPFC projection neurons were then inhibited during extinction by administering clozapine-N-oxide. FST was performed 24 h later. We found that inhibiting vmPFC during extinction blocked the antidepressant effects of extinction in the FST. In sum, we have generalized the utility of extinction as a model of cognitive-behavioral psychotherapy in rats, extending our previous findings of beneficial effects on cognitive flexibility and stress coping behavior to other core depressive-like behaviors on the forced swim test and sucrose preference test.

Disclosures: J. Liu: None. **D.A. Morilak:** None. **A.D. Rigodanzo:** None.

Poster

778. Depression and Bipolar Disorders: Treatment Strategies in Animal Studies

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 778.23/X17

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: CONACyT 221356 to MA

Title: Antidepressant effect of Buddleja cordata extract in a mice model of chronic stress

Authors: G. GARCIA-ALONSO[1], A. MONROY[2], G. FLORES[3], M. MIRANDA-MORALES[4], A. RANGEL[1], R. D. CUEVAS OLGUIN[1], *M. ATZORI[5];

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Abstract: *Buddleja cordata* is a medicinal plant with wide use in traditional Mexican pharmacopeia with the name of tepozan. It is used as remedy for spasms, muscle contracture, as well as for respiratory and skin inflammatory conditions. Some of its identified active compounds are principally verbascosides (fenilpropanoids, esters and terpenoids). The methanolic extract of B.cordata has shown antioxidant and neuroprotecting activity *in vitro* as well as Parkinson disease animal model. Previous biochemical studies indicated suggested that Hydroxityrosol-one of its verbascoside metabolites may be the active compound of tepozan. We tested the antidepressant effect of tepozan using a chronic stress-based mice model of depression. Four groups (n= 8-12 per group) of C57BL/6 were submitted to chronic stress protocol (CS) consisting of early maternal separation (Postnatal Day, PND 2-21) plus restriction (PN week 10-12). The four groups were submitted to different treatments during 4 weeks (8-12 weeks PN). Group 1 was subject only to CS, group 2 was subject to CS plus oral intake of vehicle, group 3 to intake of fluoxetine (20 mg/kg/d) and group 4 to intake of tepozan hydroethanolic extract (100 mg/kg/day). Behavioral tests were conducted during the weeks immediately after each treatment. One-way ANOVA indicated between groups differences ($p < 0.005$, $F= 6.25$). Post hoc Tukey test indicated that group 2 (vehicle: inactivity 32.8% ± 6.7%) did not differ from group 1 (control: inactivity 45.4% ± 7.8%), group 3 (fluoxetine: inactivity 20.3% ± 4.5%) differed both from group 1 and 2, and group 4 (tepozan: inactivity 8.2% ± 3.6%) was significantly lower vs. all other groups. Our experiments suggest that tepozan extract has a potential as antidepressant, even on top of the well described effects of fluoxetine.

Disclosures: G. Garcia-Alonso: None. **A. Monroy:** None. **G. Flores:** None. **M. Miranda-Morales:** None. **A. Rangel:** None. **R.D. Cuevas Olguin:** None. **M. Atzori:** None.

Poster

778. Depression and Bipolar Disorders: Treatment Strategies in Animal Studies

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 778.24/X18

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Title: Acute administration of propofol in mice pre-treated with fluoxetine does not improve performance on the FST

Authors: N. G. J. DANIEL[1], D. T. G. DANIEL[2], ***D. G. DANIEL**[3], L. C. FLYNN[4], M. ALLEN[5];
[1]Dartmouth Col., Hanover, NH; [2]Brown Univ., Providence, RI; [3]Bioniche Global Development,

LLC, McLean, VA; [4]LCF Consulting, LLC, Lake Forest, IL; [5]Univ. of Colorado Sch. of Med., Aurora, CO

Abstract: Objective:*Acute*intraperitoneal injection of fluoxetine 30 minutes prior to administration of the FST in C57Bl/6 micehas previously been shown to significantly improve performance on the Forced Swimmimg Test (FST) a rodent model of depression. [1] Propofol (2,6-diisopropylphenol) is a GABA-A agonist intravenous anesthetic agent. Based on anecdotal reports of improved mood in humans following propofol (a GABA-A agonist) induced anesthesia, we tested the effect of acute propofol treatment alone or in combination with sub-chronic fluoxetine dosing on FST performance.
Design:72 adult male mice (C57/BL6, CRL-provided) were pre-treated daily with saline or fluoxetine (20 mg/kg, i.p.) (21 days for cohort 1; 24 days for cohort 2). 24 hours after the last pre-treatment injection, mice received saline or propofol (35-50 mg/kg, i.p.) treatment. 45 minutes later, mice underwent a 5-min FST. Immobility time was quantified and evaluated with a custom video-analysis software. Experiments were performed at Charles River Laboratories (SF, CA). The Grubb's test identified statistically significant outliers which were excluded from data analysis.
Results: A two-way ANOVA indicated that pre-treatment with fluoxetine affected immobility time independently of treatment. Further Dunnett's post hoc comparison revealed that fluoxetine-treated mice spent more time immobile than the saline groups.
Discussion: *Acute*intraperitoneal (IP) injection of fluoxetine 30 minutes prior to administration of the FST in C57Bl/6 micehas previously been shown to significantly improve FST performance. [Jin et al, 2017] In contrast, *subchronic and chronic*adminstration of fluoxetine are more problematic to interpret. Mouse strain influences in responsivity to chronic and subchronic oral fluoxetine treatment have previously been reported by Dulawa, et al 2014. [2] In their experiment, chronic oral fluoxetine treatment failed to decrease immobility time in the FST in C57Bl/6 mice. [2] In our experiment subchronic intraperitoneal administration of fluoxetine to C57Bl/6 mice alone or combination with acute IP administration of propofol in did not decrease immobility time on the FST.
1. Jin ZL, Chen XF, Ran YH, Li XR, Xiong J, Zheng YY, et al. Mouse strain differences in SSRI sensitivity correlate with serotonin transporter binding and function. Scientific Reports. 2017 Aug 17;7(1):8631.
2. Dulawa SC, Holick KA, Gundersen B, Hen R. Effects of chronic fluoxetine in animal models of anxiety and depression. Neuropsychopharma. 2004 Jul;29(7):1321.

Disclosures: N.G.J. Daniel: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); ioniche Global Development, LLC. **D.T.G. Daniel:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); ioniche Global Development, LLC. **D.G. Daniel:** A. Employment/Salary (full or part-time):; ioniche Global Development, LLC. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Bioniche Global Development, LLC. **L.C. Flynn:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); ioniche Global

Development, LLC. **M. Allen:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); ioniche Global Development.

Poster

778. Depression and Bipolar Disorders: Treatment Strategies in Animal Studies

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 778.25/X19

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Title: Combined treatment with aripiprazole and sertraline increases extracellular dopamine levels in the nucleus accumbens of rats more than sertraline alone

Authors: *Y. OYANAGI, Y. KITAICHI, Y. AN, I. KUSUMI;
Dept. of Psychiatry, Hokkaido Univ. Grad, Sapporo/Hokkaido, Japan

Abstract: Combined treatment with aripiprazole and selective serotonin reuptake inhibitors has been used as augmentation therapy of depression. However, the augmentation mechanism of aripiprazole remains unclear. This study was designed to investigate abilities of systemically administered aripiprazole and sertraline to increase the extracellular levels of monoamines acutely in two brain regions of male Sprague Dawley rats. We examined effects of aripiprazole and sertraline on extracellular serotonin, dopamine, and noradrenaline levels in the nucleus accumbens (Nacc) and the medial prefrontal cortex (mPFC) using *in vivo* microdialysis. The Hokkaido University School of Medicine Animal Care and Use Committee approved all procedures. The aripiprazole alone (0.3, 3 and 9 mg/kg) had no effect on extracellular monoamine levels. However, co-administration of high dose aripiprazole (3 and 9 mg/kg) and sertraline increased extracellular dopamine levels in the Nacc more than sertraline alone. There were no differences in extracellular serotonin and noradrenaline levels in the Nacc between the sertraline with aripiprazole group and the sertraline alone group. There were no differences in all three monoamines in the mPFC between all groups. These results suggest that co-administration of high dose of aripiprazole and sertraline increased extracellular dopamine levels in the Nacc more than sertraline alone, though aripiprazole is a dopamine partial agonist. Antidepressant effects of aripiprazole may be mediated by the reinforcement of dopamine neurotransmission in the Nacc.

Disclosures: Y. Oyanagi: None. **Y. Kitaichi:** None. **Y. An:** None. **I. Kusumi:** None.

Poster

778. Depression and Bipolar Disorders: Treatment Strategies in Animal Studies

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 778.26/X20

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Title: Valeriana fauriei exerts antidepressant-like effects through anti-inflammatory and anti-oxidant activities by inhibiting brain-derived neurotrophic factor associated in chronic restrained stress

Authors: *J. OH, J. CHOI, Y. CHANG, B. CHEON, I.-H. CHO;
Kyung Hee Univ., Seoul, Korea, Republic of

Abstract: Background: Depression is the most common psychiatric disorder, but its pharmacological properties are not well-known. Although *Valeriana fauriei* (VF) extract has been reported to exert beneficial effects in several neurological studies, little information is available regarding its antidepressant activity.
Methods: In present study, we demonstrated the antidepressant activity and its underlying mechanism of VF extract in a chronic restraint stress (CRS)-induced depression model in mice.
Results: Oral treatment of VF extract for 14 days significantly ameliorated depression-like behaviors (immobility time) in tail suspended and forced swim tests following CRS induction, in accordance with decrease of the levels of serum corticosterone. VF extract ameliorated c-Fos expression, microglial activation and phosphorylated p38 expression, and inflammatory response (the level of protein expression of cyclooxygenase-2 and inducible nitric oxide) in the hippocampus and amygdala of mice after CRS induction. However, VF extract enhanced the stimulation of the nuclear factor erythroid 2 related factor 2 pathways, which correspondence with the up-regulation in protein expression of brain-derived neurotrophic factor (BDNF).
Conclusion: Collectively, our findings provide that VF extract has antidepressant-like activity against CRS-induced depression through anti-inflammatory and antioxidant effects via inhibiting BDNF expression. Further studies are warranted to investigate the possibility of VF extract's fraction and components as future antidepressant.

Disclosures: J. Oh: None. **J. Choi:** None. **Y. Chang:** None. **B. Cheon:** None. **I. Cho:** None.

Poster

778. Depression and Bipolar Disorders: Treatment Strategies in Animal Studies

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Program #/Poster #: 778.27/X21

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: BBSRC SWBio DTP : BB/M009122/1

Title: Comparison of delayed and rapid onset antidepressants in a rodent probabilistic reversal learning task

Authors: *M. P. WILKINSON, J. R. MELLOR, E. S. J. ROBINSON;
Univ. of Bristol, Bristol, United Kingdom

Abstract: Patients with major depressive disorder exhibit deficits in reward processing and have altered feedback sensitivity in probabilistic reward learning tasks (Murphy et al., 2003; Pizzagalli et al., 2008). One of the most exciting discoveries in modern psychiatry is the rapid antidepressant action of compounds such as ketamine or scopolamine (Zarate et al, 2006; Jaffe et al, 2013). We have utilised a translational probabilistic reward learning task (PRLT, Bari et al, 2010) to compare the effects of conventional and rapid-onset antidepressants on reward learning. Reinforcement learning models allow probing of the underlying computational substrates of reward learning therefore we utilised a Q-learning model to further explain the effects of these drugs on behaviour.
Twelve adult male rats were trained in a PRLT. Rats learnt to spatially bias responses to receive food reward with stimuli being probabilistically rewarded so that there was a rich stimulus and a lean stimulus rewarded 80% and 20% of the time respectively. After 8 consecutive rich stimulus choices the reward contingencies switched. Rats were treated before testing (experimenter blind to treatment, within subject randomised) with either a delayed onset antidepressant (citalopram, venlafaxine or reboxetine) or a rapid onset antidepressant (ketamine or scopolamine). A Qlearn model, utilising a single learning rate for positive and negative information, was fitted using vehicle data and then used to analyse data from each drug dose and animal individually. Citalopram treatment increased positive feedback sensitivity and improved reward learning ability while reboxetine had the opposite effect. Venlafaxine had no effect on any parameter tested. Both ketamine and scopolamine reduced reward learning, positive feedback sensitivity and motivation. The reinforcement learning model suggested that reboxetine caused a decrease in accuracy compared to a model predicted perfect strategy and ketamine significantly decreased the model-based learning rate. Although all the tested drugs have well characterised antidepressant efficacy the incongruity of results in this study suggest that modification of probabilistic reward learning, as measured by this task, is not a key part of their mechanism of action.

Disclosures: **M.P. Wilkinson:** None. **J.R. Mellor:** None. **E.S.J. Robinson:** None.

Poster

778. Depression and Bipolar Disorders: Treatment Strategies in Animal Studies

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 778.28/X22

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: NIH R01MH086828
Beta Beta Beta
Sigma Xi

Title: Antidepressant efficacy of L-655,708 following infusions into the medial prefrontal cortex

Authors: *A. M. BAILEY, B. STEINHOFF, K. ROBEY;
St. Mary's Col. of Maryland, St. Mary's City, MD

Abstract: Major Depressive Disorder (MDD) is a serious and widespread mental health condition that has a significant negative impact on overall quality of life. Current treatments for depression such as selective serotonin reuptake inhibitors (SSRIs) are slow to take effect, have negative side effects, and fail to achieve remission in a large number of patients. The recent success of ketamine as a fast-acting antidepressant has led to research using other pharmaceutical compounds, with the goal to discover a safe, fast-acting antidepressant without the addictive and psychotomimetic effects of ketamine. L-655,708, a negative allosteric modulator of GABA-A receptors (GABA-NAMs) with an alpha5 subunit, has been shown to produce an antidepressant-like effect when injected systemically and when infused directly into the hippocampus in rodent models of depression. The present study evaluated the effects of the direct infusion of L-655,708 (5ng/0.2 µL) via bilateral guide cannula insertion directly into the medial prefrontal of male rats exposed to a chronic unpredictable stress (CUS) paradigm. Depressive-like behaviors, including anhedonia, were quantified using the sucrose preference test, social interaction test, and the novelty suppressed feeding test. Direct infusions of L-655,708 in the mPFC improved anhedonic measures of sucrose preference and sucrose intake (η^2= .21) although not significantly. Additionally, direct infusions in the mPFC increased latency to interact in the social interaction test but failed to reach statistical significance (η^2= .24). Our data compliments other studies reporting the antidepressant-like effects of GABA-NAMs.

Disclosures: **A.M. Bailey:** None. **B. Steinhoff:** None. **K. Robey:** None.

Poster

779. Post-Traumatic Stress Disorder

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 779.01/X23

Topic: G.06. Post-traumatic Stress Disorder

Support: CNPq
FAPEMIG

Title: Incidence and risk factors for post-traumatic stress, anxiety and depression in sepsis survivors after ICU discharge

Authors: *A. J. CALSAVARA[1], P. A. COSTA[2], V. NOBRE[3], A. L. TEIXEIRA[4];
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Abstract: Introduction: Anxiety, depression and post-traumatic stress disorder may develop in sepsis survivors and have a profound effect on their everyday functioning.
Objective: To study the incidence and predictors of anxiety, depression and post-traumatic stress symptoms in severe sepsis and septic shock survivors 24h and 1-year post ICU discharge.
Methods: A prospective study of 33 patients who survived severe sepsis or septic shock and completed the PTSD Checklist-Civilian Version, Beck Depression Inventory-II and Beck Anxiety Inventory at 24h and 1year after ICU discharge. Demographic and clinical data where measured during ICU stay and laboratory, including HMGB1, BDNF, S100B and NSE, performed 24h and 1-year after ICU discharge. Difference in psychiatric symptoms over time, controlling for possible confounding factors, and the influence of the variables on these symptoms were calculated with marginal models.
Results: The prevalence of clinically meaningful symptoms of anxiety, depression and PTSD 24h after ICU discharge was 67%, 49% and 46%, respectively, and among patients re-evaluated 1 year after ICU discharge the prevalence was 38%, 50% and 31%, respectively. Factors associated with symptoms of PTSD in a multivariate model included serum S100B (OR 1.12, 95% CI 1.01 to 1.23), age (OR 0.56, 95% CI 0.33 to 0.96) and IQCODE (OR 0.22, 95% CI 0.08 to 0.63). Factors associated with depression symptoms included patient age (OR 0.44, 95% CI 0.24 to 0.79) and dobutamine accumulated dose during ICU stay (OR 2.48, 95% CI 1.08 to 5.68). The multivariate model also identified IQCODE score (OR 0.28, 95% CI 0.10 to 0.75) and accumulated dose of haloperidol in ICU (OR 0.12, 95% CI 0.03 to 0.50) associated with

symptoms of anxiety after discharge from ICU.
Conclusion: More than three quarters of the patients exhibited clinically meaningful psychiatric symptoms during the follow-up period. IQCODE score was strongly associated with post-traumatic stress and anxiety symptoms; while accumulated dose of dobutamine and haloperidol was also strongly associated with depression and anxiety, respectively.

Disclosures: **A.J. Calsavara:** None. **P.A. Costa:** None. **V. Nobre:** None. **A.L. Teixeira:** None.

Poster

779. Post-Traumatic Stress Disorder

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Topic: G.06. Post-traumatic Stress Disorder

Support: NIH Grant K00 MH119603
NIH Grant R01 MH094757
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NIH Grant F32 MH101976
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NIH Grant U01 MH110925

Title: Multimodal structural brain imaging of recently traumatized individuals

Authors: *N. G. HARNETT[1,2], J. S. STEVENS[3], N. FANI[3], T. JOVANOVIC[3,4], S. J. H. VAN ROOIJ[3], T. D. ELY[3], L. D. NICKERSON[5], K. J. RESSLER[1,2];
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Abstract: Exposure to traumatic events can have adverse effects on cognitive and affective functions. However, traumatized individuals vary in their individual susceptibility to posttraumatic stress disorder (PTSD) development. Although prior research has suggested the structural morphology of the brain may partially underlie this susceptibility, minimal research to date has sought to combine different measures of brain structure to elucidate multivariate structural profiles in recently (~1-2 months) traumatized individuals. Multimodal brain structure profiles acquired acutely following trauma may better help characterize the neurobiology that underlies future development of PTSD. In the present study, we utilized multimodal magnetic resonance imaging (MRI) to investigate brain structure in recently traumatized (~1-2 month) individuals (n = 78). Participants were recruited in a Level-I trauma center within 24 hours of trauma exposure and completed a series of questionnaires on demographics and past-trauma

history. Participants returned to the lab to report on their PTSD symptom severity over the next year, completing the PTSD Symptom Scale (PSS) 1, 3, 6, and 12 months post-trauma. MRI scans were completed to assess brain grey matter characteristics (T1-weighted anatomical scans) and white matter integrity (via diffusion tensor imaging). Linked independent component analysis (LICA) was completed to perform multimodal data fusion on structural brain features derived from the MRI data and correlated with participant questionnaires. The LICA features included grey matter density, cortical surface area and thickness , and fractional anisotropy/mean diffusivity/diffusion tensor mode of the white matter skeleton. We identified several multimodal components that were stable across different LICA dimensionalities, including components reported previously to be associated with aging ($r = 0.55$, $p < 0.001$). Further, we also identified a multimodal structural profile that was associated with variation in PSS scores, assessed 1-month post-trauma ($r = -0.27$, $p = 0.016$). The structural profile reflected lower grey matter density within a structural covariance network comprised of prefrontal cortex, insula, and hippocampus, lower cortical thickness within the cingulate gyrus, and greater FA within the cingulum. These findings suggest that variability in brain structure is associated with acute expression of PTSD symptoms. Further, these data provide an initial, data-driven characterization of multimodal structural profiles in recently traumatized individuals.

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Poster

779. Post-Traumatic Stress Disorder

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Topic: G.06. Post-traumatic Stress Disorder

Support: NIH Grant K23 MH090366-01
NIH Grant RC1 MH089704-01

Title: Influence of anhedonic symptom severity on reward circuit connectivity in PTSD

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Abstract: Anhedonia, marked by deficits in the consummatory and motivational reward processing phases, is a prominent symptom of several psychiatric conditions and has been shown to influence functional connectivity between reward-relation regions. However, the unique neural mechanisms of the reward circuit in posttraumatic stress disorder (PTSD) as influenced by anhedonia severity remain unclear. To address this, we examined resting-state functional connectivity (rsFC) of the ventral striatum as a function of anhedonia for individuals with PTSD.

Resting-state functional MRI scans and behavioral assessments were collected for 71 women diagnosed with PTSD (M_{age} = 31.93, SD_{age} = 9.39) as part of a larger R01 funded study. Standard seed-based rsFC analyses for left and right nucleus accumbens seed regions of interest were performed. Regression analyses were conducted to examine the relationship between anhedonia severity and the standardized rsFC correlations. All rsFC analyses were family-wise error (FWE) cluster-corrected at the whole brain level ($p_{FWE} < .05$). Results indicated that anhedonia severity correlated with reduced rsFC between the left nucleus accumbens and left caudate extending to the thalamus. These findings support reward circuit dysfunction at rest associated with anhedonia in PTSD. This association furthermore contributes to a better understanding of the neural correlates of consummatory anhedonia.

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Poster

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Title: NTRK2 methylation is negatively related to traumatic memories and PTSD risk in two independent African cohorts of trauma survivors

Authors: *N. R. GHAFFARI[1], **D. COYNEL**[1], V. VUKOJEVIC[2], T. ELBERT[3], I. T. KOLASSA[4], S. WILKER[4], J. L. MCGAUGH[5], A. PAPASSOTIROPOULOS[2], D. J. DE QUERVAIN[1];
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Abstract: We have recently shown that an epigenetic modification of the glucocorticoid receptor (GR) gene is linked to traumatic memories and PTSD risk in genocide survivors as well as recognition memory in healthy individuals. In the current study, we aimed to uncover further GR-related epigenetic markers of memory and PTSD by focusing on the GR signaling pathway in two independent African cohorts of heavily traumatized individuals: Survivors of the rebel war in Northern Uganda (N=473) and Survivors of the 1994 Rwandan civil war (N=380). Additionally, we assessed recognition memory and functional brain activity using fMRI in a

sample of healthy Swiss individuals (N=568). DNA was isolated from saliva or blood in African and European cohorts, respectively. Gene pathway analysis revealed that DNA methylation of the glucocorticoid receptor signaling pathway was significantly associated with lifetime post-traumatic diagnostic scale sum scores, with 4 nominally associated pathway members (*NR3C1, KCNH3, PER1*, and *NTRK2*). After applying Bonferroni correction, one gene (*NTRK2*) remained significant. NTRK2 encodes the transmembrane receptor tropomyosin-related kinase B, which binds brain-derived neurotrophic factor (BDNF), and has been shown to play an important role in memory formation. *NTRK2* methylation was negatively associated with intrusion and avoidance symptoms in both Rwandan and Ugandan samples, independent of trauma load. Furthermore, methylation of *NTKR2* was also negatively associated with PTSD risk in both samples. Analysis of *NTRK2* methylation in the healthy sample revealed a significant negative association with recognition memory performance, independent of valence. Furthermore, independent component analysis (ICA) revealed NTRK2 methylation-dependent differences in brain activity in various networks relevant for correct recognition of previously seen pictures. Differential methylation was specific to the enhancer region of *NTRK2*, which has been previously shown as relevant for functional control of *NTRK2* expression. NTRK2 DNA methylation in the two traumatized cohorts was not associated with trauma load and had independent effects on PTSD symptoms, suggesting that methylation differences pre-existed the trauma. The current study replicates our previous GR findings and demonstrates that epigenetic differences in *NTRK2* are also related to traumatic memories and PTSD risk in genocide survivors and memory functions in healthy subjects. Thus, epigenetic modifications of the GR signaling pathway contribute to PTSD symptomatology and might provide novel biomarkers or drug targets.

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Poster

779. Post-Traumatic Stress Disorder

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ControlExtraData.DynamicPosterDisplay:
Dynamic Poster
Topic: G.06. Post-traumatic Stress Disorder

Support: NIMH Grant R01-MH-103287

Title: A multi-domain objective classification of recent post-traumatic stress disorder

Authors: Z. BEN-ZION[1], Y. ZEEVI[1], J. N. KEYNAN[1], R. ADMON[2], H. SHARON[1], P. HALPERIN[1], I. LIBERZON[3], A. Y. SHALEV[4], Y. BENJAMINI[1], *T. HENDLER[1]; [1]Tel-Aviv Univ., Tel-Aviv, Israel; [2]Haifa Univ., Haifa, Israel; [3]Psychiatry, Texas A&M Hlth. Sci. Ctr., Bryan, TX; [4]NYU Langone Med. Ctr., New-York, Israel

Abstract: Introduction: Contemporary symptom-based diagnosis of Post Traumatic Stress Disorder (PTSD) largely overlooks related neurobehavioral findings, possibly explaining the limited efficacy of treatments. Extant neurobehavioral measurements, however, may objectively depict the neurobiology and neuropsychology underlying PTSD phenotype. Here, we evaluated the feasibility and accuracy of a multi-domain objective classification of PTSD in a cohort of recent trauma survivors, using a newly developed semi-unsupervised bioinformatics approach.
Methods: Our 3-staged methodology combines a ***c****ategorization* using the Diagnostic and Statistical Manual of Mental Disorders (DSM) diagnostic criteria with ***c****lustering* and ***c****lassification* using psychometric tools and neurobehavioral measurements (alias a "3C" method). We used this approach to classify 101 adult civilian trauma survivors (age=34.80±11.95, 51 females), evaluated one month after their traumatic experiences. Measurements obtained simultaneously at one month included: total scores of a PTSD diagnostic instrument (the Clinician-Administered PTSD Scale), self-reported rating scales measuring depression and anxiety, participants' performance in eleven neurogognitive domains (a WebNeuro battery), structural MRI indices (volumes and thickness of cortical and subcortical areas); and functional MRI indices of activity and connectivity during emotional face matching task.
Results: Measurements of traumatic stress symptoms, depression, anxiety and general clinical status best explained PTSD severity according to total CAPS scores *(FDR-adjusted p<0.2).* Unsupervised clustering performed based on these four clinical variables, divided the group into two clusters of high and low "disease load". The objecive variables that best differentiated between the clusters were entorhinal and rostral
anterior cingulate cortices volumes (brain structure domain); amygdala functional connectivity with the caudate/thalamus during emotional face matching task (brain function domain); and cognitive flexibility (neurocognitive domain) *(Importance=0.88, 0.43, 0.42, 0.49, respectively).*
Discussion: The 3C classification yielded an objective categorization of PTSD in recent trauma survivors. As such it provides an alternative case-identification model based on objective indicators from neural and neurocognitive domains, all theoretically related to PTSD pathogenic (pathophysiological) mechanism. Biomarkers identified by our classification may generate novel hypotheses and new targets for neurobehavioral, mechanism-driven interventions for PTSD.

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Poster

779. Post-Traumatic Stress Disorder

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Topic: G.06. Post-traumatic Stress Disorder

Support: NIH Grant K23 MH090366
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Title: Neural substrates of rumination in women with PTSD

Authors: *C. L. PHILIPPI, S. E. BRUCE;
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Abstract: Elevated rumination, characterized by repetitive negative thoughts about oneself, is common in posttraumatic stress disorder (PTSD) and has been shown to predict the onset of the disorder. In healthy and depressed participants, cortical midline brain structures, including the rostral anterior cingulate cortex (rACC), posterior cingulate cortex (PCC), and isthmus cingulate (IsthC), have been frequently implicated in self-focused thought, including rumination. Past research has revealed dysfunction in cortical midline regions in PTSD. However, no studies have investigated the neural substrates of rumination in women with PTSD using both structural and functional MRI. In the current study, we used structural MRI and resting-state functional MRI to examine relationships between rumination and brain volume as well as resting-state functional connectivity (rsFC) of cortical midline structures in women with PTSD due to interpersonal trauma (n = 71; mean age = 31.9, s.d. = 9.4). We performed multiple linear regression analyses to relate brain volume in rACC, PCC, and IsthC regions to self-reported rumination, after controlling for age and intracranial volume. We also conducted standard seed-based voxelwise rsFC analyses for significant regions identified in the structural analysis. All rsFC results were family-wise error (FWE) cluster-corrected for multiple comparisons at the whole brain level ($p_{FWE} < .01$). We found a significant relationship between greater rumination and volume in the left IsthC (p = .025) and trend-level relationships between rumination and volume in the right rACC (p = .087) and right PCC (p = .061). Results from the rsFC analyses revealed a significant relationship between greater rumination and diminished rsFC between the left IsthC and left precuneus ($p_{FWE} < .01$). Together, these findings provide support for alterations in structural and functional neural substrates of rumination in women with PTSD. More broadly, our results extend previous research on aberrant cortical midline structures in PTSD.

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Poster

779. Post-Traumatic Stress Disorder

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Topic: G.06. Post-traumatic Stress Disorder

Support: Herman Dana Foundation
NATO SPS Programme
Milgrome Family Foundation

Title: Early childhood adversity associated epigenetic alterations and neuroendocrine stress reactivity at adolescence

Authors: *R. SEGMAN[1,2], D. PEVZNER[1,2], T. GOLTSER DUBNER[3,2], C. KALLA[3,4], A. SHALEV[2], F. BENARROCH[2], R. GIESSER[2], A. BEN YEHUDA[4], R. HABER[3,2], C. SALONER[3,2], L. CANNETI[3], E. GALILI-WEISSTUB[2], O. OZ[3,2], I. VASHDI[3,2], A. MIRMAN[3], O. BONNE[3];
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Abstract: Background: Early adversity (EA) has been previously implicated with lifelong altered stress reactivity. Maladaptive stress reactivity may result in compromised neurocognitive and emotional regulation aptitudes and may lead to acute and chronic post traumatic stress disorder and depression. The current study explores the predictive value of EA associated DNA methylation patterns in genes coding key neuroendocrine regulators and their correlation with neuroendocrine stress reactivity for identifying individual stress related vulnerability.
Methods: Several hundred adolescent trainees undergoing combat military training were screened for exposure to early childhood trauma. An extremes case control sample compared those with high and low childhood trauma for prospective anxiety depressive and post traumatic symptoms, neuropsychological measures, and saliva and blood sampling, at rest and during exposure to extreme stress under simulated combat training conditions. Premorbid characteristics and neuropsychological and biological measures were employed to predict mal/adaptive outcomes following simulated combat.
Results: The correlations of EA associated patterns DNA methylation patterns in the glucocorticoid receptor gene and additional neuroendocrine regulators with baseline and reactive hormonal profiles will be described. Methylation related differential reactivity to acute stress exposure among adolescents reporting EA, and psychological measures mark stress vulnerability and may help predict longer term outcomes before and immediately following exposure to

trauma.
Conclusion: Distinct neuroendocrine signatures may help focus preventive and interceptive efforts on vulnerable subjects during stress exposure and at its immediate aftermath, before chronic Posttraumatic Stress Disorder (PTSD) or depression develop. Results may further shed light on the role of neuro endocrine reactivity in mediating the transduction of stress into long term maladaptive neuropsychiatric outcomes.
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Disclosures: **R. Segman:** A. Employment/Salary (full or part-time):; Molecular Psychiatry Laboratory - Department of Psychiatry, Hadassah - Hebrew University Medical center, Jerusalem, Israel,, The Herman-Danna Division of Pediatric Psychiatry, Department of Psychiatry, Hadassah - Hebrew University Medical Center; Jerusalem Israel, [3]Dept. of Mental Healthy. Israel Def. Forces., Jerusalem, I. **D. Pevzner:** None. **T. Goltser Dubner:** None. **C. Kalla:** None. **A. Shalev:** None. **F. Benarroch:** None. **R. Giesser:** None. **A. Ben Yehuda:** None. **R. Haber:** None. **C. Saloner:** None. **L. Canneti:** None. **E. Galili-Weisstub:** None. **O. Oz:** None. **I. Vashdi:** None. **A. Mirman:** None. **O. Bonne:** None.

Poster

779. Post-Traumatic Stress Disorder

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Program #/Poster #: 779.08/X30

Topic: G.06. Post-traumatic Stress Disorder

Support: NIH

Title: Emotion dysregulation mediates the association between acute sleep disturbance and PTSD symptoms in trauma exposed patients

Authors: *M. MCDANIEL[1], N. CHRIST[1], H. XIE[1], M. T. TULL[1], J. ELHAI[1], J. J. MATHEWS[1], R. V. N. BODDAPATI[1], I. LIBERZON[2], X. WANG[1];
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Abstract: Sleep disturbances are common within days after experiencing a traumatic event, and may exacerbate the development of posttraumatic stress disorder (PTSD) symptoms. However, the mechanisms between acute sleep disturbances and PTSD symptom development remain unclear. Sleep disturbances have been associated with emotion dysregulation, and emotion dysregulation has been identified as a factor that underlies the development and maintenance of PTSD. Therefore, it is plausible that acute sleep disturbances following a traumatic event interfere with emotion regulation abilities which contributes to the development of PTSD symptoms.

To test this hypothesis, the current study examined relations between acute sleep disturbance [Pittsburg Sleep Quality Index PTSD Addendum (PSQI-A)] and emotion dysregulation [Difficulty in Emotion Regulation Scale (DERS)] within 2 weeks after trauma, and the severity of PTSD symptoms [PTSD Checklist Stressor Specific (PCL)] 3 months later.
Preliminary analyses revealed that trauma survivors with acute sleep disturbances (PSQI-A $\geq$ 4) reported worse PCL, DERS scores at 2 weeks and PCL scores at 3 months after trauma (all p's < 0.01). Multiple regression analyses demonstrates overall model fit (X^2=2.51, p=0.29; RMSEA=0.04; CFI=0.99; TLI=0.96; SRMR=0.03). There was a significant mediating effect of DERS total scores (β=0.13, p<0.01) on the relationship between sleep disturbance and PTSD symptoms after adjusting for age and gender. When individually modeled as mediators, DERS subscales of non-acceptance (β=0.13, p<0.05), inability to engage in goal-directed behavior (β=0.14, p<0.05), and lack of strategies (β=0.19, p<0.01) explained significant amounts of variance in the relationship. However, in a full model adjusting for multivariate effects of other DERS subscales, only the strategies scale (β=0.19, p<0.01) remained significant.
Our findings suggest that while acute sleep disturbances are associated with the development and severity of PTSD symptoms over weeks to months, acute emotion dysregulation explains part of this association. Those with limited emotion regulation strategies, non-acceptance of emotions and inability to engage in goal-directed behavior are at particular risk for developing elevated PTSD symptoms.MM and NC contributed equally

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Poster

779. Post-Traumatic Stress Disorder

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Topic: G.06. Post-traumatic Stress Disorder

Support: Department of Physical Medicine and Rehabilitation's Functional Neurorecovery Pilot Grants Initiative

Title: Cortical and subcortical brain volume vary with acute posttraumatic stress symptoms after a medical trauma

Authors: *H. E. DARK[1], N. G. HARNETT[2], A. J. KNIGHT[3], D. C. KNIGHT[4];
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Abstract: Posttraumatic stress disorder (PTSD) is characterized by a combination of re-experiencing, avoidance, and hyperarousal symptoms that are associated with stimuli linked to a traumatic event. The amygdala, hippocampus, and anterior cingulate cortex (ACC) play an important role in the pathophysiology of PTSD. Smaller amygdala, hippocampal, and ACC volumes have been linked to greater PTSD symptom severity. However, few studies have assessed the brain volume of patients recently exposed to a traumatic event to determine the relationship with symptom expression over time. The present study examined the relationship between brain volume and posttraumatic stress symptoms at ≤1 and 3 months post-trauma to determine whether brain volume was associated with PTSD symptom expression. Thirty-seven participants (Age: M=27.0; SD=7.4) were recruited for the present study; 19 trauma exposed (TE) participants and 18 non-trauma exposed (NTE) controls. TE participants were recruited from University of Alabama at Birmingham Hospital within 30 days of trauma exposure. There were no differences in race, sex, or estimated IQ between groups. TE participants were slightly older (~5 years) than NTE participants. All participants completed a T1 weighted magnetic resonance imaging (MRI) scan on a 3T Siemens Allegra scanner. A volumetric analysis was performed to determine bilateral amygdala, hippocampal, and rostral ACC (rACC) volumes, as well as the total intracranial volume for each participant. The Posttraumatic Diagnostic Scale (PDS) was used to assess PTSD symptoms at ≤1 and 3 months after the event. Pearson correlations and linear mixed effects models were used to examine the relationship between posttraumatic stress symptoms and brain volume (assessed <1 month post-trauma). Within the TE group, hippocampal volume varied negatively, while rACC volume varied positively with PDS scores at <1 month ($p<.05$). Hippocampal and amygdala volume (assessed <1 month post-trauma) varied negatively with PDS scores at the 3 month follow-up assessment ($p<.05$). Changes in PTSD symptoms from <1 to 3 months did not vary with brain volume. Findings from the present study suggest brain volume may be an important correlate of acute PTSD symptom severity in adults exposed to a traumatic event.

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Poster

779. Post-Traumatic Stress Disorder

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Topic: G.06. Post-traumatic Stress Disorder

Support: R01MH103287-01

Title: Resting-state functional connectivity predicts change in PTSD symptoms

Authors: *Y. LOKSHINA[1,2], J. SHEYNIN[2,3,4], T. NICKELSEN[2], E. R. DUVAL[3], M. ANGSTADT[3], J. N. KEYNAN[5,6], Z. BEN-ZION[5,6], R. ADMON[9], M. HALEVI[5,7], N. GREEN[5,7],

T. HENDLER[7,8,5,6], A. Y. SHALEV[10], I. LIBERZON[2,3,4];
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Abstract: Neurobiological processes that take place following a traumatic event may determine who will develop posttraumatic stress disorder (PTSD) and who will not. Such processes might be reflected in resting-state functional connectivity (rsFC), which was found to be altered in PTSD. In this project, we study the progression of these alterations as trauma survivors either recover from early PTSD symptoms, or develop sustained PTSD symptomology. This report focuses on the association between these alterations and early PTSD symptoms severity, as well as with change in symptom severity over time. Data were collected from adult civilians within 30 days (T1; *n*=151; 47.6% male; mean age = 33.7 years), 6 months (T2; *n*=107; 46.7% male; mean age = 35.3 years) and 14 months (*n*=91; 46.1% male; mean age = 34.1 years) of admission to an emergency department following a traumatic event. Functional magnetic resonance imaging was used to assess intrinsic connectivity during a resting-state scan and CAPS-5 was used to assess symptom severity. We followed a seed-based approach, using seeds from salience network (SN) and default-mode network (DMN), where alterations have been previously reported in PTSD. All analyses controlled for sex, age and motion. Results show that connectivity between insula and precuneus correlated with PTSD symptoms at T1 and T2, and connectivity between vmPFC, insula and regions within the dorsal attention network (DAN) correlated with symptoms at T2. Additionally, we found that connectivity between PCC, insula and DAN correlated with change in symptoms over time. Connectivity between vmPFC and parahippocampus also predicted greater improvement in symptoms (all $p < .050$, FWE corrected). In sum, this study demonstrates greater functional connectivity between DMN, SN and DAN (i.e., greater desegregation) in individuals with early PTSD symptoms, and suggests that specific connectivity patterns between and within these three networks can be used as potential biomarkers to predict change in PTSD symptoms after a traumatic event.
YL and JS contributed equally to this work.

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Poster

779. Post-Traumatic Stress Disorder

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Title: The effects of psilocybin assisted group therapy on demoralization, depression, and PTSD symptoms in older long-term AIDS survivors

Authors: B. T. ANDERSON[1], A. L. DANFORTH[1], R. B. DAROFF[1], C. S. STAUFFER[1], J. W. DILLEY[1], ***J. M. MITCHELL**[2], J. D. WOOLLEY[1];
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Abstract: Demoralization is a syndrome characterized by a sense of hopelessness, helplessness, and a loss of meaning in life, and it is highly prevalent among patients with serious medical illness.[1] Older Long-term AIDS Survivors (OLTAS) are a subset of older people living with the human immunodeficiency virus (OPLWH) who were diagnosed prior to the advent of combined antiretroviral therapy and have lived to be >50 years of age. OPLWH suffer high rates of depression, anxiety, PTSD, social isolation and loneliness.[2,3] OLTAS suffered high rates of traumatic loss during the AIDS epidemic, and many now endorse symptoms of significant demoralization. Psilocybin is a tryptamine psychedelic[4] that acts primarily as a 5HT2A/1A receptor agonist and can diminish the subjective pain of interpersonal loss.[5] Previous clinical data suggest that psilocybin might be effective at improving treatment-resistant depression and that the extent of this improvement correlates with decreased cortical blood flow in the amygdala.[6] **Methods:** Here we conducted an open-label pilot study to assess the safety and efficacy of single dose psilocybin in conjunction with group psychotherapy on demoralization, depression, and PTSD symptoms in a group of 18 male OLTAS. Single dose psilocybin (4-phosphoryloxy-N,N-dimethyltryptamine) was administered once (0.3mg/kg or 0.36mg/kg po) during an individual medication visit. Patients additionally underwent 10 group psychotherapy sessions (4 prior to the medication visit; 6 subjects per group). **Results:** There was a significant attenuation in demoralization (DS-II; n = 18; Hedge's g = 0.99; p = .0004), depression (CESD; n = 18; Hedge's g = 0.76; p = .02), and PTSD (PCL-5; n = 18; Hedge's g = 0.74; p = .004) related symptoms at baseline versus endpoint (1-month post drug). There were no treatment-emergent serious adverse events. **Conclusions:** These data provide preliminary evidence to suggest that psilocybin is a safe and potentially advantageous therapeutic to treat demoralization, depression, and PTSD in certain subject populations. Further studies are needed to determine the durability of these effects and CNS mechanisms by which they are exerted.

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Poster

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Program #/Poster #: 779.12/X34

Topic: G.06. Post-traumatic Stress Disorder

Title: Intracranial neurophysiology of hypervigilance in posttraumatic stress disorder

Authors: *Z. M. AGHAJAN[1], J.-P. LANGEVIN[1,2], D. VILLAROMAN[1], A. BARI[1], S. HILLER[1], U. TOPALOVIC[1], R. KOEK[1,2], S. KRAHL[1], J. W. Y. CHEN[1], N. R. HASULAK[3], M. FANSELOW[1], N. SUTHANA[1];
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Abstract: Neural mechanisms underlying hypervigilance and an enhanced fear state in posttraumatic stress disorder (PTSD) patients remain largely unknown. There is mounting evidence that the circuitry implicated in fear conditioning involves the basolateral amygdala (BLA), medial prefrontal cortex (mPFC), and hippocampus (HPC). Namely, that theta synchrony has been suggested as a mechanism that coordinates activity in these regions leading to the expression or suppression of fear.
In a rare opportunity, we recorded the activity of these regions in a PTSD patient implanted with depth electrodes, while performing an International Affective Picture System (IAPS) task. We found a significant—sustained—increase in right BLA theta and, in contrast, a decrease in mPFC theta after presentation of aversive stimuli (but not neutral or positive stimuli). BLA theta also significantly interacted with BLA and HPC gamma oscillations further corroborating the framework that the regulation of emotional states is mediated by specific oscillatory patterns within the BLA, mPFC and HPC. We were able to replicate the results in another patient who completed the IAPS task while implanted with foramen ovale electrodes for the work-up of possible seizures. This second patient had also been diagnosed with severe generalized anxiety disorder (GAD) and panic disorder. Here, too, the right BLA exhibited significantly higher theta power after negative stimuli. As a control, we recorded the activity of right BLA and HPC in an epilepsy patient implanted with the NeuroPace RNS® System (for epilepsy treatment) who performed the IAPS task. This patient was not suffering from an anxiety disorder, and we did not find any significant differences in either the BLA or HPC theta power after the negative versus positive/neutral stimuli.
Taken together, our results suggest that the activity of the right BLA—in particular the pattern of theta oscillations—after aversive stimuli may be unique or perhaps triggered at a lower threshold in anxiety disorders such as PTSD or GAD such that it is conducive to the coordination of an enhanced fear and a hypervigilance state.

Disclosures: **Z. M. Aghajan:** None. **J. Langevin:** None. **D. Villaroman:** None. **A. Bari:** None. **S. Hiller:** None. **U. Topalovic:** None. **R. Koek:** None. **S. Krahl:** None. **J.W.Y. Chen:** None. **N.R. Hasulak:** A. Employment/Salary (full or part-time):; Employee of NeuroPace. **M. Fanselow:** None. **N. Suthana:** None.

Poster

779. Post-Traumatic Stress Disorder

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 779.13/X35

Topic: G.06. Post-traumatic Stress Disorder

Support: 1I21RX002588

Title: Decoding stress levels from fMRI data obtained in a virtual reality environment

Authors: ***T. TSE**[1], R. GOEL[1], A. FLOREN[3], B. NAYLOR[1], C. PAO[4,5], D. RESS[1], W. WILLIAMS[5], R. SALAS[2,5,1];
[1]Neurosci., [2]Psychiatry, Baylor Col. of Med., Houston, TX; [3]Univ. of Texas at Austin, Austin, TX; [4]Psychological, Health, and Learning Sci., Univ. of Houston, Houston, TX; [5]Michael E. DeBakey VA Med. Ctr., Houston, TX

Abstract: Introduction:
The ability to decode stress levels from functional magnetic resonance imaging (fMRI) would open up exciting avenues for the treatment of post-traumatic stress disorder (PTSD). Virtual reality (VR) exposure therapy has been used to treat PTSD in veterans. VR settings are ideal as they can be presented in the scanner. We are combining VR, fMRI, and machine-learning to investigate new treatment options for PTSD.
Methods:
A therapist first worked with two participants (a veteran with PTSD and a healthy participant) to create an in-vivo hierarchy, a ranked list of stimuli that evoke fear or anxiety in the participant. For the veteran with PTSD, we used a VR environment called Bravemind (developed by Albert Rizzo and his team) as a realistic stimulus to elicit stress responses. For the healthy subject, we used a variety of video clips to evoke stress. Using each participant's in-vivo hierarchy, individualized videos were created to evoke varying levels of stress. The two participants were asked to lie in an MRI scanner while viewing the videos and rate their subjective stress levels every 15 seconds on a scale of 1-8 via a button box. Participants underwent five 8-min runs each of these experiments. The data were collected using SMS EPI (1.5-s TR, 2-mm voxels, 60 slices) on a 3T scanner. Standard motion compensation and slice timing correction were applied to the fMRI data along with a Wiener filter to mitigate hemodynamic delay. Support vector regression (SVR) and support vector classification (SVC) were used to predict the stress levels of the participants from their cortical fMRI data.

Results:
The veteran participant reported stress levels ranging from 1-7, whereas the healthy participant reported levels ranging from 1-8. For the veteran participant, we were able to achieve a classification accuracy of 40% (well above a chance level of 14.3%) using SVC, and a root-mean-squared error (RMSE) of 1.47 using SVR. For the healthy participant, we achieved a classification accuracy of 36% (chance is 12.5%) using SVC and a RMSE of 1.05 using SVR.
Discussion:
Using machine learning techniques, we were able to decode the subjective stress levels of the two participants at well above chance levels. The low RMSE for SVR is very promising for applying our methods to both extinction and biofeedback therapy. Future work will add pulse, respiration rate, and sub-cortical fMRI inputs to the machine-learning computations to further improve performance. We also plan to apply the machine learning to see if the performance holds across sessions and in real time.

Disclosures: T. Tse: None. **R. Goel:** None. **A. Floren:** None. **B. Naylor:** None. **C. Pao:** None. **D. Ress:** None. **R. Salas:** None.

Poster

779. Post-Traumatic Stress Disorder

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 779.14/X36

Topic: G.06. Post-traumatic Stress Disorder

Support: NIMH K01 MH086809
R49/CE001175

Title: Periaqueductal gray resting state functional connectivity prospectively predicts post traumatic stress symptom severity

Authors: *E. WEBB[1], A. HUGGINS[1], E. BELLEAU[2], L. TAUBITZ[3], J. HANSON[1], T. DEROON-CASSINI[4], C. L. LARSON[1];
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Abstract: Introduction: The periaqueductal gray (PAG) plays a central role in generating behavioral responses to physical and psychological stressors. Posttraumatic stress disorder (PTSD) is characterized by avoidance, hyperarousal, and intrusive/re-experiencing symptoms. Distinct columns of the PAG elicit opposing reactions to threatening or stressful stimuli; the ventrolateral PAG evokes passive coping strategies (e.g. analgesia) and the dorsolateral PAG promotes active responses (e.g. fight or flight). We investigated whether altered resting state

functional connectivity of PAG sub-regions prospectively predicted PTSD symptom severity. **Methods:** Trauma exposed participants (*n* = 46; 70% female; age 33 ± 12.2 years) were recruited from the emergency department. Participants underwent a resting state fMRI scan two-weeks post-trauma. Self-report measures of PTSD (Impact of Event Scale; IES) and Pain (Visual Analogue Scale for Pain) were collected during the two-week visit and six-months post-trauma. The effect of six-month IES scores, adjusted for self-reported pain, on whole brain seed-to-voxel functional connectivity of the PAG was analyzed. **Results:** Greater PAG-frontal pole connectivity predicted an increase in total PTSD symptoms as well as hyperarousal and intrusion symptoms. Greater PAG-posterior cingulate connectivity predicted increased hyperarousal symptoms. PAG-inferior parietal lobule connectivity was negatively correlated with total PTSD symptoms, hyperarousal and intrusions symptoms. **Conclusions:** Altered PAG connectivity two-weeks post-trauma prospectively predicted total PTSD, hyperarousal, and intrusion, symptom severity. These findings suggest altered PAG function may serve as a marker of risk for chronic PTSD symptoms, possibly by driving hyperarousal and more broadly, that connectivity of specific brain regions may underlie specific symptom profiles.

Disclosures: E. Webb: None. **A. Huggins:** None. **E. Belleau:** None. **L. Taubitz:** None. **J. Hanson:** None. **T. deRoon-Cassini:** None. **C.L. Larson:** None.

Poster

779. Post-Traumatic Stress Disorder

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 779.15/X37

Topic: G.06. Post-traumatic Stress Disorder

Support: University of Northern Colorado
Stress and Motivated Behavior Institute

Title: Early findings of enhanced eyeblink conditioning in individuals with high levels of manifest anxiety support a learning diathesis model of PTSD

Authors: *T. ALLEN;
Univ. of Northern Colorado, Greeley, CO

Abstract: Classical eyeblink conditioning has a long history of study in humans and several mammalian species with application to the study of the neural and learning mechanisms underlying psychopathologies such as PTSD. While recent eyeblink conditioning studies have focused more so on rabbits, rats, and mice, human eyeblink conditioning preceded the development of the non-human animal paradigms in that human eyeblink conditioning was the dominant conditioning paradigm in the 1950s. Many studies in the 1950s and 1960s by Kenneth Spence and colleagues used the Manifest Anxiety Scale (MAS), developed by Janet Taylor

Spence, to group undergraduates as high or low manifest anxiety. These studies consistently revealed that individuals with high levels of manifest anxiety exhibited enhanced acquisition of conditioned eyeblinks. In addition, females had higher MAS scores and faster acquisition of conditioned eyeblinks than males. While Spence used MAS scores as a measure of drive based on Hull's theory of learning, Taylor hypothesized that MAS scores signified the presence or lack of various personality traits. More recently, the exploration of personality effects on eyeblink conditioning has continued in studies in humans and rats that investigated inhibited personality temperaments such as behavioral inhibition (BI) as risk factors for the development of PTSD. Much like the findings with MAS, individuals expressing BI exhibit enhanced acquisition of conditioned eyeblinks. In addition, current theories hypothesize that BI and female gender interact as vulnerability factors to increase the risk for anxiety disorders and PTSD. Overall, there is a high degree of consistency between findings of enhanced conditioning and gender effects from early human eyeblink studies and current work which support the theory that inhibited personality temperaments are associated with enhanced associative learning as a mechanism for the development of PTSD. This review indicates how early findings can serve as a foundation for the development of current theories and empirical studies.

Disclosures: T. Allen: None.

Poster

779. Post-Traumatic Stress Disorder

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 779.16/X38

Topic: G.06. Post-traumatic Stress Disorder

Title: Post-traumatic stress disorder: Quantitative EEG biomarkers and treatment via the reconsolidation of traumatic memories (RTM) protocol

Authors: *J. D. LEWINE[1], R. GRAY[2], D. BUDDEN-POTTS[2], N. GOODREAU[1], K. PAULSON[1], N. BANGERA[1], J. DAVIS[1], W. MURRAY[2], F. BOURKE[2];
[1]Mind Res. Network, Albuquerque, NM; [2]Res. and Recognition Project, Corning, NY

Abstract: Post-Traumatic Stress Disorder (PTSD) is a potentially debilitating disorder that is triggered by exposure to a significantly stressful traumatic event threatening death or physical injury to oneself or others. Core features of PTSD include intrusive re-experiencing (nightmares and flashbacks), avoidance, negative cognition and mood, and disturbances in arousal and reactivity. Multiple treatment approaches are used for PTSD, including pharmacotherapy and a range of cognitive and behavioral approaches including exposure therapy, cognitive processing therapy, mindfulness and EMDR therapy, but available data suggest that these various approaches generally provide significant relief of PTSD symptoms in only 25-50% of patients. Given the current situation, there is mounting hope that a better understanding of the

neurobiology of PTSD will lead to the development of better and more efficient therapies. This study evaluated how quantitative electroencephalography (qEEG) and clinical measures (PCL and PSSI) from subjects with PTSD were modulated by a novel treatment approach, the Reconsolidation of Traumatic Memories (RTM) protocol. RTM uses a dissociative reimaging procedure that renders reconsolidated memories of the trauma to be less emotionally impactful and intrusive. Twelve PTSD subjects underwent qEEG and clinical assessments at baseline and 1 month after three 90-minute RTM treatment sessions (administered over the course of 1 week). Ten additional PTSD subjects were evaluated at baseline and 1-month following a no-treatment waiting period. qEEG data were evaluated with respect to a normative database. Baseline EEG data were also evaluated from twenty-two age and sex matched neurotypical control subjects. At baseline, 3/22 control subjects, but 15/22 PTSD subjects, showed excessive power in the high-beta range (Chi-square = 13.6, $p<0.0005$). Waitlist PTSD subjects showed minimal clinical or EEG changes between baseline and follow-up evaluations, whereas RTM subjects showed highly significant ($p<0.001$) reductions in PCL and PSSI scores, along with normalization of excessive high-beta activity. Source modelling (LORETA) showed that the baseline abnormalities in high-beta were mostly generated in mesial temporal (hippocampus and amygdala), insular, frontal, and parietal regions. Post-treatment normalization mostly reflected changes in mesial temporal areas. High-beta activity may be a useful biomarker of PTSD that can be used to objectively track the neurobiological impact of behavioral therapies. The RTM protocol appears to be efficacious in reducing the clinical symptoms of PTSD and in normalizing brain activity.

Disclosures: **J.D. Lewine:** None. **R. Gray:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); research and recognition project. **D. Budden-Potts:** None. **N. Goodreau:** None. **K. Paulson:** None. **N. Bangera:** None. **J. Davis:** None. **W. Murray:** None. **F. Bourke:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Research and Recognition Project.

Poster

779. Post-Traumatic Stress Disorder

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 779.17/X39

Topic: G.06. Post-traumatic Stress Disorder

Support: NWO-453-12-0010
StG2012-313749

Title: Frontal emotion regulation capacity predicts acute cortisol-responses as well as long-term resilience to post-traumatic stress: Evidence from a prospective longitudinal study

Authors: *R. KALDEWAIJ[1,2], S. B. J. KOCH[1,2], W. ZHANG[1,2], M. M. HASHEMI[1,2], F. KLUMPERS[1,2], K. ROELOFS[1,2];
[1]Donders Ctr. For Cognitive Neuroimaging, [2]Behavioural Sci. Inst., Radboud Univ. Nijmegen, Nijmegen, Netherlands

Abstract: Regulating social emotional actions is essential for coping with daily life stressors and depends largely on the anterior prefrontal cortex (aPFC) and its connections to downstream regions including the amygdala. However, it remains unclear to what extent frontal emotion regulation capacities contribute to resilience for effects of long-term trauma exposure.
We addressed this question in a large longitudinal study among 226 police officers (176 males, age range 18-43), who were tested before and after trauma exposure as part of a 15-month lasting stressful period in their training. At baseline, they performed a well-established fMRI approach-avoidance task, mapping impulsive and controlled emotional actions. This was immediately followed by a formal stress-induction (social evaluative cold pressure task) and the measurement of cortisol, alpha-amylase and subjective stress-responses. Post-Traumatic Stress Disorder (PTSD) symptoms were assessed with the PTSD-checklist (PCL-5) at baseline and at 15-months follow-up.
For the approach-avoidance-task, the typical neural and behavioural emotion-control effects were replicated, including increased aPFC activation, longer reaction times and more errors during approach-avoidance trials that required control over emotional actions. At baseline, relatively high emotion control-related bilateral aPFC activity predicted relatively low reactivity on all stress-measures (all $p < .05$). For the long-term prediction analyses, 178 officers (136 males) who experienced their core traumatic event in the line of duty between the assessment waves were selected. PTSD symptoms increased after exposure to traumatic events. Critically, higher activation of the left aPFC during emotion regulation at baseline was associated with less increase in PTSD symptoms at 15 months follow-up ($T = 4.59$, p(FWE) < .002, small-volume corrected).
These findings implicate that neural emotion regulation capabilities are not only predictive of reduced acute stress-responses, but are also linked to increased resilience to developing post-traumatic stress symptoms. This adds to our understanding of neurobiological vulnerability factors for the development of stress- and trauma-related disorders, which may ultimately contribute to novel prevention and treatment strategies in high risk populations and professions.

Disclosures: R. Kaldewaij: None. **S.B.J. Koch:** None. **W. Zhang:** None. **M.M. Hashemi:** None. **F. Klumpers:** None. **K. Roelofs:** None.

Poster

779. Post-Traumatic Stress Disorder

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 779.18/X40

Topic: G.06. Post-traumatic Stress Disorder

Support: National Center for PTSD Brain Bank

Title: Sex-specific transcriptomic alterations in posttraumatic stress disorder across multiple regions of human frontal cortex

Authors: *M. J. GIRGENTI[1], J. WANG[2], D. JI[2], D. CRUZ[3], D. WILLIAMSON[4], M. FRIEDMAN[5], H. ZHAO[2], J. H. KRYSTAL[1], T. STUDY GROUP[6], R. S. DUMAN[7]; [1]Yale Univ. Sch. of Med., New Haven, CT; [2]Yale Sch. of Med., New Haven, CT; [3]Duke Univ. Sch. of Med., Durham, NC; [4]Dure Univ. Sch. of Med., Durham, NC; [5]Dartmouth Sch. of Med., Hanover, NH; [6]Veterans Admin. Natl. Ctr. for PTSD, West Haven, CT; [7]Dept. of Psychiatry, Yale Univ. Sch. Med., New Haven, CT

Abstract: Posttraumatic stress disorder (PTSD) is a maladaptive and debilitating psychiatric disorder characterized by an extreme sense of fear at the time of trauma occurrence, with characteristic reexperiencing, avoidance, and hyperarousal symptoms in the months and years following the trauma. PTSD has a prevalence of approximately 6%, but can occur in 25-35% of subjectrs who have experienced severe psychological trauma, such as combat veterans, refugees, and assault victims. The incidence and symptoms of PTSD all point toward major sex differences. However, the molecular mechanisms underlying the sexual dimorphism remain largely unknown. Here, combining differential expression and gene coexpression analysis, we provide comprehensive characterization of male and female transcriptional profiles associated with PTSD across 5 cortical brain regions: the subgenual prefrontal cortex (area 25), medial orbital frontal cortex (area 11), dorsal anterior cingulate (area 24), dorsolateral prefrontal cortex (area 9), and motor cortex (area 4). Our results show a major rearrangement of transcriptional patterns between healthy controls compared to PTSD subjects or MDD subjects (non-PTSD psychiatric controls). We identify key regulators of sex-specific gene networks and hub genes underlying PTSD in female SgPFC that differ from those in male subjects, which have their own unique networks and hub in the dACC. We also show differential contributions of cell types to gene expression patterns in males (neurons) and females (astrocytes and microglia). Together, our findings demonstrate PFC subregions as key sites of transcriptional regulation in PTSD brain and highlight sex-specific and cell-type specific gene expression across these cortical regions.

Disclosures: M.J. Girgenti: None. **J. Wang:** None. **D. Ji:** None. **D. Cruz:** None. **D. Williamson:** None. **M. Friedman:** None. **H. Zhao:** None. **J.H. Krystal:** None. **T. Study Group:** None. **R.S. Duman:** None.

Poster

779. Post-Traumatic Stress Disorder

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 779.19/X41

Topic: G.06. Post-traumatic Stress Disorder

Support: Faculty Research Grant (EWU FGRCW 2018-19)

Title: Intranasal oxytocin increases dopamine signaling in the dorsal striatum of anesthetized rats

Authors: *D. E. GINDER, C. RAMELOW, M. P. GAINER, D. P. DABERKOW;
Eastern Washington Univ., Cheney, WA

Abstract: BACKGROUND: The neuropeptide oxytocin (OXT), commonly considered the "love hormone", has been suggested to be involved in many aspects of brain function, such as learning and memory. Current research suggests that OXT treatment is therapeutic for individuals suffering from post-traumatic stress disorder (PTSD), possibly due to OXT's modulatory effects on the brain circuitry involved with learning and memory. Defining the neural mechanisms of OXT is important in order to understand how OXT could be beneficial for individuals with PTSD, and possibly other psychological disorders. The neurotransmitter dopamine (DA) is highly implicated in learning and memory. DA neurons express OXT receptors and therefore could be a site of OXT action. We hypothesize that OXT increases DA neurotransmission in the dorsal striatum, a brain region highly innervated by DA neurons. METHODS: Using fast-scan cyclic voltammetry (FSCV) we monitored electrically evoked DA signals before and after intranasal OXT administration. Male Sprague-Dawley rats (n = 6) were anesthetized and underwent DA electrode placement surgery. DA microelectrodes were placed in the dorsal striatum (coordinates AP= +1.0; ML= +2.0; DV= -4.5) and a bipolar stimulating electrode was incrementally lowered above the medial forebrain bundle (coordinates AP=-4.6; ML=+1.4; DV=-7.0), a brain region containing DA neurons that project to the dorsal striatum. Once stable DA signals were recorded, intranasal OXT at 0.5 µg/kg (or an equivalent volume of saline in controls) was administered. RESULTS: Intranasal OXT treatment increased electrically evoked DA signals (peak amplitude), compared to saline-treated controls. CONCLUSION: OXT increases DA neurotransmission and therefore could have a modulatory effect on learning and memory. FUNDING: Eastern Washington University Department of Biology and David Daberkow EWU Faculty Research Grant (EWU FGRCW 2018-19).

Disclosures: D.E. Ginder: None. **C. Ramelow:** None. **M.P. Gainer:** None. **D.P. Daberkow:** None.

Poster

779. Post-Traumatic Stress Disorder

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 779.20/X42

Topic: G.06. Post-traumatic Stress Disorder

Support: Eastern Washington University Department of Biology

Title: Effects of intranasal oxytocin pre- and post-treatment in a rat model of PTSD

Authors: *D. P. D. DABERKOW, S. M. HILFIKER, R. A. WESTERMAN, S. R. STORACI, D. H. OWNBEY, T. M. MOORHEAD, C. F. GUZMAN, R. BARIDO, C. W. JASPER; Eastern Washington Univ., Cheney, WA

Abstract: Oxytocin (OXT) treatment reduces signs of emotional stress after exposure to trauma. The objective of this study was to investigate the time dependent effects of intranasal oxytocin (i.e. before and after fear conditioning) on behavioral (i.e. freezing) and physiological (i.e. corticosterone levels) signs of fear. METHODS: Male Sprague-Dawley rats (8-10 weeks old) were separated into 4 groups (n = 6, per group): *Control* (no shock, no OXT), *Shock* (shocked, no OXT), *pre-OXT* (shocked, 1.0µg/kg intranasal OXT 1h before shock treatment), and *post-OXT* (shocked, 1.0µg/kg intranasal OXT 24h after shock treatment). Rats were handled for 2 weeks prior to fear conditioning. On the day of fear conditioning, rats were enclosed in a sound attenuating box with a shock grid floor (Coulbourn Instruments). After a 120s adaptation period, CS (tone) was presented for 20s, the US (shock) was presented in the last 2s of the CS. Rats were exposed to 5 presentations of the CS/US at 60s intervals. At both 24h and 7d after fear conditioning, rats were re-exposed to the fear conditioning box and CS. After a 30s adaptation period, the CS was presented for 20s (no US). During the re-exposure sessions, each rat had 5 presentations of the CS at 60s intervals. After each re-exposure session, feces were collected for analysis of corticosterone levels (ELISA kit, Cayman Chemical). Re-exposure sessions were video recorded and freezing behavior was analyzed (Actimetrics FreezeFrame). RESULTS: OXT-treated rats demonstrated less freezing behavior and had lower corticosterone levels than saline-treated controls. CONCLUSION: The results of this study suggest that intranasal OXT attenuates behavioral and physiological signs of fear.

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Poster

779. Post-Traumatic Stress Disorder

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 779.21/X43

Topic: G.06. Post-traumatic Stress Disorder

Support: EWU Department of Biology

Title: Impact of prophylactic intranasal oxytocin on signs of fear in a mouse model of PTSD

Authors: *C. W. JASPER, K. A. WHITWORTH, M. A. CHAMPION, C. A. ALVIS, E. M. KOEHLER, M. L. MCNEILL, R. L. BARIDO, D. P. DABERKOW;
Eastern Washington Univ., Cheney, WA

Abstract: Oxytocin (OXT) is a hormone that has a wide range of central and peripheral effects. OXT is involved in reproduction and has also been seen to attenuate the effects of stress and anxiety. The purpose of this study was to investigate the anxiolytic effects of intranasal OXT pretreatment on the behavioral and physiological signs of fear in mice. METHODS: Three groups (n=10, per group) of adult male mice (4-6 month old) were used. One hour before exposure, OXT was administered intranasally at a dosage of 1.0 µg/kg. OXT (VetOne®) was dissolved in saline (0.9% NaCl) and ~1.3 µl was gently injected, via micropipette, into each nostril of the Shock+OXT group. The Control group (no shock, no OXT) and Shock+saline group (shocked and no OXT) were given an equivalent administration volume of saline. The mice were then placed in a fear conditioning box (Coulbourn Instruments) and allotted a 120s acclimation period followed by 20s of the conditioned stimulus (CS), tone exposure at 2.8kHz delivered by external speaker. A 15s trace interval was used following the CS, followed by the unconditioned stimulus (US), a 0.7 mA scrambled current foot shock for 2s. The mice were exposed to 5 CS-US presentations with an interstimulus period of 10s. One week post fear conditioning, mice were re-exposed to the context and tone. Results: Intranasal OXT pretreatment decreased freezing behavior in mice when re-exposed to the context, relative to saline treated controls. Mice pretreated with intranasal OXT demonstrated slightly more activity in the open field, relative to saline-treated controls (although not significant). The results of this study suggest that intranasal OXT pretreatment ameliorates signs of fear in mice. FUNDING: Eastern Washington University Department of Biology.

Disclosures: C.W. Jasper: None. **K.A. Whitworth:** None. **M.A. Champion:** None. **C.A. Alvis:** None. **E.M. Koehler:** None. **M.L. McNeill:** None. **R.L. Barido:** None. **D.P. Daberkow:** None.

Poster

780. Post-Traumatic Stress Disorder: Preclinical Models

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 780.01/X44

Topic: G.06. Post-traumatic Stress Disorder

Support: National Plan on Drugs (reference 2015/16)
Spanish National Network on Addictive Disorders (RETICS) (Reference RD12/0028/0019 and RD16/0017/0014)
Ministry of Health, Carlos III Health Institute, Ministry of Economy, Industry and Competitivity and FEDER (Fondo Europeo de Desarrollo Regional)

Title: Cannabidiol and sertraline-mediated regulation of behavioral and neurochemical disturbances induced by a new long-lasting animal model of pot-traumatic stress disorder

Authors: *J. MANZANARES, F. NAVARRETE, A. GASPARYAN;
INSTITUTO DE NEUROCIENCIAS, UNIVERSIDAD MIGUEL HERNANDEZ-CSIC, SAN JUAN DE ALICANTE, Spain

Abstract: The main goals of this study were to validate and characterize a new chronic animal model of post-traumatic stress disorder (PTSD), and to evaluate the effects of cannabidiol (CBD) and/or sertraline (SERT) on PTSD-like behavioral and neurochemical alterations. To induce the animal model of PTSD, C57BL/6J mice were exposed to stressful stimuli for 5 weeks, alternating 3 weeks of exposure with 2 weeks of resting. PTSD-induced basal (weeks 6-7) and long-lasting (weeks 11-14) behavioral alterations were evaluated by fear conditioning (FC), novelty suppressed feeding test (NSFT), light-dark box (LDB) and elevated plus maze (EPM) paradigms. Effects of CBD (20 mg/kg, i.p.) and/or SERT (10 mg/kg, p.o.) administration on PTSD-induced disturbances were analyzed between weeks 11 to 14. In addition, relative gene expression analysis of corticotropin release factor (CRF) in the paraventricular nucleus, proopiomelanocortin (POMC) in the arcuate nucleus, glucocorticoid receptor (GCr) in the hippocampus, cannabinoid receptors 1 (CB1r) and 2 (CB2r) in the amygdala, and serotonin transporter (5HTT) in the dorsal raphe were carried out by real time PCR. C57BL/6J mice exposed to the PTSD animal model showed significantly increased fear-related memories (FC) and anxiety-like behavior (NSFT, LDB, EPM) under basal (weeks 6-7) and long-term (weeks 11-14) conditions (t-test, $p<0.001$). The pharmacological treatment with CBD or SERT significantly improved PTSD-related emotional alterations, achieving remarkable additive effects with the CBD plus SERT combination (Two-way ANOVA, $p<0.001$). Real time PCR experiments showed higher CRF (+138%) and POMC (+29%) but lower GCr (-16%) gene expression levels in mice exposed to the PTSD model at week 5 (t-test; $p<0.001$). Although increased CRF (+27%) gene expression was maintained until week 14, a significant reduction of POMC (-21%) and increase of GCr (+16%) were observed (t-test; $p<0.001$). Additionally, stressed animals had higher CB1r (+11%) and CB2r (+63%) while lower 5HTT (-42%) gene expression levels at week 14 (t-test; $p<0.05$). Interestingly, the pharmacological treatment with CBD and/or SERT significantly normalized all these neurochemical alterations (Two-way ANOVA, $p<0.05$). In summary, our results show that this new animal model of PTSD induces long-lasting behavioral and neurochemical alterations allowing us to investigate new pharmacological approaches for PTSD. Indeed, this study demonstrates for the first time that CBD actions are comparable to SERT and their combination produces an enhancing effect. Further studies are necessary to explore the therapeutic potential of CBD plus SERT in PTSD patients.

Disclosures: J. Manzanares: None. **F. Navarrete:** None. **A. Gasparyan:** None.

Poster

780. Post-Traumatic Stress Disorder: Preclinical Models

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 780.02/X45

Topic: G.06. Post-traumatic Stress Disorder

Support: NIH Grant R15HL132322

Title: A predator-based psychosocial stress model of post-traumatic stress disorder in females: Influence of estrous phase and ovarian hormones

Authors: *C. S. GOODMAN[1], P. A. D'ALESSIO[1], S. L. SEELEY[2], C. D. KASLER[1], K. E. MUCHER[1], A. S. ALLISON[1], I. F. SMITH[1], J. L. DODSON[1], T. S. STOOPS[2], K. M. ELMOUHAWESSE[1], B. R. RORABAUGH[2], P. R. ZOLADZ[1];
[1]Psychology, Sociology, & Criminal Justice, [2]Pharmaceut. & Biomed. Sci., Ohio Northern Univ., Ada, OH

Abstract: For reasons that are still not entirely clear, traumatized females are significantly more likely than traumatized males to develop post-traumatic stress disorder (PTSD). Still, the inclusion of females in animal models of PTSD has largely been avoided, likely due to the highly variable hormone profile of female rodents. Because a valid animal model of PTSD that incorporates females is still needed, we examined the influence of estrous stage and ovarian hormones on the female rat response to a predator-based psychosocial stress model of PTSD. Female Sprague-Dawley rats were exposed to psychosocial stress or control conditions for 31 days. Stressed rats were given two separate cat exposures and daily social instability; control rats were handled daily. Beginning on Day 32, rats underwent physiological or behavioral testing. In Experiment 1, vaginal smears were collected on days of the first and second cat exposures and each day of behavioral testing to determine estrous stage. In Experiments 2 and 3, ovariectomized or sham control rats were exposed to stress or control conditions. Then, they were given behavioral testing (Exp 2), or their hearts were isolated and subjected to 20-min ischemia / 2-hr reperfusion on a Langendorff isolated heart system (Exp 3). The results indicated that chronic stress increased anxiety-like behavior, irrespective of estrous stage or ovariectomy condition. Ovariectomized females displayed greater startle responses and anxiety-like behavior than sham controls. Stress had no impact on myocardial sensitivity to ischemic injury; however, ovariectomized females exhibited greater ischemia-induced infarction than sham controls. These findings suggest that ovarian hormones may prevent anxiety-like behavior and be cardioprotective in non-stressed controls, but they do not interact with chronic stress to influence the development of PTSD-like sequelae in female rats.

Disclosures: **C.S. Goodman:** None. **P.A. D'Alessio:** None. **S.L. Seeley:** None. **C.D. Kasler:** None. **K.E. Mucher:** None. **A.S. Allison:** None. **I.F. Smith:** None. **J.L. Dodson:** None. **T.S. Stoops:** None. **K.M. Elmouhawesse:** None. **B.R. Rorabaugh:** None. **P.R. Zoladz:** None.

Poster

780. Post-Traumatic Stress Disorder: Preclinical Models

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 780.03/X46

Topic: G.06. Post-traumatic Stress Disorder

Support: Acadia Pharmaceuticals

Title: A 5HT2A receptor inverse agonist reduces anxiety measures in a rodent model of PTSD

Authors: J. R. CAMPBELL[1], P. TSAI[2], H. L. CHAPMAN[2], V. E. BAILEY[2], L. D. BRATVEDT[2], ***C. P. WARD**[2], E. S. BURSTEIN[3], D. H. MALIN[1];
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Abstract: In post-traumatic stress disorder (PTSD), trauma causes long-lasting anxiety and hyper-reactivity. While PTSD often results from combat, it is widespread in the civilian population, with a majority of cases in females. This is a difficult subject to study, since, both in humans and animal models, only 30 - 50% might develop PTSD after extreme stress. We introduce a rat model resulting in relatively robust PTSD-like effects. The subjects were 37 female Lewis rats (an emotionally reactive strain). In the stressed group, the rats were conditioned on day 1 and throughout by single housing (particularly stressful to female rats). On days 21 and 31, the rats were exposed for 90 minutes to predator odor threat by reconstituted wildcat urine. For an hour of this, the rats were kept in a tubular restrainer (restraint stress). The rats were also exposed to an intermittent 70 decibel (dB) auditory stimulus (replayed during some later tests). A non-stressed control group was group-housed for 34 days. On days 21 and 31, they were exposed to water in place of predator urine and the same intermittent auditory stimulus. The restrainer was present, but the rats were not restrained in it.On days 41 and 42 all rats were tested under "blind" conditions for acoustic startle response at 100 and 110 dB, anxiety measurement in the elevated plus-maze and anxiety-related alterations of open field behavior. One hour before testing on each day, the non-stressed controls were injected s.c. with saline alone. The stressed rats were injected s.c. with either saline alone or 1.0 mg/kg of the 5HT2A serotonin receptor inverse agonist pimavanserin. Following one-way ANOVAs, post-hoc statistical tests revealed that, compared with the non-stressed/saline controls, the stressed/saline group had stronger startle responses, p=.013; spent less time in the open arm of the plus-maze, p=.011, had less distance traveled in the exposed inner zone of the open field, p=.059; less rearing, p=.002; more freezing, p=.001. Compared with the stressed/saline controls, the

stressed/pimavanserin group had significantly lower acoustic startle scores, p=.012; significantly more time in the open arms of the plus-maze, p=.002; significantly more distance traveled in the exposed inner zone of the open field, p=.022, significantly more rearing, p=.002 and significantly less freezing, p=.001. There were no significant differences between the stressed/pimavanserin, group and the non-stressed/saline group. The results indicate that pimavanserin reversed the long-lasting anxiogenic and hyper-reactive effects of the combined stressors, suggesting a major role for the 5HT2A serotonin receptor in PTSD-like behaviors.

Disclosures: J.R. Campbell: None. **P. Tsai:** None. **H.L. Chapman:** None. **V.E. Bailey:** None. **L.D. Bratvedt:** None. **C.P. Ward:** 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. **E.S. Burstein:** A. Employment/Salary (full or part-time):; Acadia Pharmaceuticals. **D.H. Malin:** 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.

Poster

780. Post-Traumatic Stress Disorder: Preclinical Models

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 780.04/Y1

Topic: G.06. Post-traumatic Stress Disorder

Support: JSPS KAKENHI Grant Number JP15k20867

Title: Anterior amygdalohippocampal area was reduced by severe stress event in adult male rats - Longitudinal structural MRI study

Authors: *R. RYOKE, M. HIROBE, H. NONAKA, R. KAWASHIMA;
Dept. Functional Brain Imaging, Tohoku Univ., Sendai, Japan

Abstract: Introduction: Posttraumatic Stress Disorder (PTSD) is an anxiety disorder that may develop following to an exposure to a highly traumatic event. It has been needed to study the neurobiological mechanisms underlying PTSD using animal models. Most of these models have been derived from Pavlovian fear conditioning, and it is known that prior exposure to traumatic stress enhances conditional fear responding to subsequent mild stress. We previously reported that the multiple stress consisted of foot shocks and forced swimming had long-lasting effects on subsequent fear conditioning, even the multiple stress was administrated a day. In this study, we examined the longitudinal study that combined the multiple stress and in vivo magnetic resonance imaging (MRI) to reveal the effects of the traumatic single experience on adult male

rat's brain.
Methods: Two different shock chambers, Context A chamber and Context B chamber, were used for delivering the multiple stress and conducting the fear conditioning, respectively. Male Wistar rats (8 weeks old -)were exposed to the multiple stress consisted of 4 spaced foot shocks (1 mA, 1 s) for 25 min in the Context A chamber and forced swimming for 20 min in a plastic bucket. Non-stressed rats were placed in the chamber and a plastic cage for the same amount of time as the multiple stress animals without foot shocks and swimming, respectively. The T2W MRI images were acquired by 7T MRI (Bruker). MRI was conducted before the multiple stress and after the third retention test of fear conditioning. We used voxel-based morphometry (VBM) that can map changes in regional gray matter volume over the time across the entire rat brain. Contextual fear conditioning was conducted 14 days after the multiple stress for testing the effect of the multiple stress. All animals were exposed 2 mild foot shocks (0.1 mA, 2 s) in the Context B chamber. Conditioned fear response (freezing) in the Context B chamber was assessed in three retention tests, which were conducted on the next, 7 and 14 days after the conditioning.
Results: Rats exposed the multiple stress showed the enhancement of fear conditioning on all retention tests even they experienced MRI before the multiple stress. The results of longitudinal VBM analysis revealed that the gray matter volumes in anterior amygdalohippocampal area was less than non-stressed rats. There were the association between the magnitude of fear conditioning and the regional gray matter volumes which statistically differed between two groups.
Conclusion: It's suggested that amygdalohippocampal area could be related to express enhanced fear response after encountering severe stress.

Disclosures: R. Ryoke: None. **M. Hirobe:** None. **H. Nonaka:** None. **R. Kawashima:** None.

Poster

780. Post-Traumatic Stress Disorder: Preclinical Models

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 780.05/Y2

Topic: G.06. Post-traumatic Stress Disorder

Title: Examinations of environmental enrichment and morphine for the symptoms of post-traumatic stress disorder in mice

Authors: F. WU[1], A. C.-W. HUANG[2];
[1]Dept. of Psychology, Fo Guang Univ., Yilan, Taiwan; [2]Psychology, Fo Guang Univ., Yilan County, Taiwan

Abstract: Fear and its comorbid depression and anxiety are the essential symptoms of post-traumatic stress disorder (PTSD). However, there was a little research to examine the neural substrates of PTSD. This present study concerned this issue of whether c-Fos activations

involved in the medial prefrontal cortex (mPFC) and amygdala for fear symptom of post-traumatic stress disorder (PTSD). In the study, all mice were tested fear behavior of the PTSD symptoms in behavioral level. Moreover, c-Fos expressions were also measured using immunohistochemical staining (IHC) in the mPFC and amygdala after encountering footshock traumatic events. During the footshock treatment, all mice were divided into two groups. The control group is no footshock treatment. The footshock group was given a severe footshock (3mA, 10s) once a day. Later, all of mice were given a situational reminder treatment once a day for 3 days. During the period of time, mice were put in the footshock box for 2 min and measured the freezing behavior. On the last day of the situational reminder phase, all mice were tested behaviors and then c-Fos expressions were tested. The present results indicated that c-Fos was higher expressions in the mPFC but amygdala was lower expressions for fear behavior testing when the combination of environmental enrichment and morphine injection. In conclusion, our data suggest that the mPFC and amygdala play important roles in PTSD. The present findings might offer some implications for PTSD.
Keywords: medial prefrontal cortex, amygdala, posttraumatic stress disorder, mice
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* indicated the correspondence author.

Disclosures: **F. Wu:** None. **A.C. Huang:** None.

Poster

780. Post-Traumatic Stress Disorder: Preclinical Models

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 780.06/Y3

Topic: G.06. Post-traumatic Stress Disorder

Support: NCCR Synapsy

Title: Genetic selection for blunted glucocorticoid responsiveness leads to impaired fear extinction and sleep abnormalities in rats

Authors: *S. MONARI, S. E. WALKER, J. GROSSE, I. GUILLOT DE SUDUIRAUT, S. ASTORI, C. SANDI;
Brain Mind Institute, EPFL, Lausanne, Switzerland

Abstract: Humans show inter-individual differences in vulnerability to develop post-traumatic stress disorder (PTSD) following exposure to traumatic events. Although initial observations linked low cortisol levels to PTSD pathophysiology, whether inter-individual differences in glucocorticoid responsiveness are implicated in the development of PTSD is not yet clear. To address this question, our lab has generated lines of Wistar rats genetically-selected for their differential habituation of the glucocorticoid response to repeated stressor exposure at puberty.

Here, we assessed physiological and behavioral phenotypes of subjects drawn from these lines. Strikingly, when compared to rats with 'normative' glucocorticoid responses, rats with blunted corticosterone responses to stress exhibit strong fear extinction deficits. Importantly, similar to PTSD patients, these rats show smaller hippocampi than controls. We tested whether supplementing with corticosterone would revert the extinction defects. Indeed, post-extinction corticosterone treatment in the low-line rats largely prevented immediate deficits in extinction memory and fear relapse. Given that glucocorticoids are known to modulate memory consolidation during sleep, and sleep disturbances are commonly observed in PTSD patients, we examined sleep/wake cycle and sleep rhythms through polysomnographic (EEG/EMG) recordings. Low responder rats displayed an altered sleep architecture, with shorter bouts of NREM sleep and markedly longer bouts of REM sleep, reminiscent of the excessive REM sleep described in PTSD patients. Our findings strongly support a causal involvement of blunted glucocorticoid responsiveness in physiological and behavioral traits indicative of higher vulnerability to PTSD, consistent with the evidence linking low cortisol levels to PTSD pathophysiology in humans.

Disclosures: **S. Monari:** None. **S.E. Walker:** None. **J. Grosse:** None. **I. Guillot de Suduiraut:** None. **S. Astori:** None. **C. Sandi:** None.

Poster

780. Post-Traumatic Stress Disorder: Preclinical Models

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 780.07/Y4

Topic: G.06. Post-traumatic Stress Disorder

Support: F32MH117913
VA Merit Grant 2I01BX001075

Title: Interleukin 1 receptor (IL-1R) within the subfornical organ is a novel neuroimmune regulator of panic-PTSD

Authors: *K. M. MCMURRAY[1,2], R. SAH[1,2];
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Abstract: Panic Disorder (PD) and Post-Traumatic Stress Disorder (PTSD) are prevalent, co-morbid psychiatric conditions with high disability and treatment resistance. Currently, mechanisms underlying PD-PTSD vulnerability are unclear. Accumulating evidence supports a potential role of neuroimmune modulators in PD-PTSD physiology. Recent studies have shown elevated pro-inflammatory cytokines in panic and PTSD patients and importantly, polymorphisms in the interleukin 1 beta (IL-1b) gene in PTSD suggesting a potential role of IL-1b and IL-1R signaling in development of these conditions. The association of IL-1b signaling in

the regulation of panic-PTSD relevant behaviors is currently unclear. We previously reported a role of neuroimmune mechanisms within a BBB-devoid area, subfornical organ (SFO) in fear evoked by carbon dioxide (CO_2), a panic challenge. The SFO has been recognized as an interoceptive locus and projects to panic and fear regulatory regions. Recently, we developed a conjunct panic- and PTSD relevant paradigm using CO_2 inhalation and fear conditioning in mice wherein PTSD-relevant behaviors (fear conditioning extinction deficits, heightened acoustic startle) are observed 1 week after CO_2 inhalation. Our previous data show central IL-1b/IL-1R signaling regulates CO_2-evoked fear. Here, we tested the hypothesis that inhibiting IL-1R signaling specifically within SFO during CO_2 inhalation reduces both immediate (CO_2-evoked fear) and long-term fear outcomes (fear conditioning, acoustic startle 1 week later). IL-1R antagonist (IL-1ra) or vehicle was infused via cannulas targeted to the SFO 30m prior to 5% CO_2 inhalation. One week later, mice underwent acoustic startle, followed by contextual fear conditioning the next day. Sustained region-specific neural activity was quantified by IHC (FosB) in tissue collected 24h after final behavioral testing. Consistent with our hypothesis, a single infusion of IL-1ra attenuated freezing (fear) during CO_2-inhalation and prevented the delayed expression of potentiated startle and contextual fear extinction deficits. Ongoing studies are investigating neuronal activation in SFO-target areas and fear regulatory regions such as the mPFC, BNST, hippocampus and amygdala to delineate associated circuits. Collectively, our data provide the first evidence for an important role of neuroimmune mediators within specialized blood brain barrier devoid loci in regulating fear behavior and highlight SFO IL-1R as a novel target in panic and PTSD physiology.

Disclosures: K.M. McMurray: None. **R. Sah:** None.

Poster

780. Post-Traumatic Stress Disorder: Preclinical Models

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 780.08/Y5

Topic: G.06. Post-traumatic Stress Disorder

Support: MOST 107-2410-H-431-004

Title: Tests of freezing and anxiety behaviors in the animal model of post traumatic stress disorder

Authors: *H.-L. CHENG, A. C. W. HUANG;
Fo Guang Univ., Yilan, Taiwan

Abstract: This purpose of the present study imitates the symptoms of PTSD. In the initial period of time, all rats received habituation procedure for 7 days in colony room. Then, rats were given the footshock treatment to induce a traumatic event. On the footshock treatment, all of rats were

divided into two groups: nonfootshock and footshock groups. The control group is given a nonfootshock treatment. The footshock group was conducted a severe footshock (3mA, 10s) once a day. These animals received a situational reminder treatment once a day for 3 days. The rats were placed in the footshock box for 2 min and measured rats' freezing behavior. After the last session of the situational reminder, rats were given an anxiety test in the zero-maze task for 10 min. The spent time were measured in the open arm served as the anxiety index. The results indicated that a 2 x 3 mixed two-way ANOVA showed that the group [$F(1, 17) = 83.62$, $p < 0.05$] and session [$F(2, 34) = 4.04$, $p < 0.05$] were significant differences. However, a nonsignificant difference occurred at the interaction of group and sessions [$F(2, 34) = 0.55$, $p > 0.05$]. For the zero-maze test, a significant difference occurred for nonfootshock and footshock groups [$F(1, 17) = 8.38$, $p < 0.05$].
In conclusion, footshock treatments induced freezing behavior. Moreover, footshock induced anxiety behavior in the zero-maze task. The present data can offer a novel PTSD animal model. The findings should be discussed further.

Disclosures: H. Cheng: None. **A.C.W. Huang:** None.

Poster

780. Post-Traumatic Stress Disorder: Preclinical Models

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 780.09/Y6

Topic: G.06. Post-traumatic Stress Disorder

Support: CNPq/ 113624/2018-2

Title: The blockade of NK1 receptors in the dorsal periaqueductal gray facilitated extinction memory and reduced anxiety-like behavior

Authors: *M. C. CARVALHO[1], C. R. LEITE-PANISSI[3], N. C. COIMBRA[2];
[2]Pharmacol., [1]Univ. of São Paulo/ FMRP, Ribeirão Preto, Brazil; [3]Psychology, Univ. of São Paulo/ FFCLRP, Ribeirão Preto, Brazil

Abstract: Extinction is defined as the learned inhibition of retrieval. It is the mainstay of exposure therapy to treat fear disorders such as post-traumatic stress disorder (PTSD). It is known that extinction requires retrieval involving memory destabilization and relevant protein synthesis-dependent processes in hippocampus and amygdaloid complex, but no attention has been given to the role of mesencephalic structures in this process. The periaqueductal gray matter (dPAG) is involved in coordinating aspects of the fear-related responses. We showed that aversive stimulus-induced reactions related to dPAG activity send information toward higher brain structures (hippocampus and amygdala) that are responsible for the storage of memories of intense threatening stimuli within a given time window (Carvalho et al., 2018). It led us to think

that the dPAG could contribute to the extinction of aversive memories. The behavioral sensitization induced by dPAG electrical stimulation was long-lasting counteracted by NK1 receptor antagonism in the ventral hippocampus and central nucleus of the amygdala of rats submitted to the elevated plus maze (EPM). Then, we evaluated the effects of spantide (SPA), a NK1 antagonist, infused into the dPAG, on extinction memory in rats incapable of showing contextual fear condition (CFC) extinction because of weak training. Male Wistar rats with guide cannulae implanted in the dPAG were submitted to a weak extinction protocol in a CFC apparatus. Rats that received intra-dPAG infusion of SPA (100 pmol/0.2 μL) 5 min before the training expressed less freezing behavior than PBS-treated rats during both extinction training and retention, 1 and 7 days later. These rats showed anxiolytic-like effects in the EPM 8 days after the extinction training. These results suggest that NK1 inhibition in the dPAG is able to induce the consolidation of extinction memory and to reduce anxiety-like behaviors consequent to the trauma. In addition, these findings suggest that the dPAG is an important structure involved in the modulation of extinction memory, a function not addressed in previous works. This ancient structure seems to be part of neural circuitry responsible for modulating long-term memories of intense threatening conditions, similar to what occurs in PTSD.

Disclosures: M.C. Carvalho: None. **C.R. Leite-Panissi:** None. **N.C. Coimbra:** None.

Poster

780. Post-Traumatic Stress Disorder: Preclinical Models

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 780.10/Y7

Topic: G.06. Post-traumatic Stress Disorder

Support: AA026537

Title: Pharmacological inactivation of the nucleus reuniens during predator odor exposure and context re-exposure

Authors: *L. C. ORNELAS[1], J. BESHEER[2];
[1]Bowles Ctr. for Alcohol Studies, The Univ. of North Carolina Sch. of Med., Chapel Hill, NC;
[2]Psychiatry; Bowles Ctr. for Alcohol Studies, Univ. of North Carolina - Chapel Hill, Chapel Hill, NC

Abstract: Post-traumatic stress disorder (PTSD) is highly comorbid with alcohol use disorder. Defining models of traumatic stress and alcohol consumption may lead to a better understanding of the neurobiological mechanisms that underlie this comorbidity. The nucleus reuniens (RE), a midline thalamic nucleus, is an emerging area of the brain underlying symptom profiles of PTSD, such as stress and depression. Here we examined pharmacological inactivation (by a baclofen/muscimol cocktail) of the RE prior to traumatic stress to better understand the neural

circuitry involved in regulating response to traumatic stress.
Female (n=32) Long Evans rats were implanted with a unilateral cannula into the RE. One week after surgery, rats received baclofen (1.0 mM) + muscimol (0.1 mM; BM) or aCSF microinjections. 10 min post infusion, rats in the stress group underwent predator odor (PO) exposure using trimethylthiazoline (TMT; synthetically derived fox feces component), for 20 min in a distinct context. 48-72 hr later rats underwent testing for general locomotor activity (open field test; OFT), anxiety-like behavior (light/dark test), and hyperarousal (acoustic startle response, ASR). To measure reactivity to the PO-paired context, 4 weeks following the initial PO exposure, rats were re-exposed to the PO-paired context in the absence of TMT.
During PO exposure, rats administered aCSF showed a significant decrease in total distance traveled and midline crossings, increase time freezing and avoidance of the side of the chamber near the TMT compared to control counterparts. In addition, during PO exposure rats administered BM avoided the side of the chamber near the TMT compared to control counterparts. There were no changes in locomotor behavior in the OFT, Light/Dark test, or ASR. During PO context re-exposure, the PO-exposed groups did not show reactivity to the paired context, which could be due to the 4 week delay between exposure and re-exposure. As a follow up study, in a new cohort of animals, we tested motor activity in the open field after BM administration. There were no changes in distance travel in BM group vs. controls indicating this BM dose does not produces changes in locomotor behavior.
The results indicate that PO exposure produces stress-induced effects as indicated by decreased in total distance traveled and midline crossings, increased time freezing and avoidance of the side of the chamber near the TMT. In addition, pharmacological inactivation of the RE produces no changes in behavioral responses during PO or behavioral reactivity to PO-paired context. Together, these results indicate that inactivation of the RE does not impair fear expression during PO exposure.

Disclosures: L.C. Ornelas: None. **J. Besheer:** None.

Poster

780. Post-Traumatic Stress Disorder: Preclinical Models

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 780.11/Y8

Topic: G.06. Post-traumatic Stress Disorder

Support: NIH Grant 1P20GM103653

Title: Estrogen receptor activation and susceptibility to traumatic stress in an animal model of PTSD

Authors: *M. BIDDLE, D. K. KNOX;
Psychological and Brain Sci., Univ. of Delaware, Newark, DE

Abstract: Post-Traumatic Stress Disorder (PTSD) is an anxiety disorder which occurs following exposure to traumatic stress and results in the inability to properly modulate expression of fear memory. Women are twice as likely to suffer from PTSD as men, but this enhanced susceptibility has been difficult to replicate in rodent-based models of PTSD. One reason for this is female rats are resilient to the effects traumatic stress has on persistent fear memory. A possible cause of this is differences in the natural variation of the ovarian hormone estrogen in female humans vs. female rats. In humans, the menstrual cycle typically lasts between 21 and 45 days, with a period of 5-7 days of notably lower levels of estrogen. This can lead to periods where estrogen receptor activation is low in fear circuits, which in turn could represent a window of stress susceptibility in women. In support of this interpretation a number of studies have shown that low estrogen receptor activation leads to either enhanced susceptibility to PTSD or deficits in extinction memory. In rodents, the estrous cycle is typically only 4-5 days, and the period of lower estrogen levels is comparably shorter as well. Thus, there may not be naturally low levels of estrogen receptor activation in female rats. One way to circumvent this potential issue is to pharmacologically antagonize estrogen receptors prior to traumatic stress. By doing this the effects of low estrogen receptor activation on traumatic stress effects in females and males can be examined. To accomplish this goal we used the single prolonged stress (SPS) model of PTSD. SPS consists of serial exposure to restraint forced swim and ether, and approximates core behavioral and neurobiological PTSD symptoms. Prior to conducting SPS or control stress in rats, the estrogen receptor antagonist (ICI182,780; 0.05mg/kg and 0.005mg/kg) was administered subcutaneously to lower estrogen receptor activation prior to SPS. Rats were then fear conditioned, then subjected to extinction training and testing. Rats were then euthanized and key nodes of the fear circuit examined to identify sex differences in sensitivity to SPS when SPS is conducted under low estrogen receptor activation. While the study is ongoing, preliminary findings suggest an overall decrease in fear conditioning in female SPS rats that received a high dose (i.e. 0.05mg/kg) of the estrogen receptor antagonist prior to SPS. The overall results of the study will help determine if low estrogen receptor activation prior to traumatic stress can lead to stress susceptibility and identify key nodes in the fear circuit through which this susceptibility may manifest.

Disclosures: **M. Biddle:** None. **D.K. Knox:** None.

Poster

780. Post-Traumatic Stress Disorder: Preclinical Models

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Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 780.12/Y9

Topic: G.06. Post-traumatic Stress Disorder

Support: Samuel C. Johnson for Genomics of Addiction Program
the Ulm Foundation

the Godby Foundation
National Institute on Alcohol Abuse and Alcoholism (AA018779) to DSC

Title: The effect of ethanol consumption on cue-dependent fear memory in mice

Authors: *K. WININGER[1], A. HO[2], S. PAEK[1], D.-S. CHOI[3];
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Abstract: Significant comorbidity is known between posttraumatic stress disorder (PTSD) and alcohol use disorder (AUD). Traumatic events are a common denominator for stress disorders including PTSD, which is highly associated with increased alcohol drinking. Acute alcohol use mitigates and short term relieves PTSD symptomology. However, chronic alcohol use alters circuitry and signaling in the brain and alcohol withdrawal exacerbates PTSD symptoms.This study aims to investigate the effects of chronic pre-exposure to alcohol on cue-dependent fear memory. For this study, three cohorts of C57BL/6J mice underwent fear conditioning training, followed by cue-dependent fear memory testing, extinction training and testing. The first cohort (*n*=32) is ethanol-naïve, while the second (*n*=24) and third (*n*=24) cohorts were pre-exposed to a 2-bottle choice ethanol drinking paradigm (escalating progressively from 3% to 15%) prior to fear conditioning training, and only the third cohort continued with the drinking paradigm (15% ethanol) throughout the study. Cue-dependent fear memory was measured by freezing response during the presentation of cue. Ethanol consumption and preference were recorded every two days. Ethanol pre-exposure significantly reduced freezing response during fear conditioning training, however continued ethanol exposure had no effect on cue-dependent fear memory or fear extinction. Baseline ethanol consumption was correlated with freezing to cue upon re-exposure with no correlation in fear conditioning training or extinction. Ethanol consumption and preference significantly decreased after fear conditioning testing regardless of fear conditioning training. Our findings demonstrate that ethanol consumption prior to fear conditioning reduces fear response during initial fear conditioning however is correlated with the severity of cue-dependent fear response upon re-exposure.

Disclosures: K. Wininger: None. **A. Ho:** None. **S. Paek:** None. **D. Choi:** None.

Poster

780. Post-Traumatic Stress Disorder: Preclinical Models

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 780.13/Y10

Topic: G.06. Post-traumatic Stress Disorder

Support: TSNRP

Title: Sex differences in intravenous ketamine infusion on stress and fear in rats

Authors: K. D. RADFORD[1], M. ZHANG[2], R. Y. BERMAN[1], T.-Y. J. WU[1], ***K. CHOI**[2];
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Abstract: The U.S. Department of Defense has recently opened combat roles to women that were previously restricted to men. As a result of this policy change, military health care providers can anticipate an increased frequency of combat-related injuries in female service members in the future. Ketamine, an NMDA receptor antagonist, is a preferred battlefield analgesic due to its hemodynamic stability and a lack of respiratory suppression in wounded service members. However, ketamine administration in the peri-trauma period may produce dissociation and hallucination which may worsen traumatic memory consolidation. We previously reported that subanesthetic intravenous (IV) ketamine infusion dose-dependently increased stress hormone corticosterone (CORT) levels and fear memory in male rats. Here, we investigated the effects of IV ketamine infusion on CORT and fear memory in female rats. Adult female Sprague-Dawley rats received a 2-hour IV ketamine infusion (0 and 10 mg/kg) after auditory fear conditioning (3 times of tone and footshock pairing). Spontaneous locomotor activity was monitored during the infusion and plasma CORT levels were measured after the infusion. Fear memory retrieval, fear extinction, and fear recall were tested between 2 and 4 days after the fear conditioning/ketamine infusion. The IV ketamine infusion suppressed locomotor activity and elevated plasma CORT levels in female rats. The IV ketamine infusion following fear conditioning enhanced fear memory retrieval and delayed fear extinction in rats. These results indicate that subanesthetic dose of IV ketamine infusion stimulates stress hormone pathway and enhances fear memory in intact female rats.

Disclosures: K.D. Radford: None. **M. Zhang:** None. **R.Y. Berman:** None. **K. Choi:** None. **T.J. Wu:** None.

Poster

780. Post-Traumatic Stress Disorder: Preclinical Models

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Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 780.14/Y11

Topic: G.06. Post-traumatic Stress Disorder

Support: NIH/NIDA DA016511

Title: Glutamatergic mechanisms enduring vulnerability to maladaptive coping strategies and transient synaptic plasticity following and acute stressor

Authors: C. GARCIA-KELLER, A. M. KEARNS, J. S. CARTER, J. JOPKINS, T. PENALOZA, P. W. KALIVAS, ***C. M. REICHEL**;
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Abstract: Exposure to acute life-threatening stress, such as occurs in combat or a sexual assault, increases the incidence of post-traumatic stress disorder (PTSD), and a diagnosis of PTSD substantially increases a diagnosis of substance use disorder (SUD) relative to the general population. In fact, 30-50% of people seeking treatment for SUDs have a comorbid diagnosis for PTSD. The severity of stress exposure correlates with greater substance use and this relationship supports a self-medication hypothesis, which posits that drug use is a means to cope with anxiety and reduce PTSD symptoms. Using animal models, we showed a remarkable overlap between the enduring neuroadaptations produced in nucleus accumbens core (NAcore) excitatory transmission after acute stress and drug use. Specifically, we discovered that 3 weeks after a single acute stress (2 hr restraint) glutamatergic synapses on NAcore medium spine neurons (MSNs) show increased AMPA/NMDA ratio and dendritic spine density, and a marked reduction in glial glutamate transporter (GLT-1) expression and function. How these neuroadaptations relate to PTSD symptomology and behavior have not been determined. We paired the stressful event with a novel odor, stress conditioned cue (CS), in male and female rats. Using a defensive burying task with the CS, we found stressed rats spent more time burying the CS and immobile during the session relative to control animals. This increased reactivity to the CS is consistent with maladaptive coping strategy reminiscent of PTSD. We hypothesize that exposure to the CS elicits transient-Synaptic Plasticity (t-SP: evokes transient increased in A/N, dh, matrix metalloprotease (MMPs) activity and adaptations in astroglial processes) similar to that seen following 15 min exposure to drug associated cues. We also found stressed female rats have greater preference for sweet solutions relative to their same sex and male counterparts and, in further work, will determine if this preference is related to stress induced changes in motivation. These experiments have the potential to reveal novel behavioral and neurobiological mechanisms of PTSD that induce the increased vulnerability to SUDs. Understanding this link will enhance our ability for rational drug design to treat comorbid PTSD and SUDs.

Disclosures: C. Garcia-Keller: None. **A.M. Kearns:** None. **J.S. Carter:** None. **J. Jopkins:** None. **T. Penaloza:** None. **P.W. Kalivas:** None. **C.M. Reichel:** None.

Poster

780. Post-Traumatic Stress Disorder: Preclinical Models

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 780.15/Y12

Topic: G.06. Post-traumatic Stress Disorder

Title: Changes in the gut-associated microbiome as a result of exposure to a predator-based psychosocial stress model of PTSD

Authors: *I. F. SMITH[1], C. D. KASLER[1], K. L. KRYNAK[2], P. R. ZOLADZ[1];
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Abstract: Recent work has established a relationship between physiological responses to stress and the gut-associated microbiome. Research has also shown that changes in the makeup of the gut microbiome can lead to anxiety-like behaviors. However, work concerning how specific anxiety-related illnesses influence the microbiome is limited. The purpose of the present study was to observe changes in the gut-associated microbiome of Sprague-Dawley rats that had been exposed to a predator-based psychosocial stress model of post-traumatic stress disorder (PTSD). We hypothesized that exposure to this model would lead to significant changes in the composition of the gut-associated bacterial microbiome. Ten male rats underwent a well-validated 31-day PTSD model consisting of two exposures to a cat (each exposure separated by 10 days) and daily social instability, which began on the day of the first cat exposure. Ten additional rats served as controls and were handled daily. Before and after the 31-day paradigm, all rats underwent behavioral testing to assess anxiety-like behavior and symptoms of hyperarousal. Fecal samples were collected weekly from both the stressed and control rats in order to assess gut-bacterial composition. DNA was extracted from these fecal samples, polymerase chain reaction (PCR) was used to amplify the 16S rRNA gene region of bacterial DNA, and terminal fragment length polymorphism (TRFLP) analysis was used to assess differences in gut-associated bacterial composition across treatments. Behavioral analyses revealed that stress significantly increased rats' anxiety-like behavior on the elevated plus maze (EPM) and in the open field and significantly increased rats' startle responses. PERMANOVA results revealed significant main and interactive effects of stress and fecal sample collection time point on gut-microbiota composition. However, bacterial community similarities shown by a non-metric multidimensional scaling ordination did not support our prediction that stress would result in a significant shift in gut-bacterial composition relative to controls. Future work is needed to further elucidate the mechanisms by which gut-associated bacteria interact with stress.

Disclosures: I.F. Smith: None. **C.D. Kasler:** None. **K.L. Krynak:** None. **P.R. Zoladz:** None.

Poster

780. Post-Traumatic Stress Disorder: Preclinical Models

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 780.16/Y13

Topic: G.06. Post-traumatic Stress Disorder

Support: R01MH105400

Title: Mir-598-3p mediates susceptibility to stress-enhanced remote fear memory

Authors: *M. E. JONES[1], S. E. SILLIVAN[1], S. JAMIESON[1], G. RUMBAUGH[2], C. A. MILLER[3];
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Abstract: Post-traumatic stress disorder (PTSD) is a debilitating psychiatric disorder that is exacerbated by persistent, maladaptive traumatic memories. We developed a stress-enhanced fear learning (SEFL) paradigm to examine susceptibility and/or resilience to the development of enhanced fear memories in C57Bl/6J mice. In SEFL, mice exposed to 2 hours of restraint stress seven days prior to cued fear conditioning display an enhanced, extinction-resistant memory relative to non-stressed controls. Further, male SEFL mice display greater variability in memory strength than non-stressed controls, such that two distinct subgroups emerge; stress susceptible (SS; enhanced memory) and stress resilient (SR; memory comparable to controls). Interestingly, stressed females do not cluster into distinct susceptible and resilient subgroups, but rather display a more uniform SS-like phenotype. Enhanced fear memory strength observed in SS males is associated with neurobiological changes known to be associated with PTSD, including enhanced immediate early gene expression (IEG) in the basolateral amygdala (BLA), decreased IEG expression in the prelimbic cortex, and enhanced BLA expression of genes associated with PTSD (i.e. PACAP, BDNF, TH, DRD1/2). Identifying mechanisms governing stress-enhanced fear memory in susceptible mice may identify novel therapeutic targets for the selective disruption of pathogenic memories that contribute to PTSD. To this end, we examined the role of microRNAs (miRNAs) in remote fear memory, which have emerged as potent regulators of learning, recent memory and extinction. We first performed small-RNA sequencing on BLA tissue one month after fear conditioning, without retrieval. mir-598-3p, a highly conserved miRNA, was downregulated by fear conditioning, but elevated in SS males. While further decreasing BLA mir-598-3p levels did not alter the expression or extinction of the remote fear memory in non-stressed mice, intra-BLA inhibition of mir-598-3p interfered with expression and extinction of the remote stress-enhanced fear memory in SS males. This effect could not be attributed to an anxiolytic effect of inhibiting this miRNA in the BLA. Further, BLA mir-598-3p was not differentially expressed in females by SEFL. Consistent with this, intra-BLA inhibition did not alter stress-enhanced fear memory expression in females. Finally, bioinformatic analysis following quantitative proteomics on BLA tissue collected 30 days post-SEFL training identified putative mir-598-3p targets and related pathways mediating the differential susceptibility, with evidence for regulation of the actin cytoskeleton.

Disclosures: **M.E. Jones:** None. **S.E. Sillivan:** None. **S. Jamieson:** None. **G. Rumbaugh:** None. **C.A. Miller:** None.

Poster

780. Post-Traumatic Stress Disorder: Preclinical Models

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Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 780.17/Y14

Topic: G.06. Post-traumatic Stress Disorder

Support: NIH Grant GM060507
NIH Grant MD006988

Title: Therapeutic potential of neuregulin-1 for diet-induced cognitive deficits

Authors: P. ONTIVEROS-ANGEL[1], J. D. VEGA-TORRES[1], A. JULLIENNE[3], E. HADDAD[4], A. AVITUA[6], B. D. FORD[7], A. OBENAUS[5], *J. D. FIGUEROA[2];
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Abstract: Childhood obesity hastens the onset of cognitive and psychiatry morbidity. Emerging evidence from our laboratory indicates that the consumption of diets rich in saturated fatty acids and sugars during adolescence reduces the volume of the hippocampus while heightening emotional reactivity to traumatic stress. However, the mechanisms underlying these structural and functional vulnerabilities are poorly understood. Neuregulin-1 (NRG1) and ErbB receptors play critical roles in hippocampal neurogenesis, maturation, and resilience. Furthermore, genetic studies have demonstrated a link between ErbB4 and metabolic disorders, including obesity. In this study, we aimed to determine whether deficits in NRG1-ErbB4 signaling might be present in the hippocampus of adolescent rats exposed to an obesogenic Western diet (WD). We examined whether chronic NRG1 administration during adolescence increases hippocampal volume, cued learning, and ErbB4 phosphorylation. Lewis rats were randomly divided into four groups (12 rats/group): 1) control diet (CD) + vehicle; 2) CD + NRG1; 3) WD + vehicle; 4) WD + NRG1 (NRG1 intraperitoneal injections: 5 μg/kg/day for 21 days between P21-P41). Behavioral tests and magnetic resonance imaging were performed, and several organs and brain regions were harvested to determine NRG1 effects on ErbB activation and signaling. We found that the rats that consumed the WD exhibited reduced hippocampal volumes (8% reduction relative to CD rats). WD rats exhibited deficits in trace cued fear conditioning (fear-potentiated startle, FPS). Chronic NRG1 administration reduced hippocampal volume (9% reduction relative to vehicle), altered working memory and exploratory behavior (Y-maze), and attenuated FPS responses in CD rats (55% reduction relative to vehicle). Interestingly, NRG1 administration had no effects on hippocampal volume and behaviors in WD rats. Consistent with this observation, the rats that

consumed the WD exhibited a reduction in peripheral NRG1 levels in the liver (33% relative to controls). Further, we found that the mRNA levels of the ErbB4 isoforms JMa (18%) and Cyt1 (32%) were elevated in the hippocampus of WD rats. These data suggest a novel interaction between exposure to obesogenic diets and NRG1-ErbB4 signaling in the maturing hippocampus. In conclusion, our results indicate that NRG1-ErbB4 may contribute to the abnormal hippocampal structure and cognitive vulnerabilities observed in obese individuals.

Disclosures: P. Ontiveros-Angel: None. **J.D. Vega-Torres:** None. **A. Jullienne:** None. **E. Haddad:** None. **A. Avitua:** None. **B.D. Ford:** None. **A. Obenaus:** None. **J.D. Figueroa:** None.

Poster

780. Post-Traumatic Stress Disorder: Preclinical Models

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 780.18/Y15

Topic: G.06. Post-traumatic Stress Disorder

Support: Whitehall Foundation
NIMH 1R01MH117421-01A1
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Title: Activity dependent dissection of lateral septal circuits that control stress susceptibility

Authors: D. ALLEN[1], M. HASHIMOTO[1], D. J. ANDERSON[2], ***T. E. ANTHONY**[1]; [1]Neurobio., Boston Children's Hosp., Boston, MA; [2]Caltech, Pasadena, CA

Abstract: A single traumatic experience is sufficient to induce an acute stress reaction that in susceptible individuals can progress to chronic mental illness lasting months to years. The neural and molecular pathways that control the induction, maintenance, and termination of stress-induced states, and how their dysfunction may lead to persistent affective disorders, have not been clearly defined. Functional mapping and optogenetic manipulations indicate that the pattern and intensity of activity in the lateral septum (LS) during stressor exposure determines the nature and severity of the ensuing behavioral responses. However, the mechanisms by which distinct subsets of stress-activated LS neurons promote susceptibility or resilience are largely unknown. To fill this gap in knowledge, we developed a novel approach for genetic tagging of activated neurons which we call tetracycline-regulated activity-dependent cell marking (TRACM). TRACM combines an immediate early gene promoter-driven doxycycline (DOX)-suppressible transcriptional activator (tTA) with a constitutively expressed DOX-activated transcriptional repressor (rtTS), and yields robust and highly specific genetic marking of acute stress-activated

LS neurons with negligible background in naive home cage controls. Notably, the required genetic elements can be delivered entirely via adeno-associated viral vectors (AAVs), thus enabling activity-dependent neuronal tagging in nontransgenic animals. Optogenetic circuit mapping and *in vivo* fiber photometry calcium imaging indicates that acute stress-activated neurons in anterolateral LS influence behavioral responses to salient environmental stimuli via local intraseptal inhibitory connections as well as through long range projections to medial hypothalamus. To determine whether these stress-activated anterolateral LS neurons promote active or passive coping responses to threat, TRACM-mediated chemogenetic and optogenetic functional studies are ongoing and will be presented.

Disclosures: D. Allen: None. **M. Hashimoto:** None. **D.J. Anderson:** None. **T.E. Anthony:** None.

Poster

780. Post-Traumatic Stress Disorder: Preclinical Models

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 780.19/Y16

Topic: G.06. Post-traumatic Stress Disorder

Support: DoD W81XWH-13-1-0377

Title: NR2B mRNA expression decreased in ventral hippocampus after exposure to single prolonged stress trauma, a rodent model of PTSD

Authors: *C. V. CHEN[1], N. RAJARAM[2], I. LIBERZON[1];
[1]Texas A&M Univ., Bryan, TX; [2]Ann Arbor VA Healthcare Syst., Ann Arbor, MI

Abstract: Post-traumatic stress disorder (PTSD) is a chronic, debilitating disorder that can emerge following exposure to a traumatic event. It is the 4th most common psychiatric disorder, with lifetime prevalence in the US at 6.8%. PTSD is characterized by a wide range of symptoms including the impaired extinction of traumatic memory. Although this deficit is a hallmark of PTSD, the underlying mechanisms of impaired extinction is not well understood and existing treatment is not equally effective in all cases. Here we investigated the involvement of NMDA receptors in this deficit. For this, we used the animal model of PTSD, Single Prolonged Stress (SPS). Adult male Sprague Dawley rats were exposed to SPS trauma or not (control) and, after a 7-day quiescent period necessary for the development of symptomatology, rats were euthanized and their brains collected for molecular assays. Rats exposed to SPS trauma showed a decrease in NR2B mRNA expression in the ventral hippocampus, which has been implicated in contextual memory and memory consolidation. Further studies will determine the neuron type that express NR2B and the target of their efferent projections to determine function.

Disclosures: **C.V. Chen:** None. **N. Rajaram:** None. **I. Liberzon:** None.

Poster

780. Post-Traumatic Stress Disorder: Preclinical Models

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Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 780.20/Y17

Topic: G.06. Post-traumatic Stress Disorder

Support: NIDA R01042057
VA I01RX002252
Fund for Anesthesiology Research -WSU

Title: Time-dependent effects of single-prolonged stress on amino acid neurotransmitter levels in rat prelimbic and infralimbic cortices: A magnetic resonance spectroscopy study

Authors: *F. GHODDOUSSI[1], A. HARUTYUNYAN[2,3], S. A. PERRINE[2,3];
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Abstract: **Introduction**: Post-traumatic stress disorder (PTSD) is a costly psychiatric disorder characterized by anxiety, avoidance behavior, and hyper-reactivity to trauma-associated stimuli that affects nearly 25 million people in United States. However, the biological mechanisms underlying this disease are still largely unknown or poorly understood. Considerable evidence indicates that PTSD results from dysfunction in highly-conserved brain systems involved in stress, anxiety, fear, and reward. Single-prolonged stress (SPS) is a pre-clinical rodent model that displays behavioral, molecular, and physiological alterations that recapitulate many characteristics observed in PTSD. Our previous research using proton-magnetic resonance spectroscopy (^{1}H-MRS) has shown that glutamate (Glu) and glutamine (Gln) levels are decreased in the medial prefrontal cortex (mPFC), which is believed to be involved in dysregulation of fear learning and extinction. In this study, we measured levels of GABA, glutamate, and glutamine in sub-regions of the medial PFC, including the pre-limbic (PL) and infra-limbic (IL) cortices, following SPS to determine the time-dependent and sub-regional effects within the mPFC. **Methods:** Levels of GABA, Glu, and Gln were determined using, magic-angle spinning 1H-MRS at 11.7T in PL and IL sub-regions of the mPFC in controls rats and animals subjected to SPS and euthanized 1, 7 or 14 days later. **Results:** Glu level was significantly decreased after 1 day and GABA level was significantly increased 7 days after SPS in PL, with no effect on GLN levels at any of the 3 time points. On the other hand, Glu levels were significantly decreased 1 day after SPS in IL and Gln levels were significantly decreased at 7 & 14 days . GABA levels were unaffected in IL at any of the 3 time points.. **Discussion:** Our data indicate that SPS differentially affects sub-regions of the mPCF, with increased inhibitor

control in the PL and decreased excitatory control in the IL. We speculate that this differential sub-regional effect is critical in top-down control of mPFC to amygdala and striatum and inherently involved in the dysregulated fear and reward behaviors observed in PTSD.

Disclosures: F. Ghoddoussi: None. **A. Harutyunyan:** None. **S.A. Perrine:** None.

Poster

780. Post-Traumatic Stress Disorder: Preclinical Models

Location: Hall A

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Program #/Poster #: 780.21/Y18

Topic: G.06. Post-traumatic Stress Disorder

Support: NIH Grant MH098003
NIH Grant MH114224
NIH Grant NS085200

Title: Differential brain activity in response to trauma in a predator scent stress rat PTSD model

Authors: *D. DOPFEL[1], C. MESSNER[1], N. ZHANG[2];
[1]Pennsylvania State Univ., University Park, PA; [2]The Pennsylvania State Univ., University Park, PA

Abstract: Post-traumatic stress disorder (PTSD) is caused by an initial traumatic experience. However, only a subset of those who experience trauma will go on to develop PTSD. Individual variability in the perception of that trauma is known to play a role in the likelihood of future PTSD development. Work in our lab suggests this is also true in the predator scent stress rodent model of PTSD, supporting that there is individual variability of functional responses to traumatic experiences. Therefore, understanding the response to trauma is important in the study of PTSD susceptibility. Here, we characterize brain regions that are critical in stress perception and response by exploring brain activity, through BOLD fMRI, during the trauma itself.
We exposed awake Long Evans rats to fox urine during fMRI scans with a total fox urine exposure time of 10 minutes, consistent with our previous study, alternating between scented and unscented airflow. Elevated plus maze was then performed 7 days post-exposure to assess PTSD-like symptomology, which showed a general decrease in open arm exploration in the fox urine exposed animals.
The fMRI data supports that the activity of several brain regions, e.g. the pituitary and retrosplenial cortex, are differentially influenced by fox urine airflow, compared to lemon and unscented airflow. Further work will assess the variations in this response given baseline resting state functional connectivity and long-term PTSD-like symptom assessment. This will determine brain regions that are crucial in stress perception, the stress response and in PTSD susceptibility.

Disclosures: **D. Dopfel:** None. **C. Messner:** None. **N. Zhang:** None.

Poster

780. Post-Traumatic Stress Disorder: Preclinical Models

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 780.22/Y19

Topic: G.06. Post-traumatic Stress Disorder

Title: CBD effects on measures of anxiety and depression in a preclinical model of post traumatic stress disorder

Authors: C. N. MULTON, D. C. COOPER, *T. E. KOELTZOW;
Bradley Univ., Peoria, IL

Abstract: The cannabis industry in the US has experienced tremendous growth in recent years, in part due to a more permissive regulatory environment. The availability of cannabidiol (CBD) in a variety of commercial products has fueled consumer experimentation as a dietary supplement for a variety of ailments. There is growing interest in the potential for CBD to provide therapeutic efficacy across numerous pathologies related to inflammation, metabolism and mental health, like anxiety and Post-Traumatic Stress Disorder (PTSD). The first objective of the study evaluated the therapeutic potential of CBD on measures of anxiety and depression. We administered CBD doses (0-5 mg/kg, i.p.) and measured open field activity, elevated plus maze, forced swim and nocturnal locomotor activity in adult, male rats (Sprague-Dawley, 200-225 g, n=8 per condition). CBD increased exploration of the open arms of the elevated plus maze without evidence of deleterious effects across the dose range. The second objective assessed the effects of CBD in male, adolescent rats (Sprague-Dawley, Post-natal day 30-34) to a modification of the single prolonged stress (SPS) model (Liberzon et al., 1999) of PTSD. Rats were randomly assigned to the SPS (two hours restraint stress, 20 minutes forced swim, CO2-induced loss of consciousness, n=16) or sham control (n=22). Antecedent results indicate that SPS decreases the number of open arm entries ($F(1,37) = 5.32$, $p = 0.013$, $d = 0.63$) when tested two weeks later. In contrast, SPS increased spontaneous locomotor activity ($F(1,37) = 10.01$, $p = 0.002$, $d = 1.89$). The final phase of the experiment delivered CBD immediately following SPS induction to assess its ability to ameliorate PTSD-related symptoms. Findings suggest a role for CBD in the treatment of anxiety and depressive symptoms related to PTSD.

Disclosures: **C.N. Multon:** None. **D.C. Cooper:** None. **T.E. Koeltzow:** None.

Poster

780. Post-Traumatic Stress Disorder: Preclinical Models

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Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 780.23/Y20

Topic: G.06. Post-traumatic Stress Disorder

Support: R03 DA044483
T32 DA007237
P30 DA013429

Title: Individual resilience or vulnerability to traumatic-stress exposure based on behavioral profile and subsequent ethanol drinking predicted by machine learning

Authors: *R. R. DENNY[1], E. M. UNTERWALD[2];
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Abstract: Post-traumatic stress disorder (PTSD) begins by traumatic-stress exposure and develops into several symptoms including persistent memories and increased sympathetic nervous system arousal. PTSD is also highly co-morbid with alcoholism. The present study investigated individual differences to traumatic-stress and subsequent ethanol consumption. A rat model of traumatic stress, single prolonged stress (SPS), was used in young adult female rats. This modified SPS model included restraint stress, forced swim, and isoflurane exposure followed by 7 days of isolation. After traumatic-stress exposure, rats were behaviorally characterized with elevated plus maze, open field, and cue-reactivity. It was hypothesized vulnerable rats would exhibit both enhanced anxiety-like behaviors and ethanol consumption compared to resilient and control rats. Open field time in center and elevated plus maze number of open arm entries after traumatic-stress were the most predictive of subsequent ethanol consumption. Using a machine learning, individual rats were identified as vulnerable, resilient, or neither based on their open field time in center and elevated plus maze number of open arm entries with 75% accuracy ($P < .00001$). Vulnerable rats had increased anxiety-like behaviors on open field time in center ($P < .0001$), elevated plus maze number of open arm entries ($P < .0001$), and consumed significantly more ethanol compared to resilient rats ($P = .0018$). Overall, these data indicate behavior after traumatic-stress exposure predicts subsequent ethanol consumption. Future studies will use behavioral scores predicting ethanol consumption to investigate neurochemical alterations leading to enhanced ethanol consumption. [supported by R03 DA044483 EMU, T32 DA007237 EMU/RRD, P30 DA013429 EMU]

Disclosures: R.R. Denny: None. **E.M. Unterwald:** None.

Poster

780. Post-Traumatic Stress Disorder: Preclinical Models

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 780.24/Y21

Topic: G.06. Post-traumatic Stress Disorder

Support: NIMH R21MH115370-01

Title: The adult consequences of trauma exposure are dependent upon developmental period and sex

Authors: *G. I. ELMER[1], C. L. MAYO[1], D. B. BELL[1], J. D. TAPOCIK[2], P. D. SHEPARD[1]; [1]Maryland Psychiatric Res. Ctr., Univ. of Maryland, Baltimore, Baltimore, MD; [2]NIAAA, NIH, Bethesda, DC

Abstract: Childhood trauma dramatically increases the risk of adult psychiatric illness and significantly alters symptom complexity and treatment outcome - it is a pervasive theme in mental illness. Stress can differentially impact CNS function depending upon the type of stressor (psychic, physical, physiological), its relevance to the rodent and controllability. In addition, differences in the neurodevelopmental timing and sex likely impacts the neurobiological and behavioral outcomes. The purpose of this study was to explore the consequences of live-predator trauma during different neurodevelopmental periods in male and female rats.

We have developed a live predator paradigm (snake) with the proposition that a highly salient, ethologically-relevant trauma will engage the nervous system in a manner relevant to studies of psychiatric disorders. The paradigm directly exposes the subject in close contact with the snake yet prevents physical harm. Male and female Wistar rats were exposed to a snake (rat, corn, small python; all 60-100cm long) for 10 min by placing rats in a perforated restrainer tube within a larger arena that holds the live snake. Rats were exposed to live predator (or left in home cage as control) in one of four conditions: A) post-natal days (PND) 31, 45 and 61, B) PND 31, 33, and 36, C) PND 45 and 61, D) PND 61. Since we have no *a priori* reason to suspect specific behavioral consequences for each constellation of trauma exposures we characterized a range of behavioral endpoints in a standardized test battery. The tests include exploratory behavior, sucrose preference, elevated plus maze, t-maze reaction, novelty suppressed feeding, cold pain and learned helplessness (n = 6-12 per condition and sex). Subjects were run at PND 75 in order to assess enduring effects.

The consequences of live-predator exposure were dependent upon the timing during the neurodevelopmental period and sex of the subject. In general, early trauma, conditions A and B versus C and D, had a greater impact as characterized by the number of behavioral endpoints affected (e.g. exploratory behavior, novelty suppressed feeding, learned helplessness). For some behavioral endpoints, a sex X trauma (control vs snake) interaction was observed wherein

opposite effects of the predator exposure were seen. Further investigation is required to identify differences in the neurobiological consequences of trauma exposure at different time frames, the influence of the subject's sex on these variables and the differences between resilient and susceptible subjects. Understanding these differences will help to identify causal factors and potential biomarkers for psychiatric illness.

Disclosures: G.I. Elmer: None. **C.L. Mayo:** None. **D.B. Bell:** None. **P.D. Shepard:** None. **J.D. Tapocik:** None.

Poster

780. Post-Traumatic Stress Disorder: Preclinical Models

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 780.25/Y22

Topic: G.06. Post-traumatic Stress Disorder

Support: CAPES
CNPq
FAPESP 2017/19731-6

Title: Cannabidiol reverses stress-induced impairment of conditioned fear in rats: Involvement of serotonergic, cannabinoid and nitrergic systems

Authors: *S. F. LISBOA[1,2], C. VILA-VERDE[3], D. L. ULIANA[4], L. B. RESSTEL[5], F. S. G. GUIMARAES[3];
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Abstract: Aims: To test if cannabidiol (CBD), a non-psychotomimetic component of *Cannabis sativa with anxiolytic properties,* could prevent the changes in fear processing induced by severe stress. We also investigated possible mechanisms of this effect. Methods: Male Wistar rats were exposed to single prolonged stress (SPS), a model of PTSD. Fear sensitization and impaired extinction of conditioned fear were evaluated one week later. Starting 2-h after SPS, the animals were treated daily with vehicle, paroxetine (5-20mg/kg) or CBD (2.5-10mg/kg) for 7 days. In a second experiment, a 5-HT_{1A} (WAY100635, 0.3 mg/kg) or CB_1 (AM281, 0.5mg/kg)-receptor antagonist was administered 30 minutes before CBD (5 mg/kg). Twenty-four-h after the last drug injection, the rats were submitted to the contextual conditioned fear procedure (three random electric footshocks, 0.35mA/2s). Fear sensitization and extinction were assessed in two distinct sessions in the next 48 h. The brain levels of phosphorylated neuronal NO synthase enzyme

(pnNOS) were measured at different time points after stress. Results: SPS induced fear sensitization (increased freezing in the first context re-exposure) and impaired fear extinction ($p<0.05$). Paroxetine (10mg/kg) and CBD (5 and 10mg/kg) attenuated these effects. CBD effects were abolished by pre-treatment with WAY100635 or AM281. Increased pnNOS expression in the ventral hippocampus was observed 1h after SPS ($p<0.05$), but not later. Conclusions: CBD attenuates stress-induced impairment in fear processing by facilitating 5-HT_{1A} and CB_1-mediated neurotransmission. Moreover, the stress-induced changes in behavioral responses were associated with early modifications in the nitrergic system. Financial support: FAPESP, CNPq

Disclosures: S.F. Lisboa: None. **C. Vila-Verde:** None. **D.L. Uliana:** None. **L.B. Resstel:** None. **F.S.G. Guimaraes:** None.

Poster

780. Post-Traumatic Stress Disorder: Preclinical Models

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 780.26/Y23

Topic: G.06. Post-traumatic Stress Disorder

Support: 1I01BX003890-01
NSF1258111

Title: Post-traumatic stress disorder (PTSD)-like phenotype in female rats

Authors: K. ALEXANDER[1], R. NALLOOR[2], K. BUNTING[2], *A. I. V. VAZDARJANOVA[3,1]; [1]Pharm&Tox, [2]Augusta Univ., Augusta, GA; [3]Charlie Norwood VA Med. Ctr., Augusta, GA

Abstract: Post-Traumatic Stress Disorder (PTSD) is associated with cognitive deficits in humans as well as in rodent models of PTSD using emotional trauma. Our lab has developed a predictive model of PTSD, the Revealing Individual Susceptibility to PTSD-like Phenotype (RISP) model, in which rats are classified as Susceptible, Resilient or Intermediate based on their pre-trauma startle and anxiety-like behavior. We have shown that impairments in learning and memory exist in Susceptible rats prior to trauma and are associated with developing a PTSD-like phenotype after exposure to trauma. However, this model was developed in male rats and the same parameters are not predictive of PTSD-like phenotype in female rats as they do not consistently show the same fear responses as male rats, i.e. freezing. While the literature reports many differences in males and females in terms of fear and stress response, there is no PTSD-phenotype that can be used to study PTSD pre-clinically. Thus, we explored other measures of fear behavior in female rats and found that avoidance, instead of freezing, is a reliable measure of fear behavior and along with increased acoustic startle response and increased anxiety-like behavior can be characterized as a PTSD-like phenotype in female rats.

Disclosures: **K. Alexander:** None. **R. Nalloor:** None. **K. Bunting:** None. **A.I.V. Vazdarjanova:** None.

Poster

780. Post-Traumatic Stress Disorder: Preclinical Models

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 780.27/Y24

Topic: G.06. Post-traumatic Stress Disorder

Support: Whitehall Foundation

Title: Sex differences in fear conditioned-induced alternative splicing events in mouse hippocampus

Authors: *S. I. LOMBROSO, S.-J. XU, E. A. HELLER;
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Abstract: Posttraumatic stress disorder (PTSD) is characterized by persistent disturbing thoughts and symptoms related to a traumatic experience (APA, 2018). It is estimated that one in 11 adults will be diagnosed with PTSD in their lifetime (DSM-5, 2013). While many people experience traumatic events, only a small subpopulation develop PTSD (Puhan et al., 2017). This, along with twin studies, has supported the hypothesis that there are heritable components of PTSD (Taylor et al., 2010). Furthermore, it has recently been shown that females present with PTSD nearly twice as often as males (Tolin & Foa, 2006). Yet, little is known about mechanisms underlying sex-differences of prevalence and presentation of PTSD. Fear conditioning is frequently used as a model of inducible PTSD (Puhan et al., 2017a). While this paradigm does not recapitulate all aspects of PTSD, it does model aberrant fear-memory behavior (Lubin, Roth, & Sweatt, 2008; Peixoto et al., 2015) and . can be used to measure sex-specific behavioral and transcriptional effects of fear-memory (Sase et al., 2019). In this study we examine the effect of fear conditioning on alternative splicing in both male and female hippocampus. We hypothesize that sex-differences in alternative splicing may underlie differences in fear-memory. First, we analyzed global transcriptome data (Poplawski et al., 2016) from hippocampus of 8-week old, male C57BL/6J mice following fear conditioning using Modeling Alternative Junction Inclusion Quantification (MAJIQ). We identified 770 alternatively spliced junction sites in fear conditioned animals relative to their home cage controls. Using PCR, we validated a subset of these loci in an independent cohort including splice sites within Il1rap, clk1, and cpsf4. We quantified the isoform inclusion ratio at these genes and found that the splice profiles were significantly different across sex after fear conditioning. These data suggest that splice isoform ratio modulates freezing behavior in a sex-specific manner.

Disclosures: **S.I. Lombroso:** None. **E.A. Heller:** None. **S. Xu:** None.

Poster

780. Post-Traumatic Stress Disorder: Preclinical Models

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 780.28/Y25

Topic: G.06. Post-traumatic Stress Disorder

Title: Suvorexant reverses stress induced psychosis-like behavior in a rodent model of PTSD

Authors: *H. ELAM, J. DONEGAN, A. BOLEY, D. LODGE;
Pharmacol., UT Hlth. San Antonio, San Antonio, TX

Abstract: Post-traumatic stress disorder (PTSD) is a prevalent condition within the United States veteran population. Not only are approximately 20% of veterans affected by this debilitating condition but 80% of these individuals have comorbid psychiatric illness, including psychosis. A large body of literature has demonstrated a positive correlation between symptoms of psychosis and increases in dopamine neuron activity. Previous data from our lab has demonstrated potential circuits that regulate dopamine neuron activity and mediate psychosis, including projections from the paraventricular nucleus of the thalamus (PVT). Specifically, we have shown that inactivating the PVT leads to a reversal in aberrant dopamine system function. The PVT receives strong innervations from orexin/hypocretin containing neurons, making these neurons a novel target for pharmacological interventions in the treatment of PTSD and comorbid psychosis. Antagonizing these neurons may be a novel approach to reduce PVT activity and subsequently reduce dopamine neuron activity. Using the FDA-approved, orexin receptor antagonist, Suvorexant, we examine changes in psychosis-like behavior in a rodent model of PTSD. In this study, we model PTSD in male rats, using a two-day, inescapable foot shock procedure, to induce psychosis-like behavior. Following inescapable shock, administration of Suvorexant was found to reverse deficits in multiple behavioral correlates of psychosis, including pre-pulse inhibition of startle (PPI), latent inhibition (LI), and MK-801 induced locomotor response. These results suggest that Suvorexant may be a novel pharmacological intervention in the treatment of PTSD and comorbid psychosis.

Disclosures: **H. Elam:** None. **J. Donegan:** None. **A. Boley:** None. **D. Lodge:** None.

Poster

780. Post-Traumatic Stress Disorder: Preclinical Models

Location: Hall A

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Topic: G.06. Post-traumatic Stress Disorder

Support: NIH Grant R01NS085200
NIH Grant R01MH098003
NIH Grant RF1MH114224

Title: Modeling gender difference in PTSD with female rats

Authors: *Q. LI, D. DOPFEL, N. ZHANG;
Penn State Univ., State College, PA

Abstract: PTSD (Posttraumatic stress disorder) is a psychiatric disorder which affects about 3.5% of all adults in U.S. Evidence shows women are twice as likely as men suffering this disease. Thus, one of the risk factors of PTSD is gender. Nowadays, most animal models of PTSD are based on males while studies on females are underexplored. Here we studied the predator scent model of PTSD in female rats and examine the sex difference in the model. Fox urine exposure is used to induce PTSD in female rats. Behavior tests, including elevated zero maze (EZM), black-white box, startle response, novel social and novel physical tests, were conducted before and 7 days after fox urine exposure. The fear conditioning and fear extinction paradigms were also used. The results showed an opposite effect of fox urine exposure on anxiety between female and male rats. Future work will focus on imaging functional connectivity between stress related brain regions using fMRI.

Disclosures: Q. Li: None. **D. Dopfel:** None. **N. Zhang:** None.

Poster

781. Nicotine, Mechanisms of Dependence, and Reward

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 781.01/Y27

Topic: G.08. Drugs of Abuse and Addiction

Title: Delivery of vaporized nicotine: Effects of gender, dose, and weekly nicotine exposures on behavioral and physiological measures

Authors: *C. MARSTON[1], S. C. HONEYCUTT[2], P. I. GARRETT[2], T. M. HILLHOUSE[2]; [1]Psychology & Neurosci., Weber State Universtiy, Ogden, UT; [2]Psychology & Neurosci., Weber State Univ., Ogden, UT

Abstract: Over the last decade, usage of electronic nicotine delivery systems (ENDS), has seen a substantial increase with approximately 15.4% of the American adults had tried ENDS products and that 3.8% of adults (5.5 million people) were regular users. Moreover, approximately 20.8% of all teenagers (middle school and high school) reported regular ENDS use. Unlike combustible cigarettes, ENDS provides a discretionary amount of nicotine to the user that has made establishing a clear relationship between the amount of vaporized nicotine ingested and behavioral changes difficult to measure. The present study sought to understand how vaporized nicotine dose and number of nicotine exposures per week would differentially impact behavioral and physiological changes between male and female mice. An e-Vape^{TM} system was used to administer vaporized nicotine in which a three second puff was delivered every two mins for 10 mins (6 puffs total). Body temperature was measured before and after administration of vaporized nicotine. Immediately after nicotine administration mice were placed in a standard open field arena and locomotor activity was measured for 20 mins. Overall, we found effects of gender and nicotine exposure. Specifically, male mice with once a week exposure to nicotine had significantly less distance traveled at all doses and significantly less time spent in the center of the open field at 3.0 and 10 mg/ml vaporized nicotine as compared male mice with twice a week exposure. Additionally, once a week exposure significant increased body temperature in male mice at 1.0, 3.0, and 30.0 mg/ml nicotine doses. There was not a significant effect in distance traveled for female mice; however, female mice with once a week exposure to nicotine had significantly more time spent in the center of the open field at 30 mg/ml of vaporized nicotine. Overall, vaporized nicotine dose-dependently increase body temperature in female mice. These results indicated dissociable behavioral and physiological effects following administration of vaporized nicotine in mice that vary based on gender, nicotine exposure per week, and nicotine dose.

Disclosures: C. Marston: None. **S.C. Honeycutt:** None. **P.I. Garrett:** None. **T.M. Hillhouse:** None.

Poster

781. Nicotine, Mechanisms of Dependence, and Reward

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 781.02/Y28

Topic: G.08. Drugs of Abuse and Addiction

Title: Repeated vaporized nicotine administration induces behavioral sensitization in C57BL/6 mice

Authors: *S. C. HONEYCUTT, P. I. GARRETT, A. G. BARRAZA, A. N. MALOY, T. M. HILLHOUSE;
Psychology & Neurosci., Weber State Univ., Ogden, UT

Abstract: Nicotine administration via tobacco products (e.g. cigarettes, chew tobacco, etc.) has been well established as a drug of abuse. Preclinical experiments have used various methods of administration to evaluate the abuse-related and behavioral effects of nicotine (e.g. intravenous, injection, smoke-inhalation); however, there are limited data on the abuse-related effects of vaporized nicotine in rodents. The present study sought to evaluate the abuse-related effects of vaporized nicotine in male and female mice using a behavioral model of nicotine sensitization. Mice were habituated to locomotor activity chambers for three days. Following habituation, mice were administered with nicotine (0.5 mg/kg, i.p.) or vaporized nicotine (0-10.0 mg/ml) for five consecutive days and locomotor activity was measures for 30 mins each day immediately after nicotine administration. An e-Vape^{TM} system was used to administer vaporized nicotine in which a three second puff was delivered every two mins for 10 mins (6 puffs total). A nicotine challenge test was conducted following a seven day withdrawal period. Additionally, body temperature was assessed each day. The positive control 0.5 mg/kg nicotine (i.p.) produced sensitization by significantly increase locomotor activity on days 3-5. Vaporized nicotine produced a dose-dependent (0-3.0 mg/ml) sensitization effect with the most significant sensitization found at 3.0 mg/ml. Treatment with 3.0 mg/ml vaporized nicotine decreased body temperatures on days 2 and 4 for male mice, but has no significant effect on female mice. Treatment with 1.0 mg/ml vaporized nicotine produced sensitization and significantly lower average body temperatures on day 1 for both genders. Treatment with 10.0 mg/ml vaporized nicotine and vehicle vapor (0.0 mg/mL nicotine) had no effect of sensitization or body temperature changes. No significant gender effects were found on behavioral sensitization for injected or vaporized nicotine. Treatment with 0.5 mg/kg (i.p.) and 3.0 mg/ml vaporize nicotine produce a significant increase in locomotor activity on the nicotine challenge day, while the other doses failed to alter locomotor activity on the challenge day. These results suggest that vaporized nicotine produces abuse-related effects in an inverted U-shaped curve for male and female mice that is similar to other routes of nicotine administration. Additionally, the nicotine doses and administration regimen use in the present study provides a foundation for future studies to evaluate the abuse-related, behavioral, and health risk effects of vaporized nicotine.

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Poster

781. Nicotine, Mechanisms of Dependence, and Reward

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 781.03/Y29

Topic: G.08. Drugs of Abuse and Addiction

Title: Effects of nicotine enhanced incentive stimuli on dopamine release in the nucleus accumbens shell and cocaine demand in rats

Authors: *C. T. MAJORS[1], D. HARRYMAN[2], C. E. PONDER-CEPEDA[3], C. A. BRADLEY[5], A. L. SMITH[4], G. A. DEEHAN, JR[2], M. I. PALMATIER[1];
[2]Psychology, [3]Exptl. Psychology, [1]East Tennessee State Univ., Johnson City, TN; [4]Biol., East Tennessee State Univ., Elizabethton, TN; [5]Psychology, Bridgewater Col., Bridgewater, VA

Abstract: Nicotine is one of the most widely used drugs, and experimentation with nicotine typically precedes other drugs of abuse. We have previously shown that nicotine increases responding for primary reinforcers and produces long-lasting changes in the salience of environmental cues that predict reward (incentives). We have hypothesized that these incentive amplifying effects of nicotine increase the release of mesolimbic dopamine (DA) evoked by incentives. The goal of the present studies was to test the hypothesis that nicotine increases incentive-evoked DA release in the nucleus accumbens (NAc) and that nicotine-enhanced incentives promote behaviors that depend on mesolimbic DA release (cocaine self-administration). To investigate these hypotheses, rats were randomly assigned to one of two groups NIC (0.4 mg/kg base) or SAL (placebo), n=15/group. Each group received a subcutaneous injection of their assigned solutions 15 min before Pavlovian conditioned approach (PCA) testing. In each 1-hour PCA session rats received pairings between a conditioned stimulus (CS; lever extension and cue light illumination) and presentation of an unconditioned stimulus (US; 0.1 ml of 20% sucrose). Following 19 PCA acquisition sessions, rats were separated into two experiments. In Experiment 1, rats were instrumented for IV cocaine self-administration and, after learning to respond at the PCA lever for cocaine infusions (0.16 mg/infusion) were subjected to a within-session economic demand manipulation in which cocaine price was increased by systematically reducing infusion duration and thereby cocaine dose. In Experiment 2, rats were instrumented with an intracranial canula targeting the NAc shell for DA microdialysis and were subsequently tested with 3 exposures to the CS after nicotine or placebo injection. Rats pretreated with nicotine during the PCA sessions exhibited greater sign tracking behavior (approach to the CS) relative to saline pretreated rats which exhibited a bias toward approaching the US location (goal tracking). In Experiment 1, there was increased demand for cocaine when it was self-administered with a NIC-enhanced incentive (NIC group), relative to a non-NIC-enhanced incentive (e.g., SAL group). Dopamine samples are being analyzed from Experiment 2; however, preliminary evidence suggests that nicotine pretreated rats will have elevated levels compared to controls. These results indicate that nicotine has potent and long-lasting effects on incentive stimuli and increases mesolimbic DA release evoked by these stimuli in the NAc. The long-lasting nature of this effect may have implications for nicotine as a gateway drug.

Disclosures: C.T. Majors: None. **D. Harryman:** None. **C.E. Ponder-Cepeda:** None. **C.A. Bradley:** None. **M.I. Palmatier:** None. **A.L. Smith:** None. **G.A. Deehan:** None.

Poster

781. Nicotine, Mechanisms of Dependence, and Reward

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 781.04/Y30

Topic: G.08. Drugs of Abuse and Addiction

Title: Concurrent infusion of lithium chloride reduces nicotine self-administration in rats

Authors: D. C. HARRYMAN[1], C. E. PONDER-CEPEDA[1], C. T. MAJORS[1], A. L. SMITH[2], *M. I. P. PALMATIER[1];
[1]East Tennessee State Univ., Johnson City, TN; [2]Biol., East Tennessee State Univ., Elizabethton, TN

Abstract: Nicotine is considered the most addictive drug in the world and the negative health consequences of self-administering nicotine in tobacco contribute to almost 500,000 deaths annually. While smoking cessation aides remain an important avenue for improving public health, currently there are few cessation aides that are effective at promoting abstinence rates above 20% beyond 12 months after quitting. However, an alternative cessation strategy may be 'counterconditioning' in which the chemosensory stimuli associated with smoking are given negative visceral meaning via aversion conditioning. Activation of the chemoreceptor trigger zone (CTZ) has been shown to reduce responding for gustatory cues (conditioned taste aversion) and rewarding stimuli (sucrose). Activating this system in conjunction with nicotine self-administration may reduce responding for nicotine and promote 'disgust' reactions to tobacco flavors and additives. In order to test this hypothesis 13 Sprague-Dawley rats were instrumented for both intravenous nicotine and subcutaneous lithium chloride (LiCl) self-administration. Following recovery, rats were allowed to self-administer nicotine in one of two ways. For the gustatory group (GUST, n=10) two sipper tubes connected to lickometers and solenoid valves were available. Meeting the schedule of reinforcement on the active sipper tube resulted in delivery of blueberry flavored solution (0.25% v/v) orally and intravenous (IV) nicotine (15 ug/kg/infusion). After stable responding for nicotine was observed, rats began the counterconditioning phase in which LiCl (0.3 mEq/kg) were infused subcutaneously (sc) with each IV nicotine infusion and blueberry flavor presentation. After responding stabilized, sc LiCl was replaced with sc saline (0.9% w/v). For the lever group (LEV, n=3) similar procedures were used but no oral/flavor reinforcer was presented and nicotine was self-administered for meeting the schedule of reinforcement at a lever rather than sipper tube. For both groups, nicotine was self-administered at comparable rates by the end of acquisition. Both LEV and GUST groups earned similar numbers of nicotine infusions on each test session. Infusions of LiCl with nicotine robustly reduced responses and reinforcers earned in both LEV and GUST groups. Further, replacing LiCl with saline resulted in re-acquisition of nicotine self-administration. Reacquisition rates did not differ between the LEV and GUST groups. Activation of the CTZ robustly and

reliably reduced nicotine self-administration. Our findings do not suggest that this approach produces a long-term effect on gustatory cues associated with nicotine.

Disclosures: D.C. Harryman: None. **C.E. Ponder-Cepeda:** None. **C.T. Majors:** None. **A.L. Smith:** None. **M.I.P. Palmatier:** None.

Poster

781. Nicotine, Mechanisms of Dependence, and Reward

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 781.05/Y31

Topic: G.08. Drugs of Abuse and Addiction

Title: Concurrent self-administration of nicotine and alcohol in an operant lick model

Authors: M. I. PALMATIER, **M. M. KOSKY**, D. HARRYMAN, C. T. MAJORS, C. A. BRADLEY, *G. A. DEEHAN, JR;
Psychology, East Tennessee State Univ., Johnson City, TN

Abstract: Nicotine (NIC) and alcohol (ETOH) are widely co-used and people with alcohol use disorders (AUDs) smoke tobacco at higher rates than in the general population. In preclinical studies, NIC injections enhance ETOH drinking and increase responding for non-drug rewards (e.g., sucrose). However, in preclinical models of co-use, concurrent access to self-administered NIC and ETOH moderately reduces operant responding for each reinforcer, compared to groups responding for one or the other. This finding is at odds with human co-use, but fits the prediction of operant concurrent choice models (e.g., matching law). Previous studies have not modeled changes in demand that may drive increases in responding over time. We predicted that the reinforcement enhancing effects of NIC represent an increase in reinforcer demand and would promote ETOH consumption as the price of ETOH increased. Alcohol preferring (P) rats were instrumented for IV self-administration and assigned to one of three groups (NIC, ETOH, or NIC+ETOH). During testing, each rat had access to two sipper tubes attached to a lickometer and fluid delivery solenoid. For ETOH and NIC+ETOH rats, meeting the schedule of reinforcement at the ETOH sipper tube resulted in delivery of 0.1 ml of ETOH (15%, v/v) into the sipper tube; for NIC rats meeting the schedule of reinforcement at this sipper tube resulted in delivery of tap water. For NIC and NIC+ETOH rats, meeting the schedule of reinforcement on the alternative sipper tube resulted in delivery of an intravenous (IV) NIC infusion (7.5 ug/kg/infusion) and 0.1 ml of a neutral flavored solution (e.g., 0.25% blueberry extract) delivered orally into the sipper tube. For ETOH rats, meeting the schedule of reinforcement on this sipper tube resulted in oral tap water. After stable responding was observed, the price of NIC was increased from a fixed ratio of 2 (FR2) to FR15, with at least 3 days of testing at each price. In a subsequent experiment, a higher dose of NIC was used (15 ug/kg/infusion) and the price of ETOH was increased from FR2 to FR15. Non-linear regression was used to estimate economic

demand parameters (essential value and elasticity) of NIC or ETOH as the price of each reinforcer increased. Preliminary evidence suggests that concurrent access to NIC significantly increases demand for oral ETOH, relative to rats responding for ETOH alone. Surprisingly, concurrent access to ETOH also significantly increased demand for NIC relative to rats responding for NIC alone. Neither ETOH nor NIC changed the essential value of the alternative. Thus, the effects of ETOH and NIC appear to mutually enhance demand for one-another when both are concurrently available.

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Poster

781. Nicotine, Mechanisms of Dependence, and Reward

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 781.06/Y32

Topic: G.08. Drugs of Abuse and Addiction

Support: Howard University Bridge Fund Pilot Study Awards Program.
Charles and Mary Latham Fund
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Title: Metabolic changes in mice nucleus accumbens following acute IP injection of menthol

Authors: *O. DEHKORDI[1], P. WANG[2], S. LIN[2], R. M. MILLIS[4], M. I. DÁVILA-GARCÍA[3]; [1]Neurol., [2]Radiology, [3]Pharmacol., Howard Univ., Washington, DC; [4]Med., American Univ. of Antigua, Coolidge, Antigua and Barbuda

Abstract: Menthol, a commonly used flavoring additive in cigarettes, has been found to facilitate smoke initiation and nicotine addiction. Much work has been carried out to study how menthol affects gene expression and functional changes of nicotinic acetylcholine receptors (nAChRs) in the reward-addiction pathways. However biochemical and metabolomics consequences of menthol interaction with nAChRs and other receptors in the immediate milieu of ventral tegmental area and nucleus accumbens (NAcc) is not known. In the present study, we applied in-vivo ^{1}H NMR spectroscopy-based metabonomic approach to investigate the changes of cerebral metabolites in the NAcc of mice subjected to acute IP injection of menthol (100mg/kg). The data were obtained using a 9.4T Bruker AVANCE 89mm bore NMR machine and the localized ^{1}H spectra were obtained and processed by LCModel software. The region of interest (ROI) size for NAcc was 3.0×1.0×1.0 mm^3 and extended from 0.85 mm to 1.93 mm relative to bregma. The concentrations of neurometabolites were analyzed with respect to the summed concentration of creatine and phosphocreatine (Cr+PCr) and the results with a standard deviation (Cramér-Rao lower bound) of < 20% were considered acceptable for inclusion in the

statistical analysis. Multiple neurotransmitters and/or their metabolites were detected in NAcc including glutamate (Glu), glutamine (Gln) inositol, taurine, choline, Cr, PCr, and N-acetyl aspartate. Our results showed that menthol induced a significant decrease in the Glu/Cr+PCr and the Glu+Gln/Cr+PCr ratio in the NAcc compared to control ($p < 0.05$). Glutamatergic signals in NAcc are known to play an important role in addiction-related behaviors. It remains to be determined if menthol-induced disturbances in glutamatergic transmission contributes to enhanced nicotine addiction in mentholated cigarettes.

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Poster

781. Nicotine, Mechanisms of Dependence, and Reward

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 781.07/Y33

Topic: G.08. Drugs of Abuse and Addiction

Support: Acadia Pharmaceuticals grant to Univ. Houston-Clear Lake

Title: Inverse agonists of the 5-HT2a receptor reduce nicotine withdrawal signs in rats

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Abstract: Previous research has shown that chronic nicotine administration causes adaptive changes in 5-HT2A receptor expression. Based on this relationship, it was hypothesized that inactivating 5-HT2A receptors with the inverse agonists pimavanserin and volinanserin (MDL100907), would reduce the behavioral signs of nicotine withdrawal syndrome. Sprague-Dawley rats were rendered nicotine-dependent by subcutaneous infusion of nicotine bitartrate, 9 mg/kg/day for seven days. The infusions were then terminated, and 22 hours later, rats were observed under “blind” conditions for somatically expressed behavioral nicotine withdrawal signs. One hour before observations, the morphine dependent rats were injected i.p. with saline alone, or either 0.3 or 1.0 mg/kg pimavanserin in saline. Total withdrawal signs were reduced in a dose-dependent manner. A one-way ANOVA (total withdrawal signs as a function of dose) was highly significant, as was the descending linear trend of withdrawal signs as a function of dose. The 1.0 mg/kg dose reduced withdrawal signs nearly to the level exhibited by a comparison group of non-dependent rats injected with saline. A second experiment was conducted in a similar manner, which showed that that volinanserin at 1.0 mg/kg but not 0.25

mg/kg also reduced nicotine withdrawal signs to nearly the level of non-dependent rats. *In vitro* experiments demonstrated that both pimavanserin and volinanserin potently antagonize 5-HT2A receptors, with approximately 25-fold, and 300-fold selectivity over 5-HT2C receptors, respectively. The results suggest that 5-HT2A receptor activity contributes to nicotine withdrawal syndrome, and thus represents a promising target for interventions to aid smoking cessation.

Disclosures: **D.H. Malin:** 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. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Acadia Pharmaceuticals. **M. Henceroth:** None. **S. Gadam:** None. **J.R. Campbell:** None. **J. Ma:** A. Employment/Salary (full or part-time):; Acadia Pharmaceuticals Inc. **P. Tsai:** None. **J.C. Kishbaugh:** None. **E.S. Burstein:** A. Employment/Salary (full or part-time):; Acadia Pharmaceuticals Inc.

Poster

781. Nicotine, Mechanisms of Dependence, and Reward

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 781.08/Y34

Topic: G.08. Drugs of Abuse and Addiction

Support: CA TRDRP 27FT-0022
CA TRDRP 27IP-0057
NIH GM-123582
NIH DA043829

Title: Genetically encoded biosensors for nicotinic ligands

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Abstract: Nicotinic agonists play important role in studying addiction, withdrawal, neuroprotection, cognitive behavior, and neural pharmacology. Previous work with nicotine showed that, in addition to undoubted actions on the plasma membrane such as receptor activation and desensitization, pharmacological chaperoning by nicotine, and probably by other agonists, begins intracellularly in organelles such as the endoplasmic reticulum (ER). Previous work also showed that nicotine and varenicline enter the ER. We now report genetically encoded fluorescent biosensors for related nicotinic agonists cytisine, dianicline, and 5-Iodo-A-85380,

which allow comparisons among subcellular pharmacokinetics of nicotinic drugs.
Our sensors utilize OpuBC, a monomeric bacterial periplasmic binding protein (PBP), which contains (a) a binding site for amines including a cation-π box, and (b) ligand-induced "Venus flytrap" conformational change invoked by binding of target ligand. We inserted circularly permuted "superfolder" GFP (cpGFP), flanked by several-residue linkers, within inter-domain hinge regions and applied directed evolution, including X-ray crystallography, to optimize sensing for each drug of interest.
Our iDrugSnFRs ("**i**ntensity-based **Drug**-**S**e**n**sing **F**luorescent **R**eporters") can detect their drug partner with responses of $\Delta F/F0 > 1$ at 1 μM. Using targeting and retention sequences we direct the constructs to the ER or to the PM of clonal mammalian lines and cultured neurons. Live-cell video imaging shows that the kinetics of ER entry/exit differ amongst these nicotinic drugs by > 10-fold.
These differences provide additional insights into aspects of nicotinic agonists, pharmacokinetics, organellar sequestration of drugs by acid trapping, protein trafficking and upregulation—all crucial facets in the expanded understanding of "inside-out" neuropharmacology of neural drugs.
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Poster

781. Nicotine, Mechanisms of Dependence, and Reward

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 781.09/Y35

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant DA040777

Title: Role of trace-amine-associated receptor 1 in nicotine withdrawal

Authors: *R. WU, J. LIU, B. N. JOHNSON, J.-X. LI;
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Abstract: Smoking tobacco is a public health burden globally. Nicotine is one of the most addictive components in tobacco. However, it remains a major challenge to develop more efficacious therapies for nicotine addiction. Trace-amine-associated receptor 1 (TAAR1) has emerged as a target for the modulation of dopaminergic activity. We recently found that TAAR1 activation decreased nicotine-induced dopamine release in NAc and attenuated nicotine self-

administration and reinstatement of nicotine-seeking. Nicotine withdrawal-associated negative reinforcement also contributes to development of nicotine addiction. In the present study, we aimed to study the role of TAAR1 in nicotine's withdrawal effects. Rats were divided into three groups: saline, short-access nicotine (ShA, 1h/d) and long-access (LA, 21h/d) nicotine (0.03mg/kg/infusion). After one week acquisition of nicotine self-administration, the training session of LA group was increased to 21 hours per day, while the ShA group maintained with 1 hour per day. We assessed nicotine withdrawal-induced withdrawal signs, anxiety-like behaviors and hyperalgesia. We showed that the LA group of rats developed significant mecamylamine-precipitated withdrawal signs, spent less time in open arms of the elevated plus maze, and hyperalgesia in the Von Frey test. We found that selective TAAR1 agonist RO5263397 attenuated mecamylamine-precipitated withdrawal signs, anxiety-like behavior, and hyperalgesia in nicotine withdrawal rats. Taken together, our results indicated that activation of TAAR1 attenuates nicotine withdrawal, suggesting that TAAR1 is a promising target for the treatment of nicotine addiction.

Disclosures: R. Wu: None. **J. Liu:** None. **B.N. Johnson:** None. **J. Li:** None.

Poster

781. Nicotine, Mechanisms of Dependence, and Reward

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 781.10/Y36

Topic: G.08. Drugs of Abuse and Addiction

Support: Fondation pour la recherche médicale FRM FDT201904008060
Medisite Foundation for Neuroscience
French National Cancer Institute Grant TABAC-16–022

Title: Nicotinic acetylcholine receptors in the interpeduncular nucleus regulate nicotine consumption

Authors: *S. MONDOLONI[1], C. NGUYEN[1], R. DURAND DE-CUTTOLI[1], N. TORQUET[1], F. MARTI[1], S. TOLU[1], S. PONS[2], U. MASKOS[2], P. FAURE[1], A. MOUROT[1];
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Abstract: Nicotine, the main addictive component of tobacco, targets brain nicotinic acetylcholine receptors (nAChRs), which are pentameric ligand-gated cation channels. In the brain, nAChR subunits of the α (α2-10) and β (β2-4) subtypes co-assemble to form a high combinatorial diversity of receptors with distinct properties, localizations and functions [1]. Chronic nicotine consumption modifies the activity and expression levels of nAChRs and consequently the activity of various neuronal networks. The habenulo-interpeduncular (mHb-IPN) axis has recently emerged as a central pathway involved in nicotine addiction, and most

notably in nicotine consumption, withdrawal, and aversion [2, 3]. This pathway contains the highest density and diversity of nAChRs in the brain, including rare subunits such as α3 and β4. It is formed by glutamatergic and cholinergic neurons of the mHb that exclusively project to the IPN, a GABAergic nucleus. However, the long-term molecular and cellular adaptations triggered by nicotine in the Hb-IPN axis are unknown, making it difficult to interpret the role of this pathway in nicotine addiction. Here we used a combination of *ex*-and *in-vivo* electrophysiology, genetic tools and behavioral analysis to investigate the role of nAChRs of the IPN in the regulation of nicotine consumption. In a two bottle-choice paradigm, WT mice showed a decrease in nicotine consumption at high doses of nicotine (200 μg/kg), resulting in a titration at around 10 mg/kg/day. In contrast, $\beta4^{-/-}$ mice did not reduce their consumption at high doses, and therefore did not titer. Using patch-clamp recordings, we have shown that both passive (osmotic minipump) and active (two-bottle choice) nicotine treatment decreased the amplitude of nicotinic currents in neurons of the IPN of WT, but not of $\beta4^{-/-}$ mice. We aim to study the effect of nicotine on the spontaneous activity of IPN neurons *in vivo* using juxtacellular recordings. Altogether, our results suggest that β4-nAChRs of the IPN are key players in the regulation of nicotine consumption. To causally link nicotine consumption with β4-nAChRs, we now aim at manipulating nicotine consumption using house-developed, light-controllable nAChRs [4]. [1]Taly et al., 2009 [2]Antolin-Fontes et al., 2015 [3] Frahm et al., 2011 [4] Durand-de Cuttoli et al., 2018

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Poster

781. Nicotine, Mechanisms of Dependence, and Reward

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 781.11/Y37

Topic: G.08. Drugs of Abuse and Addiction

Support: BX001271

Title: Repeated nicotine exposure in mice alters spontaneous behavioral activity and synaptic function in the central nucleus of the amygdala

Authors: Q. LI[1], R. C. KLEIN[1], L. WANG[1], ***S. D. MOORE**[1,2];
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Abstract: Repeated exposure to nicotine (NIC) causes persistent changes in both behavior and neuronal circuitry in the brain. The central nucleus of the amygdala (CeA) is involved in nicotine addiction and withdrawal in human and animals but underlying mechanisms are poorly

understood. In this study, we repeatedly exposed male C57bl/6j mice to NIC vapor (24mg/ml dissolved in propylene glycol (PG)) or PG-only vapor for 10 consecutive days. In one cohort of mice (n=16) we used the automated IntelliCage system to measure spontaneous activity including corner visits, nose-pokes and licks before, during, and after NIC exposure (10 days each phase). NIC exposure resulted in a significant increase in lick number and duration compared to pre-NIC exposure. In addition, repeated NIC exposure reduced the number of visits and nose-pokes. In a separate cohort of mice, whole-cell current or voltage clamp recordings from CeA neurons in brain slices were performed 3 days after last exposure to either NIC or PG-only. NIC exposure resulted in a slightly reduced mean input resistance measured during sag and steady-state hyperpolarizations (NIC: IR_{SAG} 139.74 ± 13.25 MΩ, IR_{SS} 125.73 ± 11.21 MΩ (n=16), $ratio_{SAG/SS}$ = 1.11 ± 0.03; PG: IR_{SAG} 160.41 ± 24.23MΩ, IR_{SS} 143.31 ± 17.58 MΩ (n=9) $ratio_{SAG/SS}$ = 1.09 ± 0.03). There was also a significant increase in the mean time constant in NIC mice (NIC: 24.11 ± 3.11ms (n=15); PG: 9.35 ± 1.28ms (n=10), $p<0.05$) as well as a significantly lower firing frequency than PG mice (n=9). In addition, spontaneous $GABA_A$ receptor-mediated fast inhibitory postsynaptic current (sIPSC) frequency was significantly higher in NIC mice than PG mice (NIC: 11.7±1.89Hz (n=12);PG: 6.01 ± 1.49Hz (n=19, $p<0.05$)) while there was no effect on the mean IPSC amplitude. To confirm NIC inhalation, the NIC metabolite cotinine was measured in urine 5 days after last exposure. Cotinine from NIC mice was significantly higher than PG-only mice (NIC: 30.112 ± 4.96ng/ml (n=23 mice) vs PG only 0.383±0.08ng/ml (n=16 mice), $p<0.0000001$). Finally, somatic signs of NIC withdrawal (genital licks, scratches, paw tremor, body tremor and teeth chattering) were manifested by mecamylamine (1mg/kg, i.p) administration 20 hours after the final NIC exposure but absent with saline administration (n=6), suggesting that NIC mice entered a robust withdrawal phase after the cessation of NIC. Taken together, these results indicate that repeated NIC vapor exposure alters spontaneous exploratory and drinking behavior, neuroexcitability and inhibitory synaptic function in the CeA in mice.

Disclosures: S.D. Moore: None. **Q. Li:** None. **R.C. Klein:** None. **L. Wang:** None.

Poster

781. Nicotine, Mechanisms of Dependence, and Reward

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 781.12/Y38

Topic: G.08. Drugs of Abuse and Addiction

Support: the Swedish Brain Foundation
the Swedish Research Council

Title: Modulation of neurotransmission in rodent dorsolateral striatum after acute nicotine exposure *in vitro*

Authors: *O. LAGSTRÖM[1], A. ANDRÉN[1,2], M. E. JOHANSSON[3], B. SÖDERPALM[1,2], M. ERICSON[1], L. ADERMARK[1];
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Abstract: Nicotine is a highly addictive substance and smoking is a leading risk factor for cardiovascular and lung disease, as well as cancer. Nicotine use disorder is acknowledged as a chronic brain disease with a high risk of relapse after cessation, and the available interventions are limited. We have previously shown that nicotine produces long-lasting effects on neurotransmission in rodent dorsolateral striatum (DLS), a key brain region for both motor- and reward systems. DLS is highly involved in several reward-related behaviors and has been linked to the transition from recreational to compulsive/habitual drug use (addiction). How nicotine induces changes in DLS neurotransmission is only partly understood. In this study, we aimed to characterize acute nicotine-induced cellular mechanisms in DLS, that are suggested to drive escalated nicotine intake and compulsive drug-taking behavior. The main method for studying the acute effects of nicotine on neurotransmission was *in vitro* electrophysiological field potential recordings performed on Wistar rats and in-house bred mice with a genetic deletion of the α7 subunit of the nicotinic acetylcholine receptor (nAChR). Our results suggest that nicotine reduces excitatory inputs onto dorsal striatal neurons via a combined action at α7 and α4β2 containing nAChR in Wistar rat. Further supporting this finding, we found that the depressant effect of nicotine remained in α7 knock-out mice, and that the combined inhibition of α7 and α4β2 nAChRs was required to fully block the effect. Selective inhibition of astrocytes using the DREADDs (Designer Receptors Exclusively Activated by Designer Drugs) technology combined with electrophysiology indicated no involvement of astrocytes in mediating the effect by nicotine on DLS neurotransmission. However, ablation of cholinergic interneurons using immunotoxin (anti-ChAT-saporine) partially blocked the depressant effect by nicotine. Moreover, modulation of the muscarinic acetylcholine receptors (mAChR) with either an agonist or an antagonist appeared to inhibit the effect of nicotine. We suggest that activation of nAChRs on cholinergic interneurons increases the release of acetylcholine, which indirectly suppresses glutamate release, thereby decreasing excitatory inputs onto dorsal striatal neurons.

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Poster

781. Nicotine, Mechanisms of Dependence, and Reward

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 781.13/Y39

Topic: G.08. Drugs of Abuse and Addiction

Title: Distinct temporal structure of nicotinic ACh receptor activation determines responses of VTA neurons to endogenous ACh and nicotine

Authors: E. MOROZOVA[1], B. S. GUTKIN[2], C. LAPISH[3], P. FAURE[4], ***A. S. KUZNETSOV**[3];
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Abstract: The addictive component of tobacco, nicotine, acts through nicotinic acetylcholine receptors (nAChRs). The β2 subunit-containing nAChRs (β2-nAChRs) play a crucial role in the rewarding properties of nicotine and are particularly densely expressed in the mesolimbic dopamine (DA) system. Specifically, nAChRs directly and indirectly affect DA neurons in the ventral tegmental area (VTA). Understanding of ACh and nicotinic regulation of DA neuron activity is incomplete. We explain and provide mechanisms for several apparently contradictory experimental results. First, systemic knock out of β2-containing nAChRs drastically reduces DA neurons bursting even though the major glutamatergic (Glu) afferents that have been shown to evoke this bursting stay intact. Second, the most intuitive way to rescue this bursting - by re-expressing the nAChRs on VTA DA neurons - fails. Third, nAChR re-expression on VTA GABA neurons rescues bursting in DA neurons and increases their firing rate under the influence of ACh input, whereas nicotinic application results in the opposite changes in firing. Our model shows that, first, without ACh receptors Glu excitation of VTA DA and GABA neurons remain balanced and cancel each other. Second, re-expression of ACh receptors on DA neurons provides an input that impedes membrane repolarization and is ineffective in restoring firing of DA neurons. Third, the distinct responses to ACh and nicotine are due to distinct temporal patterns of these inputs: pulsatile vs. continuous. Altogether this study highlights how β2-nAChRs influence co-activation of VTA DA and GABA neurons required for motivation and saliency signals carried by DA neuron activity.

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Poster

781. Nicotine, Mechanisms of Dependence, and Reward

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 781.14/Y40

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant DA044760

Title: Positron emission tomography measurements of 2-[^{18}F]FA-85380 binding to nicotinic receptors in female and male mice

Authors: S. MITCHELL[1], H. J. ZHANG[1], M. P. BHUIYAN[1], H.-M. TSAI[1], L. LEONI[1], R. FREIFELDER[1], B. ROMAN[1], C.-M. KAO[1], X. ZHUANG[2], *W. N. GREEN[2], J. MUKHERJEE[3], C.-T. CHEN[1];
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Abstract: Nicotine upregulation is an increase in high-affinity nicotine binding sites in the brain and corresponds with nicotine addiction. High-affinity nicotine binding sites in the brain are largely located on α4β2-type nicotinic acetylcholine receptors (α4β2Rs). We have established a mouse model to study the α4β2R binding kinetics using 2-[^{18}F]-A85380 by PET imaging and discovered gender differences in α4β2R binding kinetics. Among all brain regions, the highest binding kinetics was observed in thalamus and midbrain and the lowest binding in the cerebellum. This is consistent in both genders and ages. This regional difference was eliminated in KO mice, demonstrating the binding specificity of 2-[^{18}F]-A85380 to α4β2 subtype of nAChRs. The α4β2R binding peaks at between 50-60 minutes after the tracer injection in all brain regions regardless gender and age, while maximum binding capacity and dissociation rate showed clear differences between female and male mice. The global brain maximum binding capacity is higher in females than males. Specifically, the averaged maximum binding in females reaches 3.06±0.38% injected dose (ID)/cm^3 tissue compared to 1.85±0.1%ID/cm^3 in the males. The averaged maximum binding was only 1.34%ID/cm^3 in the KO mice. The elevated α4β2 binding remains consistently throughout the entire scan duration with uptake of 2.26±0.13%ID/cm^3 for females, 1.06±0.1%ID/cm^3 for males, and 0.53%ID/cm^3 for KO mice at the end of 3-hour imaging. No significant age differences were observed. The specific α4β2 binding of 2-[^{18}F]-A85380 in a mouse model exhibits significant gender differences, with females showing significantly higher levels of binding. The differences observed between males and females may provide insight into the gender differences of nicotine addiction and help to design gender specific cessation regiments. The gender differences in distribution of the brain α4β2 subtype nicotine receptor in mice is consistent with publications for humans using α4β2 PET radiotracer [^{18}F]Nifene and may therefore be suitable for translational nicotine addiction studies and address gender differences. The elevated binding of 2-[^{18}F]-A85380 also seen in human suggests a higher density of α4β2 subtype receptor in the female brain than the male brain.

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Poster

781. Nicotine, Mechanisms of Dependence, and Reward

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 781.15/Y41

Topic: G.08. Drugs of Abuse and Addiction

Support: TRDRP Award 24RT-0023

Title: The role of endogenous PACAP in nicotine dependence

Authors: *K. LUTFY, S. NEGA, P. MARQUEZ, A. HAMID;
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Abstract: Nicotine dependence is a major public health and socioeconomic issue. However, there is a handful of pharmacotherapies to treat nicotine dependence. This is because the underlying mechanism of nicotine dependence is not fully characterized. In the present study, we determined the role of endogenous pituitary adenylyl cyclase activating polypeptide (PACAP) in nicotine reward and dependence. To this end, we assessed if nicotine-induced conditioned place preference (CPP) would be changed in mice lacking PACAP compared to their wild-type controls. We also examined if mecamylamine-precipitated withdrawal would be altered in the absence of PACAP. To assess the role of PACAP in nicotine reward, male and female mice were tested for baseline preference in the place conditioning paradigm on day 1, then received conditioning with saline/nicotine (1 mg/kg) or nicotine/saline (once a day for 6 days) and then tested for postconditioning place preference. On each test day, mice were placed in the central neutral chamber of the CPP apparatus and allowed to explore the three chambers for 15 min. The amount of time that mice spent in each conditioning chamber was recorded. To determine the role of PACAP in nicotine dependence, mice received 2 more conditioning with each treatment and were then tested for affective signs of nicotine precipitated withdrawal 4 days after the last conditioning. On the test day, mice were injected with mecamylamine (3 mg/kg) and tested for anxiety-like behaviors in the elevated plus maze (EPM) paradigm. The amount of time that mice spent on the open arm was recorded. Mice were then, 2 h later, forced to swim for 15 min and tested for depression-like behaviors 24 h later. The amount of time that mice remained immobile in the forced swim test (FST) was recorded for 6 minutes but the last four minutes data were used for analysis. Our results revealed that female wild-type mice spent a significantly greater amount of time in the nicotine-paired chamber compared to the saline-paired chamber ($P<0.05$). However, this response was absent in female mice lacking PACAP. In contrast, male mice lacking PACAP showed a robust CPP. Interestingly, male but not female PACAP-deficient mice exhibited reduced anxiety- and depression-like behaviors compared to their wild-type controls, suggesting that endogenous PACAP protects against the affective signs of nicotine withdrawal.

Taken together, these results suggest that endogenous PACAP is involved in nicotine reward and dependence but there is a sex-related difference in this regard.

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Poster

781. Nicotine, Mechanisms of Dependence, and Reward

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 781.16/Y42

Topic: G.08. Drugs of Abuse and Addiction

Support: R01 AA026598
4T32 DA7234-30
F31AA026782
UMN Foundation

Title: Oppositional sex-dependent regulation of α6 and β3 nicotinic receptors by protein kinase Cε: Implications for alcohol and nicotine reward mechanisms

Authors: *J. K. MOEN[1], M. C. DEBAKER[1], J. E. MYJAK[2], K. D. WICKMAN[3], A. M. LEE[3]; [1]Grad. Program in Neurosci., [3]Pharmacol., [2]Univ. of Minnesota, Minneapolis, MN

Abstract: Alcohol and nicotine are the most commonly abused substances worldwide. Emerging evidence from both rodent models and human studies show an effect of sex in drug consumption and reward, but the underlying mechanisms of these sex differences are not well understood. Nicotinic acetylcholine receptors (nAChRs) in neural reward circuitry are critical mediators of both alcohol and nicotine reward, and this receptor system is dynamically regulated at the cell level by a variety of signaling molecules. The CHRNA6-CHRNB3 gene cluster encodes transcripts for α6 and β3 nAChR subunits, which have been implicated in both alcohol and nicotine reward circuits. Previous studies by our group and others have found that protein kinase C epsilon (PKCε) regulates transcription of the CHRNA6-CHRNB3 gene cluster in male mice, such that male PKCε$^{-/-}$ mice show decreased expression of *Chrna6* and *Chrnb3* transcripts in the ventral midbrain and striatum. Additionally, male PKCε$^{-/-}$ mice show reduced alcohol and nicotine consumption, and small molecular inhibitors of PKCε can reduce alcohol consumption in male wild-type (WT) mice. In contrast, we found that female PKCε$^{-/-}$ mice show enhanced expression of *Chrna6* and *Chrnb3* transcripts in the ventral midbrain (*n*=11-15/group). This upregulation functionally impacts nAChR-dependent behaviors, as female PKCε$^{-/-}$ mice exhibit enhanced locomotor activity in response to a dose of nicotine that is subthreshold in WT animals (0.25 mg/kg; *n*=9-12/group). Indeed, we found that female PKCε$^{-/-}$ mice show distinct drug consumption patterns: female knockout mice exhibit reduced alcohol consumption only at a high concentration (20% v/v; *n*=30-35/group) and show higher nicotine consumption during the first

week of a chronic 2-bottle choice assay (*n*=15/group). Additionally, male PKCε$^{-/-}$ mice show increased sensitivity to the sedative properties of alcohol as measured by the loss of righting reflex, an expected result based on data from α6 knockout mice. This effect was absent in female PKCε$^{-/-}$ mice (*n*=6-12/group), indicating that uregulation of α6 nAChRs may be protective against deficits observed in alcohol sedation. Finally, female PKCε$^{-/-}$ mice also show reduced depression-like behavior in response to the nAChR partial agonist varenicline as measured by the tail suspension test (*n*=12-15/group). Overall, these data indicate that ablation of PKCε in female mice results in functional upregulation of α6 and β3 nicotinic receptors and reward behaviors, revealing a bidirectional effect of sex in the regulation of the CHRNA6-CHRNB3 gene cluster by PKCε.

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Poster

782. Learning and Memory

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 782.01/Y43

Topic: H.01. Animal Cognition and Behavior

Title: Functional network architectures in schizophrenia, are distorted during memory formation and consolidation: Graph theoretic analyses

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Abstract: Background: Schizophrenia is characterized by impairments in associative memory (Diwadkar et al., 2008). Disordered network interactions distort patients' ability to integrate information, leading to the "dysconnection syndrome" (Friston et al., 2016). Graph theoretic measures (e.g., betweenness centrality, BC) have been used in resting state fMRI, but rarely during learning tasks. We investigated differences in the functional organization of networks induced during periods of associative memory formation, and covert consolidation. Graph theoretic analyses (applied to measures of undirected functional connectivity) were used to summarize network profiles (van Den Heuvel, 2010).
Methods: fMRI data were collected from 59 subjects (32 SCZ, 18<Age<50, 3T Siemens Verio) during an object-location associative memory task. During Memory formation, objects were presented in associated locations for naming. During a subsequent instruction-free period of memory consolidation, participants fixated on a marker (covertly rehearsing memoranda)

(Ravishankar et al., 2019). Eight epochs were used allowing participants to reach asymptomatic performance. Data were processed in SPM12 with standard methods. From processed data, average time series were extracted from 90 regions in the cerebrum (Tzourio-Mazoyer et al., 2002). Each subject's resultant symmetric 90x90 adjacency matrix of correlation coefficients (Pearson's r) was normalized (Fischer's-Z). Average matrices ($HC_{Formation}$, $SCZ_{Formation}$, $HC_{Consolidation}$, $SCZ_{Consolidation}$) were forwarded for calculating BC.
Results: Formation: 1a) HC: Highest BC values were observed in cingulo-frontal (mid cingulate, middle frontal gyrus) and the inferior temporal cortex. 1b) SCZ: By comparison, BC was shifted to the lingual gyrus, superior temporal pole and middle frontal gyrus. BC in SCZ was also higher in visual cortex regions, but lower in the heschl's gyrus and posterior cingulate cortex. Consolidation: 2a) HC: Highest BC were observed in temporal-frontal (middle frontal, inferior temporal, superior medial frontal). 2b) SCZ: By comparison, BC was shifted to the lingual gyrus, calcarine sulcus, and middle frontal gyrus.
Discussion: This is the first study to demonstrate global disorganization of networks in schizophrenia induced during periods of memory formation and consolidation. Our findings are consistent with complementary methods for network analyses during learning and memory in SCZ (Woodcock et al., 2016) but provide a network-wide representation of effects. SCZ is a dysconnection syndrome, and graph theoretic methods can evocatively accentuate how the dysconnection is expressed.

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Poster

782. Learning and Memory

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 782.02/Y44

Topic: H.01. Animal Cognition and Behavior

Support: NIH grant GM118801

Title: The role of B2- and B3-containing GABAARs in memory and learning

Authors: *A. ABDULZAHIR[1], A. FIGUEROA[1], C. LOR[1], M. G. PERKINS[1], G. E. HOMANICS[2], M. S. FANSELOW[3], R. A. PEARCE[1];
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Abstract: Background: The general anesthetic etomidate (ETOM) causes sedation by modulating GABAA receptors that incorporate B2 subunits (B2-$GABA_A$Rs) and surgical immobility by modulating B3-$GABA_A$Rs. Its targets for suppressing learning and memory

remain undefined. Here, we examined the roles of these two receptor subtypes by testing contextual memory in mice carrying a mutation (N265M) in either the B2 or B3 subunit.
Methods: Heterozygous mice carrying the B2- or B3-N265M mutation were created in a mixed C57BL/6J x 129X1/SvJ background, and their homozygous mutant (MUT) or wild type (WT) offspring littermates were used for behavioral studies. Prior to behavioral testing, mice were habituated to the experimental room 30 min per day for one week. Contextual memory was assessed using the Context Pre-exposure Enhancement of Fear Learning (CPEFL) paradigm. On D1, the mice were administered ETOM (9 mg/kg IP) 30 min prior to placement into a conditioning chamber for 10 minutes. On D2, the mice were placed back into the same chamber and shocked 15 sec later for 2 sec at 1 mA, where they remained for 30 sec. On D3, the mice were placed back into the same chamber and allowed to explore freely for 3 min. The amount of time spent freezing was used as a surrogate for memory.
Results: Even in the absence of ETOM, both B2-MUT and B3-MUT mice had reduced freezing scores (B2-WT 34±7% vs. B2-MUT 12±3%, p=0.01; B3-WT 41±9% vs. B3-MUT 12±4%, p=0.001). Other behavioral experiments, including Elevated Plus Maze (EPM), Hot Plate (HP), and Open Field Test (OFT) yielded no differences between the two genotypes. ETOM caused sedation in WT and B3-MUT mice, but not B2-MUT mice. Surprisingly, even the sedated mice displayed learning that was not different than saline controls.
Conclusions: The memory impairment caused by the B2 or B3 mutation alone demonstrates that normal functioning of both receptor subtypes is essential for normal learning and memory. The resistance to sedation in the B2-MUT mice replicates prior findings. The lack of effect of a sedative dose of ETOM on learning suggests that impairment of contextual memory is not the most sensitive endpoint for this drug.

Disclosures: A. Abdulzahir: None. **A. Figueroa:** None. **C. Lor:** None. **M.G. Perkins:** None. **G.E. Homanics:** None. **M.S. Fanselow:** None. **R.A. Pearce:** None.

Poster

782. Learning and Memory

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Program #/Poster #: 782.03/Z1

Topic: H.01. Animal Cognition and Behavior

Support: Duke CTSA TL1 (EH)
RO1-MH103374 (SHS)

Title: Towards a neural circuit basis of neurodevelopmental disease: The role of a frontal-entorhinal projection in spatial and nonspatial forms of memory

Authors: *E. HISEY, S. H. SODERLING;
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Abstract: Multiple mutations associated with human brain disorders such as schizophrenia (SZ), intellectual disability (ID), and autism involve genes which encode regulators of the synaptic cytoskeleton. Cognitive deficits, such as working memory impairments, are co-morbid across SZ, ID, and ASD, and currently little is known regarding the neural circuit perturbations that lead to cognitive disruptions. Conditional deletion of an actin cytoskeletal regulator (ArpC3) in mice leads to a dramatic alteration of spine synapse morphology and number as well as cognitive impairments. Though preliminary evidence suggests that rescue of ArpC3 expression in frontal cortex (FC) can restore both episodic and working memory, the specific neural circuit in the FC that underlies these forms of memory is unknown. We chose to examine the functional role of FC cells projecting to the lateral entorhinal cortex (LEC), a brain region known to be involved in complex forms of object recognition and associative learning, in learning and memory. We used a combination of intersectional genetic silencing, circuit-specific conditional knockdown of ArpC3 and *in vivo* imaging in behaving mice to determine the activity signature of FC-LEC cells during spatial working memory as well as the necessity of these cells for a number of cognitive behaviors. Interestingly, we found that FC-LEC cells play a critical role in working memory, possibly encoding decision-making points in time. We also found that proper FC-LEC function is needed for more complex forms of associative learning in a naturalistic digging paradigm. These initial results suggest the pathway from FC to LEC is critical for a number of cognitive behaviors and may be adversely affected in cognitive disorders.

Disclosures: E. Hisey: None. **S.H. Soderling:** None.

Poster

782. Learning and Memory

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Topic: H.01. Animal Cognition and Behavior

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GAUK- 870218

Title: Effect of perineuronal net inhibitor on memory retention in mice

Authors: *J. VALLOVÁ[1,2], J. C. KWOK[3], N. MARTÍNEZ-VAREA[1,2], S. YANG[4], Š. KUBINOVÁ[1], J. W. FAWCETT[5];
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Abstract: Perineuronal nets (PNNs) are lattice-like extracellular matrix structures composed of hyaluronan, chondroitin sulfate proteoglycans, tenascin and link proteins, which surround the

surface of the soma and dendrites. The PNNs are responsible for synaptic stabilization in the adult brain, and disruption of PNNs may reactivate neural plasticity. In this study, we investigated the possibility of memory prolongation by reduction of PNNs formation using a PNN inhibitor (PNNi). C57BL/6 adult mice (n=16) were fed by chow containing PNNi for 6 months, in a dose 200mg/mouse/day and compared with the control group without PNNi treatment (n=8). The memory retention was tested using novel object recognition test (NOR) and spontaneous alternation test (SA). NOR test was performed after 2, 3, 6 and 7 months with intervals between the NOR sessions of 3h and 24h. A significant improvement in NOR score after both 3h and 24h was found in animals treated with PNNi during the all treatment period compared with control group. However, 1 month after the end of the treatment, the effect of PNNi did not persist. SA test was performed after 2 and 6 months. Spatial memory and activity have been determined, but no significant differences between PNNi treated group and control groups were observed. To determine if PNNi affects motor coordination, we used two types of tests including grip and rotarod tests. After 6 months of PNNi treatment, we did not observe any significant differences in motor skills between the treated (n=8) and control animals (n=4). The quantitative analysis of PNNs immunofluorescent staining for WFA in hippocampus revealed significant decrease in WFA intensity ($p<0.001$) in the treated group. Real-time qPCR showed that PNNi treatment decreased gene expression for *Has2, Hyal3* and *Ncan* and increased expression of *Acan* and *Lyve1*. The toxicity of high dose of PNNi after 6 months treatment was examined in liver, kidney and spleen. Pathological changes, such as liver steatosis and multifocal liver necrosis, extramedullary hematopoiesis in spleen and tubules vacuolization in kidney were detected in the treated group. Our results suggest that manipulation of PNNs by oral administration of PNNi may increase plasticity and might offer a novel therapeutic approach to the treatment of memory loss in neurodegenerative disorders, however the dose of PNNi must be optimized with respect to the organ toxicity.

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Poster

782. Learning and Memory

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 782.05/Z3

Topic: H.01. Animal Cognition and Behavior

Title: Progesterone pretreatment decrease acute stress effect on cognition and Sgk1 expression in Sprague-Dawley rats

Authors: ***E. S. JOHNSON**[1], J. C. GANT[1], J. R. THIBAULT[1], S. D. KRANER[2], K. HARGIS-STAGGS[1], E. M. BLALOCK[1];

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Abstract: Stress is highly prevalent, has negative health consequence, and causes deficits in cognitive function. The impact on cognition is thought to be exerted, at least in part, through stress-induced glucocorticoid action in the brain. Serum and glucocorticoid kinase 1 (Sgk1) is a key downstream effector of glucocorticoid's actions, and has reported influences on both microglial and oligodendrocytic cells. Further, progesterone antagonizes glucocorticoid signaling at transcriptional and allosteric modulating levels, as well as via the benzodiazepine- like action of its metabolite, allopregnanolone. Here, we investigated if progesterone pretreatment alleviates the cognitive deficits and molecular effects associated with acute restraint. Sprague-Dawley rats (21 males/ 10 females) trained in the Morris water maze were placed into one of four groups: unstressed + vehicle (n=9); unstressed + progesterone (n=7); stressed + vehicle (n=7); stressed + progesterone (n=8). Subjects underwent Morris water maze training for 3 days. At the end of each training day, animals were orally dosed with peanut oil (vehicle) or progesterone (10 mg/ kg). On day 4, a 3 hour restraint was applied immediately prior to the water maze probe trial. Progesterone had no effect on any outcome in unrestrained animals. Restraint stress resulted in a significant deficit in probe trial performance that was ameliorated by progesterone pretreatment. Hippocampal Sgk1 protein expression was elevated with stress and reduced by progesterone pretreatment. mRNA expression levels for the Sgk1 and Sgk1.1 splice variants were quantified by RT-PCR, and Sgk1, Iba1, and Mbp were also assessed. These data support the hypothesis that progesterone reduces stress- associated outcomes.

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Poster

782. Learning and Memory

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Topic: H.01. Animal Cognition and Behavior

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Boehringer Ingelheim Pharma
Welcome Trust (TWR 104631/z/14/z)

Title: The role of mesolimbic D2 receptors in learning from positive and negative feedback in a reversal learning task

Authors: J. SALA-BAYO[1], J. ALSIO[1], M. SELIN[1], A. MAREK[1], *J. R. NICHOLSON[2], J. W. DALLEY[1], T. W. ROBBINS[1];

[1]Dept. of Psychology, Univ. of Cambridge, Cambridge, United Kingdom; [2]Central Nervous Syst. Dis. Res., Boehringer Ingelheim Pharma GmbH & Co.KG, Biberach an der Riss, Germany

Abstract: Impaired cognitive flexibility in touchscreen-based reversal learning tasks has been linked to schizophrenia, obsessive-compulsive disorder, drug addiction and Parkinson's disease. Such cognitive inflexibility is often treatment-resistant or even worsens with pharmacotherapy. Reversal learning tasks, in which subjects learn a simple discrimination problem (approach A+; avoid B-) and then need to adapt to a change in contingencies (avoid A-; approach B+), represent one of the most robust and frequently studied forms of cognitive flexibility. Dopamine (DA) is critical for efficient reversal learning and previous studies have shown that infusions of a D2/3R agonist in the nucleus accumbens (NAc) or lesions of the core and shell sub-regions (NAcC; NAcS) impair reversal learning. However, other studies have reported no effect of NAc interventions on this type of cognitive flexibility. Furthermore, it is unclear whether these effects depend differentially on animals learning to avoid the CS- or approach the CS+. Therefore, we developed a new touchscreen-based reversal learning task for rats that assesses whether animals learn from positive or negative feedback, a task with high translational value and similarity with the human CANTAB-based reversal learning task. Rats were trained to discriminate between two stimuli (A+; B-) on a touchscreen to receive a sucrose reward. Contingencies alternated (A-; B+) until they reached a stable performance. Subsequently, a third stimulus was added to investigate learned non-reward and stimulus-perseveration: standard trials were combined with trials in which A- or B+ (or A+ or B-) was interleaved with a third neutral stimulus (C50/50) that was rewarded in 50% of the trials. We investigated the effects of local microinfusions of D2/3R agonist quinpirole into the NAcC and NAcS. In both cases, we observed a significant improvement in performance. However, whereas infusions in the NAcS improved performance mainly from effects on learning from negative feedback, in the NAcC the improvement was due to a combination of effects on learning from positive and negative feedback. These results indicate that mesolimbic DA inputs to the NAcC and NAcS contribute differentially to reversal learning.

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Poster

782. Learning and Memory

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Program #/Poster #: 782.07/Z5

Topic: H.01. Animal Cognition and Behavior

Support: NIDA/NIH

Title: Missing you? Dopaminergic error mechanisms in rat ventral tegmental area are reset by the early appearance of the same reward but not by the early appearance of a similarly-valued but differently-flavored reward

Authors: *Y. K. TAKAHASHI[1], T. A. STALNAKER[1], L. MUELLER[1,2], G. SCHOENBAUM[1,3,4];
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Abstract: Dopamine neurons respond to errors in predicting the value of an event. Thus, they increase firing when a reward appears unexpectedly and suppress firing when an expected reward is omitted. Interestingly, however the omission signal is not generally observed if the expected reward is delivered early; that is, there is an increase in firing when the now-early reward is presented, but there is no suppression at the later time when it was expected. This observation necessitated the introduction of a mechanism whereby an unexpectedly valuable early event resets the temporal difference error signaling mechanism driving dopamine neuron firing (Courville, Daw, and Touretzky, TICS, 2006). Here we attempted to replicate this finding and ask further whether a similar value is sufficient for this resetting. We recorded VTA dopamine neurons in rats performing a choice task in which odor cues signaled reward at one of two fluid wells. Reward consisted of a drop of chocolate or vanilla milk, delivered at either 0.5 or 3s in different blocks of trials. The design created two transitions (1 per well) in which the 3s reward appeared at 0.5s but remained the same, and two (1 per well) in which the 3s reward appeared at 0.5s and also changed flavor (choc->van or vice versa). A single drop of water was delivered at 5s in both wells on all trials to ensure that the rats remained in the well through both prior reward periods. As expected, the dopamine neurons exhibited robust error signals, suppressing firing when the 0.5s reward was delayed to 3s and increasing firing when the 3s reward appeared unexpectedly at 0.5s. In addition, there was no suppression of firing at 3s when the same reward appeared at 0.5s. However, contrary to models in which dopamine neurons know only about value, this apparent resetting only occurred when the earlier reward was the same flavor as the one missing at 3s. In blocks where the reward moved from 3s to 0.5s and also changed flavor, there was an increase in firing at 0.5s and also a weak suppression at 3s. This result is consistent with prior data, however it also shows that so-called resetting does not occur simply as a result of the unexpected value of the early event or for any non-specific reasons. Instead it reflects the cognitive judgement - made on the fly - that the event has moved in time. If the identity of that event is changed such that this is not the logical inference, then the error signaling mechanism is not reset. These data join a variety of other recent results showing that even single midbrain dopamine neurons use of a much richer variety of information to calculate errors than is typically considered in the simple reinforcement learning models applied to understand their firing.

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Poster

782. Learning and Memory

Location: Hall A

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Program #/Poster #: 782.08/Z6

Topic: H.01. Animal Cognition and Behavior

Title: Learning induced transformation of spiking pattern through nonlinear dendritic processing *in vivo*

Authors: *M. WANG, X. CHEN;
Third Military Med. Univ., Chongqing, China

Abstract: Cortical circuits modify their response patterns through learning to meet animal's behavioral needs. However, the specific changes on the level of single neurons remain poorly understood. Here, using two-photon Ca^{2+} imaging combined with whole-cell recordings in mouse auditory cortex *in vivo*, we demonstrate the *de novo* induction of complex spike bursts in a subpopulation of neurons by an associative learning task. Such bursts are promoted by N-methyl-D-aspartate (NMDA) receptor-mediated 'depolarizing waves'. These depolarizing waves are invariably associated with large-amplitude Ca^{2+} transients present throughout the dendrites, revealing the existence of global dendritic NMDA spikes. Thus, we demonstrate that the auditory associative learning is associated with a reliable transformation of neurons from a regular spiking to a bursting mode through mechanisms involving nonlinear dendritic signal processing.

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Poster

782. Learning and Memory

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 782.09/Z7

Topic: H.02. Human Cognition and Behavior

Title: Latent learning with multiple categorical stimuli

Authors: *Y. ZHANG[1,2], A. GORELIK[1], K. GUPTA[1], E. D. BOORMAN[2];
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Abstract: To successfully navigate our complex environments, we need to learn and infer the changing statistical structures between different stimuli and reward outcomes. But how does the human brain form and update these types of probabilistic associations? Previous research points to the significance of the lOFC and the mPFC in establishing causal relationships. Little is known, however, about the nature of the neural code for causal attributions when outcomes are received. In this study, we test the hypothesis 1 that reactivation of the causal choice at feedback alternates among subregions of the occipito-temporal cortex depending on which visual category (face, scene, body parts and tool) was selected and also the category of an associated item governed by the same cause. Conversely, hypothesis 2 posits that different visual stimuli that share the same causal association will produce a more similar neural code in lOFC and mPFC despite having distinct perceptual qualities. Hungry subjects (N=21, 9 Female, Median age = 21) participated in a food-learning task in which they tracked two systems of independent stimulus-reward probabilistic associations for specific food types. Each system is composed of 2 stimuli from different visual categories but have the same reward outcome probabilities. Subjects thus learned to interrelate the 2 stimuli of a system and update the statistics of one stimulus from information of the other stimulus. A hierarchical Bayesian computational model and multiple logistic regression analyses demonstrate that subjects learned efficiently from both the direct association and also the other inferred association within the same system. We plan to use functional localizers of category-selective cortex to test hypothesis 1. Specifically, we will test whether both the selected stimulus category and the associated stimulus will show reactivation at the time of the outcome. We will use multivariate pattern analyses to test hypothesis 2 by decoding the identity of the other stimulus within a system from the pattern elicited by the chosen stimulus, at the time of reward. We will also test if the determinant for the lOFC choice representation is indeed based on causal probabilities but not visual representations. These findings would provide insights for mechanisms of credit assignment during latent learning.

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Poster

782. Learning and Memory

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Topic: H.01. Animal Cognition and Behavior

Support: KGM4611821
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KGM4621922

Title: Evaluation of cognititive function in adult rhesus monkeys using finger maze test

Authors: *K. KEONWOO;
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Abstract: In cognitive function research, the use of experimental animals is essential in revealing human cognitive processes and mechanisms. Furthermore, research on cognitive function using non-human primates is necessary for understanding higher cognitive function. In this study, we assessed cognitive function in 12 adult rhesus monkeys using the finger maze test, which was developed to assess cognitive function in non-human primates, and which we modified to suit our testing environment. The monkeys were trained on how to move a reward in the correct direction to obtain it. If the reward was moved in an incorrect direction, then the monkeys could not obtain it. After the training, the monkeys first completed a learning trial and then completed a memory trial 2 months later. Although the time required for training varied among the monkeys, 11 of them completed the training and achieved a high success rate in the learning trial. They also achieved a high success rate in the memory trial conducted 2 months later. The finger maze test, which is considered a useful test of cognitive function in non-human primates, allowed us to assess learning, memory, and cognitive function in several monkeys simultaneously

Disclosures: K. Keonwoo: None.

Poster

782. Learning and Memory

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Title: Prefrontal subnetworks underlying cognitive flexibility

Authors: *T. SPELLMAN, M. SVEI, C. M. LISTON;
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Abstract: The capacity for volitional control of attention is a critical tool for the effective performance of self-directed behaviors, and deficits in this ability underlie core symptoms of multiple psychiatric illnesses, including schizophrenia, annorexia/bullimia nervosa, and ADHD. Despite the prevalence of these disorders and the side effects associated with standard treatments, such as phenethylamine psychostimulants, the circuit mechanisms that underlie the

control of attention within the mammalian brain remain unclear. Elucidating these mechanisms, therefore, is critical to the development of more targeted treatments for this disorder. Attentional set-shifting is a switching behavior commonly used to model the context-specific control of attention in both human and translational rodent models. In a set-shifting task, a subject must inferentially learn to ignore a previously relevant stimulus feature and instead attend to a newly relevant feature. Successful execution of this behavior, which is impaired in patients with ADHD, has been linked to the activity of the dorsolateral prefrontal cortex in humans and its rodent functional analogue, the prelimbic cortex.Theoretical circuit models have been proposed to explain how network architecture and plasticity in prefrontal circuits can give rise to the switching of cue processing across contexts. However, these models have not yet been tested against data from population-level physiology, due in part to technical obstacles to recording the activity of large populations of neurons in ways that capture their laminar and long-range connectivity profiles. To more clearly define the circuit mechanisms by which attentional set-shifting is accomplished in the mammalian cortex, we used *in vivo* calcium imaging and optogenetic manipulations to examine context-related activity in prefrontal cortico-thalamic and cortico-striatal neurons. While broadly-defined task-responsiveness was similar across the two populations, subtle differences were seen in the degree to which each represented task-relevant information, and in the stability of these representations over multiple shifts in task rules. These findings describe a joint contribution by two major prefrontal projection populations to attentional set-shifting behavior and elucidate potential circuit-level targets for future therapeutic interventions in diseases characterized by deficits in set-shifting.

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Poster

782. Learning and Memory

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KAKENHI JP 16K21686 to KW
ImPACT program (Actualize Energetic Life by Creating Brain Information Industries) to TS

Title: Functional gradient across primate frontopolar, mid-lateral, and posterior-lateral prefrontal cortices revealed by a test battery for assessing higher cognitive functions

Authors: *K. WATANABE[1], M. HIRATA[2], T. SUZUKI[3];
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Abstract: The lateral prefrontal cortex (LPFC) plays essential roles in cognition. In macaque, LPFC occupies large cortical areas anterior to the arcuate sulcus, and dorsal and ventral to the principal sulcus (PS). Despite many decades of research, functional differentiation within LPFC remains largely unknown. In monkeys, few attempts have been made to characterize neural activities in the anterior part of LPFC including frontopolar PFC (FP-PFC). In humans, a popular hypothesis postulated that there is a functional gradient along the anterior-posterior axis in LPFC, based on the level of action control or the abstractness of task-relevant rules. This hypothesis argues that the more anterior regions process more abstract and complex information, while more posterior regions process more concrete action information. At the apex of this hierarchy, FP-PFC participates in the parallel processing of multiple goals (cognitive branching). Nevertheless, this claim has recently been challenged by opposing evidence. In this study, we examined functional differentiation in macaque LPFC throughout its anterior-posterior extent. We recorded many neurons in areas 10, 46 and 8 in three monkeys while they performed 8 different tasks: (1) visual flash observation; (2) reward consumption; (3) visually-guided saccade task; (4) oculomotor delayed-response task; (5) visuospatial attention task; (6) cognitive branching task comprised of tasks 3 and 4; (7) visual object discrimination (rapid learning) task, and (8) cognitive branching task comprised of tasks 4 and 7.The result showed that task-relevant activity was almost exclusively observed in the posterior LPFC, while anterior region (FP-PFC and anterior area 46) showed much weaker responses to the task events. Notably, few neurons in FP-PFC showed task-related activity even in cognitive branching tasks (tasks 6 and 8) and rapid-learning task (task 7) that were believed to selectively activate this area. Our data show that FP-PFC exhibited notable activity only in feedback time, and this was consistent across different tasks: FP-PFC neurons retrospectively encoded the conjunction of what the subject did and whether or not that behavior was preferable in the trial just finished. Thus, our data suggest that there is distinct functional subdivision along the anterior-posterior axis of LPFC in monkey, but in a different way from that proposed by the original functional gradient hypotheses in humans.

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Poster

782. Learning and Memory

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Program #/Poster #: 782.13/Z11

Topic: H.01. Animal Cognition and Behavior

Support: NIH R01 AG049722
NIA P50 AG047266

McKnight Brain Research Foundation

Title: Aberrant response based strategies in old age are related to elevated Arc expression in the dorsal striatum

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Abstract: In advanced age, rats are slower to acquire the object-in-place rule on a bi-conditional association task (Hernandez et al., 2015) and to learn to discriminate between objects that share features (Johnson et al., 2017). On these tasks, poor performance is associated with response-driven behavior in which an animal is biased to select an object on a particular side (left versus right) regardless of the feature information of test stimuli. While it has been reported that this response-driven behavior is facilitated by the dorsal striatum (Packard and McGaugh, 1992; Gold, 2004), the neurobiological mechanisms underpinning these cognitive impairments are not completely understood. We recently showed that response-driven behavior correlated with elevated resting state functional connectivity between the anterior cingulate cortex and dorsal striatum (Colon-Perez et al., 2018), but it is unknown if this relates to neural activity during task performance. The current study tested rats on the working memory/bi-conditional association task (WM/BAT), which measures an animal's ability to select an object in a pair-wise discrimination problem based on the location on the maze while simultaneously performing a continuous alternation task. Five young (4 months old) and 4 aged (24 months) Fischer 344 x Brown Norway F1 hybrid rats were trained for 14 days on the WM/BAT. While young rats learned the object-in-place rule within that time frame, the aged rats failed to reach criterion performance and showed a significantly higher response bias compared to the young animals. On the final day of testing, rats completed the WM/BAT and a control alternation task and then sacrificed by rapid decapitation to label brain tissue for expression of the activity-dependent immediate-early gene *Arc* (Guzowski et al., 2001). When *Arc* expression in the dorsal striatum and anterior cingulate cortex was analyzed to identify neurons active during the WM/BAT and alternation task, it was observed that the proportion of active cells within the anterior cingulate cortex during both tasks was similar between young and aged rats. In contrast, in the dorsal striatum more cells were active during WM/BAT in aged compared to young rats. This pattern of elevated *Arc* expression was not observed during the alternation task. Together these data suggest that elevated activity in the dorsal striatum is associated with an increase in the use of a suboptimal response-based strategy in aged rats, which could contribute to enhanced functional connectivity between the striatum and other cortical regions.

Disclosures: K.N. Lubke: None. **S.M. Turner:** None. **L.M. Colon-Perez:** None. **M. Febo:** None. **S.N. Burke:** None.

Poster

782. Learning and Memory

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 782.14/Z12

Topic: H.01. Animal Cognition and Behavior

Title: Intralaminar thalamic neuron plays the action selection and flexible behavioral controls

Authors: *S. KATO[1], R. FUKABORI[1], K. NISHIZAWA[1], K. OKADA[2], N. YOSHIOKA[3], M. SUGAWARA[1], Y. MAEJIMA[1], K. SHIMOMURA[1], M. OKAMOTO[1], S. EIFUKU[1], K. KOBAYASHI[1];
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Abstract: The basis of learning processes contributing to adequate behavioral selection and flexible switching are mediated via the dorsal striatum, which is a key component of the basal ganglia circuit. To understand the mechanism for the information processing and its regulation through this circuit, we recently established a new vector for neuron-specific retrograde gene transfer (NeuRet) with pseudotyping of fusion glycoprotein type E with mutated P440E (FuG-E (P440E)), which consists of the N-terminal region (440 amino acids) of the extracellular domain of rabies virus glycoprotein (RVG, CVS strain) and the membrane-proximal region (15 amino acids) a short C-terminal portion of the extracellular domain and the transmembrane/cytoplasmic domains of vesicular stomatitis virus glycoprotein (VSVG) (Kato et al., 2019). This vector provides us a powerful tool for the study of neural circuit mechanisms of neural networks underlying a variety of brain functions. In our previous report, the functional elimination of the parafascicular nucleus of thalamus (PF)-derived thalamostraital pathway was involved in cognitive function in the visual discrimination task (Kato et al., 2011). In the present study, we investigated the central lateral nucleus of thalamus (CL)-derived thalamostriatal circuitry function. As a result, CL-derived thalamostriatal pathway possesses distinct roles in the control of behavioral selection and flexibility against PF-derived thalamostriatal pathway. Our results suggest that the main contribution of the CL thalamostriatal neurons might be functional control of the basal ganglia circuit linked to the prefrontal cortex.

Disclosures: S. Kato: None. **R. Fukabori:** None. **K. Nishizawa:** None. **K. Okada:** None. **N. Yoshioka:** None. **M. Sugawara:** None. **Y. Maejima:** None. **K. Shimomura:** None. **M. Okamoto:** None. **S. Eifuku:** None. **K. Kobayashi:** None.

Poster

782. Learning and Memory

Location: Hall A

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Program #/Poster #: 782.15/Z13

Topic: H.01. Animal Cognition and Behavior

Support: Intramural Research Program of the National Institute on Aging to PRR
NIH Grant K01AG061263 to JAM
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Title: Influence of normal aging on tau isoforms and post-translational modifications in transentorhinal cortex

Authors: *J. A. MCQUAIL[1], S. A. JOHNSON[1], M. N. LITENSKI[1], S. GHAY[1], B. HELLBUSCH[1], G. PEGUERO[1], S. L. ROSSI[2], P. CHAKRABARTY[1], B. I. GIASSON[1], P. R. RAPP[2], S. N. BURKE[1], J. L. BIZON[1];
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Abstract: Intracellular inclusions comprised of hyperphosphorylated tau are among the earliest neuropathological features of Alzheimer's disease (AD). Abnormal tau phosphorylation is posited to promote self-aggregation of tau associated with altered protein conformation and solubility that culminates in the formation of neurofibrillary tangles. Mouse models developed from rare disease-associated mutations are useful to study the progression of tau pathology, but few studies have characterized the contribution of normal aging, the most common risk factor for AD, on expression of naturally occurring tau isoforms and associated post-translational modifications. Critically, the transentorhinal cortex is highly sensitive to the effects of normal aging and the first cortical region to exhibit AD tau pathology. Therefore, the overarching goal of the current study was to investigate interactions between normal aging and tau biochemistry in order to identify factors that render transentorhinal neurons susceptible to tau pathology. In Experiment 1, expression of tau isoforms was measured in area 35 of the perirhinal cortex and lateral entorhinal cortex (the rat homolog of human transentorhinal cortex) of young adult (6 months) and aged (24 months) Fischer 344 × Brown Norway F1 rats. Young and aged rats expressed three distinct tau isoforms ranging from ~55-67 kDa and these same isoforms were observed in TBS-, triton-, and SDS/urea-soluble fractions. However, aging did not change the

relative expression of these tau isoforms or differentially influence tau solubility. In Experiment 2, young and aged rats received stereotaxic delivery of rAAV1 containing constructs to drive expression of human wild type 0N4R tau-eGFP (AAV-hWTtau) or eGFP alone (AAV-CON). Two months after surgery, brains were harvested for biochemical analysis. Compared to un-injected and AAV-CON-injected rats, young and aged rats injected with AAV-hWTtau expressed an additional, high-molecular weight tau isoform that contained the human-specific CP27 epitope. Rat and human tau isoforms were phosphorylated as demonstrated using the phospho-specific 7F2 antibody generated to the AT8 epitope. Ongoing studies will determine if this AAV-mediated increase in total and phosphorylated tau is associated with conformational changes (i.e. Alz50 or PHF1) and whether aging exacerbates the propagation of abnormally phosphorylated tau to interconnected brain regions such as the CA1 subregion of hippocampus.

Disclosures: **J.A. McQuail:** None. **S.A. Johnson:** None. **M.N. Litenski:** None. **S. Ghay:** None. **B. Hellbusch:** None. **G. Peguero:** None. **S.L. Rossi:** None. **P. Chakrabarty:** None. **B.I. Giasson:** None. **P.R. Rapp:** None. **S.N. Burke:** None. **J.L. Bizon:** None.

Poster

782. Learning and Memory

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 782.16/Z14

Topic: H.01. Animal Cognition and Behavior

Title: Neural correlates of ordinal knowledge during serial-order tasks in pigeons

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Abstract: Many tasks require multiple behaviours or actions to be executed in a sequential order to obtain a desired outcome. Such behaviour is known as “serial-order” behaviour, and is considered crucial for complex cognition requiring ordinal knowledge including language, learning, and memory. Most serial-order tasks can be thought of as either externally-ordered (EO) or internally-ordered (IO). An EO serial-order task has a predetermined sequence in order to obtain the reward. Conversely, in an IO serial-order task the order is chosen by the subject with the only requirement that a previously chosen item cannot be chosen again. In the current study, we trained pigeons to complete either EO or IO tasks. Half of the pigeons were trained on two three-item EO lists, with the first list consisting of colours (red→blue→green) and the second list consisting of patterns (Pattern1→Pattern2→Pattern3). The remaining pigeons were trained on a three-item IO list consisting of one colour (red). For both tasks, each stimulus response was separated by a delay period. We recorded single neurons from the nidopallium caudolaterale (NCL), the avian “prefrontal cortex” during both the stimulus response and delay periods to determine the role of the NCL in ordinal knowledge. Behaviourally, pigeons on both

the EO and IO tasks performed well above chance. Neuronally, for the EO task we found 45.66% and 43.35% of neurons fired significantly different from baseline during at least one of the stimulus or delay periods respectively. For the IO task, 66.36% and 44.55% of neurons fired significantly different from baseline during at least one of the stimulus or delay periods respectively. Many of the neurons demonstrated coding of ordinal knowledge, such that neurons showed a rank preference for the first, second, or third item or delay in each list. Across both tasks, the stimulus response neurons favoured was the first item, whereas the delay neurons tended to prefer the third delay period. One possibility is that the stimulus response neurons are involved in planning of upcoming stimulus responses, whereas the delay neurons reflect reward anticipation. Taken together, it appears the avian NCL is important for coding ordinal knowledge.

Disclosures: M. Johnston: None. **B.S. Porter:** None. **M. Colombo:** None.

Poster

782. Learning and Memory

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Program #/Poster #: 782.17/Z15

Topic: H.01. Animal Cognition and Behavior

Support: NIH R01MH099660
NIH R01DC015776
NIH R21HD053114
NIH U54HD090260

Title: Tbx1, a 22q11.2 cnv-encoded gene, in neonatal progenitor cells determines the postnatal development of affiliative social behaviors

Authors: *T. HIRAMOTO[1], S. BOKU[2], G. KANG[1], S. ABE[3], M. NAGASHIMA[4], R. GORDAN[6], P. O'BROIN[7], K. YE[5], T. V. MICHURIN[8], G. N. ENIKOLOPOV[9,10,11], N. HIROI[1]; [1]Pharmacol., Univ. of Texas Hlth. Sci. Ctr., San Antonio, TX; [2]Kobe Univ. Grad. Sch. of Med., Kobe, Japan; [3]Hosp. Pharmaceutics, Sch. of Pharm., Showa Univ., Tokyo, Japan; [4]Psychiatry and Behavioral Sci., [5]Epidemiology & Population Hlth., Albert Einstein Col. of Med., Bronx, NY; [6]Duke Ctr. for Genomic and Computat. Biol., Durham, NC; [7]Sch. of Mathematics, Statistics & Applied Mathematics, Natl. Univ. of Ireland Galway, Galway, Ireland; [8]Ctr. for Developmental Biol. and Genet., [9]Ctr. for Developmental Genet., [10]Anesthesiol., Stony Brook Univ., Stony Brook, NY; [11]Cold Spring Harbor Lab., Cold Spring Harbor, NY

Abstract: Copy number variants (CNVs) at 22q11.2, ranging from 1.5Mb to 3.0 Mb, are associated with high rates of schizophrenia and autism spectrum disorder (ASD). However, how individual 22q11.2-encoded genes contribute to dimensional aspects of diverse psychiatric

disorders is still poorly understood. We have identified the transcription factor Tbx1 as one of 22q11.2 genes that functionally contribute to social interaction deficits, a dimension relevant to schizophrenia and ASD. We have further tested the cellular and molecular substrates through which Tbx1 deficiency causes social interaction deficits. Male nestinCreERT;$Tbx1^{flox/+}$ mice were treated with Tamoxifen at postnatal days 1 to 5 (P1-5) or postnatal days 21 to 25 (P21-25) and tested for affiliative reciprocal social interaction and other behaviors 1 month later (n=9-22 mice/group). Hippocampal progenitor cells derived from P0 neonatal C57BL/6J pups were passaged and cultured to evaluate expression of Tbx1 during cell cycle (n=4-6 culture dishes/group) and the role of Tbx1 in the proliferation of progenitor cells (n=4-5 culture dishes/group). The target genes of Tbx1 were validated by ChIP, Tbx1 knockdown and deletion and mutation of the promoter region of a target gene (n=6-27 culture dishes/group). Tbx1 binding to a small promoter region was examined by NoShift assays (n=6-8 per group; duplicates of n=3-4). Conditional *Tbx1* heterozygosity in neural progenitor cells reduced reciprocal social interaction more effectively when it was initiated at P1-5 than at P21-25 ($P<0.05$). Tbx1 expression peaked shortly before cell proliferation in vitro ($P<0.05$). Knockdown of Tbx1 reduced the rate of proliferation of neural progenitor cells in vitro ($P<0.05$). ChIP identified Tbx1 binding peaks in the promoter region of Pten. Tbx1 was found to be expressed in Pten-positive cells in the hippocampal progenitor cells granule cell layer in vivo. Knockdown of Tbx1 by siRNA reduced the transcription and expression of Pten in vitro ($P<0.05$). Segmental deletions and point mutations of the Pten promoter identified a 35bp region to be a Tbx1-binding site that is functionally critical for *Pten* transcription ($P<0.05$). Moreover, NoShift assays showed that this 35bp region contained Tbx1 binding ($P<0.05$). Tbx1 deficiency in progenitor cells during the neonatal period impairs their proliferation and social interaction later. Pten was identified as one of the downstream genes of Tbx1. ASD associated with 22q11.2 CNV and Pten mutation share a molecular cascade for social interaction deficits.

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Poster

782. Learning and Memory

Location: Hall A

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Program #/Poster #: 782.18/Z16

Topic: H.01. Animal Cognition and Behavior

Support: BMBF grant 01 EO 0801
DFG grant EXC 257 NeuroCure

Title: Bortezomib levels in the brain and cerebral spinal fluid and the effects on cognition

Authors: *P. HUEHNCHEN[1], W. BOEHMERLE[1], A. SPRINGER[4], S. KOHLER[1], T. ALEXANDER[2], F. HIEPE[2], A. MEISEL[3], M. ENDRES[3];
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Abstract: Bortezomib (BTZ) is a 26S proteasome inhibitor frequently used to treat multiple myeloma. In recent years, increasing data has emerged proving bortezomib's effectiveness in the treatment of antibody-mediated autoimmune disorders such as anti-NMDA receptor encephalitis or thrombotic thrombocytopenic purpura in patients refractory to conventional therapy. However, one of bortezomib's major limiting side effects is its toxicity towards the (peripheral) nervous system with the development of a sensory axonal polyneuropathy. We have previously gathered preclinical evidence in mice that BTZ might also lead to cognitive deficits. To further extend the safety data, we have measured pharmacokinetic profiles of BTZ in the mouse brain and human cerebral spinal fluid (CSF). Furthermore, we investigated whether BTZ also affects cognitive functions in patients treated for myasthenia gravis (MG) or systemic lupus erythematodes (SLE). Male eight-week old C57Bl/6 mice were injected with 0.4mg/kg BTZ intraperitoneally and sacrificed after 5, 10, 15, 30, 60, 120, 240, 720 and 1440 minutes and BTZ levels measured in the serum, cortex and hippocampus with liquid chromatography-tandem mass spectrometry (UPLC-MS/MS). BTZ concentrations in the brain reached only 5% of serum concentrations and did not exceed 1,5nM with only slightly higher concentrations measured in the hippocampus than the cortex. CSF was collected from a patient with anti-CASPR2 antibody encephalitis at 30, 60, 90, 120, 240, 360 and 720 minutes after subcutaneous application of 1.3mg/m^{2}BTZ. BTZ levels in the CSF again reached only about 7% of serum concentrations but were considerably lower compared to BTZ concentrations measured in mice with a maximum of 0.14 nM. Patients enrolled in a clinical trial to examine the effects of BTZ therapy on MG and SLE (TAVAB trial, NCT02102594) received two cycles of BTZ resulting in a total of eight subcutaneous injections of 1.3mg/m^{2}BTZ each. Six patients underwent neuropsychological testing for verbal memory, working memory, visuo-spatial memory, executive functions and semantic fluidity using standardized tests. With the exception of a slight learning effect in executive functions, overall performance in the other cognitive domains did not change after BTZ application compared to pre-treatment values.In summary, subjects with an intact blood-brain-barrier show low BTZ concentrations in the brain and CSF after systemic application and cognitive functions remain unchanged after recurrent treatment with BTZ up to two cycles. Overall, our data demonstrate that BTZ is a safe medication with regards to central nervous system toxicity.

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Poster

782. Learning and Memory

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 782.19/Z17

Topic: H.01. Animal Cognition and Behavior

Support: DARPA Grant HR0011-17-2-0019.

Title: Vagus nerve stimulation enhances prefrontal-cortical mediated cognitive flexibility

Authors: *L. K. P. ALTIDOR[1], M. M. BRUNER[1], J. F. DESLAURIERS[1], T. S. GARMAN[1], S. RAMIREZ[1], D. G. LAMB[2,5], A. M. FINNER[1], E. W. DIRR[3], K. P. OLCZAK[3], A. P. MAURER[1,3], K. J. OTTO[3], S. N. BURKE[1], B. SETLOW[1,2], J. L. BIZON[1,4];
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Abstract: Cognitive flexibilityis a core prefrontal cortical-dependent neurocognitive process that enables modification of one's behavioral strategy in response to a change in environmental contingencies. Reversal learning is a form of cognitive flexibility in which the learned reinforcement contingencies associated with a two choice discrimination are reversed (e.g., A+/B- becomes A-/B+). Therapies to enhance cognitive flexibility may have broad functional benefit to individuals engaged in some forms of learning (e.g., acquiring a new language) and may attenuate maladaptive perseverative behavior in conditions in which cognition is compromised (e.g., aging and psychiatric disorders). Electrical stimulation of the vagus nerve (VNS) is approved for treatment of epilepsy and several other neuropsychiatric disorders, and preclinical evidence suggests that VNS can also enhance cognition. The current study evaluated whether VNS enhances cognitive flexibility in a reversal learning task.Adult male Brown Norway rats were trained in a reversal learning task performed using operant chambers in which visual stimuli are projected on a touch-sensitive video screen. In this task, rats initially received training sessions consisting of intermixed presentations of two pairwise visual discrimination problems (e.g., W+/X- and Y+/Z-). For these problems, touching the correct stimulus in each pair (W+ and Y+) earned a food pellet reward. Once rats learned to perform accurately on both problems (>80% correct on each), the contingencies were reversed for the stimuli in one of the problems, whereas they remained consistent for the other (W-/X+ and Y+/Z). In naïve rats, initial performance accuracy was markedly lower on the reversed problem in comparison to the consistent problem, but improved over the course of subsequent testing. To evaluate the effects of VNS on reversal learning accuracy, a within-subjects design was used to compare VNS (120 µs pulse width, 700 µA, 0.8 s train duration) to no-stimulation conditions. When paired with presentation of the reversed problem, VNS at 30 Hz (but not at 10 Hz or 50 Hz) significantly enhanced reversal learning performance. In contrast, 30 Hz VNS paired with presentation of the

consistent (non-reversed) problem had no effect on performance, demonstrating the temporal specificity of the enhancing effect of 30 Hz VNS on reversal learning. Importantly, the enhancing effect of VNS was not accompanied by changes in response latency or number of trials completed. Considered together, these results show that acute VNS can enhance cognitive flexibility, and that the timing of VNS delivery is critical for these effects.

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Poster

782. Learning and Memory

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 782.20/Z18

Topic: H.01. Animal Cognition and Behavior

Support: HR0011-17-2-0019

Title: Peripheral and central effects of repeated vagus nerve stimulation

Authors: *M. M. BRUNER[1], J. F. DESLAURIERS[2], D. R. CALDERON[11], L. ALTIDOR[3], C. M. HERNANDEZ, III[4], J. A. MCQUAIL[5], E. DIRR[6], K. OLCZAK[7], A. P. MAURER[8], K. J. OTTO[2], S. N. BURKE[3], D. G. LAMB[9], B. SETLOW[10], J. L. BIZON[12];
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Abstract: Electrical stimulation of the vagus nerve (VNS) is approved for treatment of epilepsy and several other neuropsychiatric disorders. Moreover, substantial prior work has demonstrated that sustained VNS can attenuate inflammation in chronic conditions. The goal of this study was to determine peripheral and central effects of a relatively short VNS regimen that has been shown to acutely enhance cognitive performance. Adult male Brown Norway rats underwent surgery to implant a cuff electrode around the left vagus nerve. After 2 weeks of recovery, rats received daily 1 h sessions for eight days during which they were tethered to a constant current stimulator. In each session, rat received either 100 VNS trains (30 Hz, 120 µs pulse width, 700 µA, 0.8 s train duration) distributed over 1 h or no stimulation (control group). Rats were sacrificed 48 hours after the final VNS session. Peripheral tissues and blood were collected, and the hippocampus and prefrontal cortex were dissected for multiplex ELISA and western blot

analysis. Locomotor activity during stimulation sessions did not differ between groups; however, rats receiving VNS tended to gain less weight across the experiment in comparison to control rats. No differences between VNS and control rats were observed in a post-mortem analysis of body fat composition and adrenal weight. VNS did, however, reliably attenuate expression of the pro-inflammatory cytokines TNF-α and interferon-γ measured in plasma. In addition, tissue inhibitors of metalloproteinases TIMP-1 and TIMP-2, which have been implicated in neuroprotection, were upregulated in the hippocampus of VNS compared to control rats. VNS also reduced RANTES, Prolactin and T-cell immunoglobin and muscin family-1 (TIM-1) in prefrontal cortex. Finally, western blot analysis indicated that VNS altered expression of glutamic acid decarboxylase and receptors for GABA in the prefrontal cortex. Together, these findings suggest that even relatively brief VNS regimens can attenuate peripheral inflammation, promote neuroprotection and shift expression of excitatory/inhibitory signaling proteins in brain regions important for cognitive function.

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Poster

782. Learning and Memory

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 782.21/Z19

Topic: H.02. Human Cognition and Behavior

Title: The effects of early and late onset oral contraceptive use on emotional working memory in women

Authors: *R. SHARMA[1], N. BOUKINA[1], B. TAYLOR[2], A. SMITH[1], N. ISMAIL[1];
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Abstract: Millions of women worldwide use oral contraceptives (OCs), often starting at a pubertal age when their brains are in a crucial developmental stage. For girls, puberty marks the transition to womanhood whereby the surge of ovarian steroid hormones confers reproductive competence and initiates brain reorganization that gives rise to the social, emotional, and cognitive development across adolescence. The influx and fluctuations of these hormones in women contribute to sex differences in mood disorders, as women are disproportionately affected. Given that OCs suppress endogenous production and that, the age of first OC onset is decreasing towards early- to mid-puberty due to their marketability as “regulators”, examining the influence of hormonal OCs on women’s brain structure, function, and mood is warranted.

Therefore, the objective of the current study was to examine the effects of early- and late-onset OC use and the natural menstrual cycle on brain activity during an emotional working memory task. We hypothesized that OC use would alter regional brain activity compared to naturally cycling (NC) women. We also hypothesized there would be differences between pubertal- and adult-onset users, as age of onset/duration of OC use has not been accounted for in the existing literature. To test these hypotheses, undergraduate women (N=74) underwent functional magnetic resonance imaging while being exposed to a working memory task comprised of emotionally arousing images. Preliminary results show that all OC users display greater frontal and insular activity during working memory for negatively arousing images and negative emotional processing compared to NC women. OC users show a positive association between salivary progesterone levels and brain activity for negative working memory. NC women, on the other hand, show a positive correlation between salivary progesterone levels and working memory for positively arousing images. The findings of the current study advance our understanding of how OCs impact the brain, especially during pubertal onset, and are relevant to women's health at both individual and societal levels.

Disclosures: R. Sharma: None. **N. Boukina:** None. **B. Taylor:** None. **A. Smith:** None. **N. Ismail:** None.

Poster

782. Learning and Memory

Location: Hall A

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Program #/Poster #: 782.22/Z20

Topic: H.01. Animal Cognition and Behavior

Support: 1R56MH119150-01
P20GM121176

Title: Reduction of circHomer1 in the orbitofrontal cortex is associated with electrophysiological alterations underlying impaired cognitive flexibility

Authors: *A. J. ZIMMERMAN[1], S. K. AMOAH[1], A. K. HAFEZ[1], M. DELLORCO[1], M. J. WEBSTER[2], N. PERRONE-BIZZOZERO[1], N. MELLIOS[1], J. L. BRIGMAN[1];
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Abstract: Schizophrenia (SCZ) and Bipolar Disorder (BD) are highly heterogeneous psychiatric disorders consisting of multiple cognitive and behavioral impairments. While they are considered to be distinct disorders, both are marked by impaired functioning of the prefrontal cortex (PFC) leading to behavioral deficits associated with executive functioning, such as cognitive flexibility. Many protein-coding genes have been associated with SCZ and BD, specifically those expressed

at the post-synaptic density (PSD), which are associated with synaptic transmission and plasticity. Homer protein homolog 1 (HOMER1), is a PSD-expressed, psychiatric disease-associated, scaffolding protein known for its interaction with group 1 metabotropic glutamate receptors and its role in regulating synaptic transmission. Recently, circular RNAs (circRNAs) have been found to be produced from *Homer1* and to be highly expressed in cortical brain regions. circRNAs, in particular *circHomer1*, have been postulated to regulate their linear counterparts as well as impact expression of multiple other targets either through direct or indirect mechanisms. We have previously shown that *circHomer1*, one circRNA derived from *HOMER1*, is reduced in postmortem orbitofrontal cortex (OFC) samples from patients with SCZ and BD. Additionally, *in vivo circHomer1* knockdown in male C57BL/6J mouse OFC alters the expression and synaptic localization of multiple targets and impairs visual reversal learning, a measure of cognitive flexibility dependent on OFC function. To examine changes in excitatory neuronal activity that may underlie OFC dysfunction, the current work uses *in vivo* electrophysiological recordings during visual discrimination and reversal learning. We analyze changes in OFC spike activity during impaired reversal stages and inter-trial phase consistency, which is a measure of coordinated regional activity important for functional inter-regional signaling. Further, we correlate mRNA expression changes with neuronal activity to uncover possible mechanisms associated with impaired firing. From this work, we are able to elucidate the impact of a circRNA on the electrophysiological properties underlying a behavioral flexibility impairment associated with SCZ and BD.

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Poster

783. Inhibitory Control

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 783.01/Z21

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant DA031695
NIH Grant DA040993
NIH Grant 1 F32 MH117836-01A1

Title: Response signals in dorsal medial striatum and behavior are dependent on medial prefrontal cortex

Authors: *A. T. BROCKETT, S. S. TENNYSON, C. A. DEBETTENCOURT, M. A. KALLMYER, M. R. ROESCH;
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Abstract: Cognitive control is the ability to flexibly adapt behavior in accordance with internally maintained goals, while simultaneously suppressing more automatic responses. This ability is an essential component of cognition and is often diminished in patients with schizophrenia and depression (Shenhav et al., 2016). Previous work has implicated the anterior cingulate cortex (ACC) and medial prefrontal cortex (mPFC) in facilitating switching between behavioral strategies that have been shown to be represented, at least in part, in areas such as the dorsal medial striatum (DMS) (Bryden et al., 2012). However, the respective roles of ACC and mPFC in facilitating cognitive control have yet to be fully distinguished. Some work suggests that ACC is important for managing conflict and changing behavior accordingly (Shenhav et al., 2016), whereas mPFC is tasked with monitoring task performance and automating behavior (Gourley and Taylor, 2017). Despite these theoretical accounts, few studies have attempted to dissociate the roles of these two brain regions in subjects performing a conflict task. In this study, we utilized a directional stop-change task, in which on 80% of trials (GO trials) a light directs rats to make an operant response in order to obtain reward (Bryden et al., 2012, 2016). On the remaining 20% of trials (STOP trials) rats must inhibit their initial response to the first light when presented with a second light instructing the rat to redirect its behavior in the opposite direction. Using this task, previous research has demonstrated that the firing of neurons in DMS appears conflicted on STOP trials, but how DMS mitigates this conflict is unclear (Bryden et al., 2012). Neurons in mPFC have been shown to signal response direction and monitor conflict, firing more strongly on STOP trials than on GO trials. However, firing does not peak until after the response epoch (Bryden et al., 2016). Here we performed unilateral lesions of rat mPFC (n = 8) while simultaneously recording downstream from DMS. We show that mPFC lesions disrupt responding to the first cue, but the ability of rats to detect/ mitigate conflict is left intact, suggesting that the primary role of mPFC is to control the automated process of rapidly responding to the first cue light.

Disclosures: **A.T. Brockett:** None. **S.S. Tennyson:** None. **C.A. deBettencourt:** None. **M.A. Kallmyer:** None. **M.R. Roesch:** None.

Poster

783. Inhibitory Control

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Program #/Poster #: 783.02/Z22

Topic: H.01. Animal Cognition and Behavior

Support: KAKENHI 17K04505

Title: Anticipatory contrast in instrumental behavior of rats

Authors: *K. KAWASAKI, M. TAGA;
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Abstract: Anticipatory contrast (AC) refers to the phenomenon of inhibition of access behavior to the prior reward which is followed by more desirable reward. AC has been interpreted as resulting from anticipation of the impending preferred reward and its comparison with the currently available first reward. And we proposed the amygdala basolateral nucleus as one of the brain region candidates responsible for comparing the two rewards underlying this phenomenon. Recently, we reported that the amygdala basolateral nucleus is involved in AC (Kawasaki et al., 2017). However, as is the case with our previous studies, most studies showing AC in rats have been conducted on consummatory behavior. Therefore, care must be taken when generalizing these results. Williams (1990) reported that pigeons trained on multiple schedules showed AC, while rats trained on the same schedule did not show AC. However, the method of Williams (1990) is not only targeted for instrumental behavior, but it differs from the experimental schedule targeting consummatory behavior because it uses a multiple lever schedule of two levers. Therefore, we conducted 3 experiments with the objective of ascertaining whether AC occurs in instrumental behaviors of rats by the method that is as close as possible to the schedule used in consummatory behavior. In the 1st experiment 45 male Wistar-Imamichi rats were trained in FR1 schedule of nose poking on both of 1st (3 min.) and 2nd (3 min.) component of daily session for 10 days. Both 1st and 2nd components were separated by a 30 second break. The reward was one 20mg food pellet on 1st component and 1, 2, or 4 of pellet(s) on 2nd. Mean numbers of nose poking on 1st component in last 5 days were suppressed in function of number of reward pellets on 2nd component. But there was no statistical significance. In 2nd experiment 24 rats were trained in FR2 schedule of nose poking on 1st component and in FR1 or FR2 on 2nd component of daily session for 14 days. The reward was one 20mg food pellet on both 1st and 2nd component. Mean numbers of nose poking on 1st component in last 4 blocks of 2 days were slightly suppressed in the rats given FR1 schedule on 2nd component. But it was not significant. In 3rd experiment 24 rats were trained in FR3 schedule of nose poking on 1st and in FR1 or FR3 schedule on 2nd component of daily session for 10 days. While one 20mg pellet was given for all the subject on 1st component and FR3 rats on 2nd component, 3 pellets for FR1 rats in 2nd component. Mean numbers of nose poking on 1st component in last 2 blocks of 2 days were significantly suppressed in the rats given FR1 schedule on 2nd component. That is, in this experiment, AC in instrumental behavior was observed for the first time.

Disclosures: K. Kawasaki: None. **M. Taga:** None.

Poster

783. Inhibitory Control

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Program #/Poster #: 783.03/Z23

Topic: H.01. Animal Cognition and Behavior

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Title: Increased impulsivity like behaviors in mice lacking Gpr88

Authors: *S. BEN HAMIDA, M. MCNICHOLAS, E. MORONCINI, E. CLARKE, E. DARCQ, B. L. KIEFFER;
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Abstract: The neural orphan G protein coupled receptor GPR88 is most enriched in the striatum of both rodent and human brains, and also in central amygdala and cortex although with lower density. Total deletion of *Gpr88* gene in mice leads to a range of phenotypes consistent with the strong striatal Gpr88 expression. In brief, these include altered dopamine signaling and enhanced medium spiny neuron excitability, increased basal activity and locomotor responses to psychostimulants, increased stereotypies, motor coordination deficits, low anxiety, as well as altered cue-based and procedural learning[1-3]. In addition, sensorimotor gating[1] and sensory processing[4] deficits are also observed in Gpr88 knockout mice, possibly related to cortical Gpr88 expression and concordant with disrupted functional connectivity at the level of several cortical areas in these mutant mice[5]. Finally, we found enhanced motivation to seek and consume alcohol in Gpr88 knockout animals, and this phenotype correlated with reduced functional connectivity between the Pre-frontal cortex (PFC) and the Nucleus Accumbens (NAC)[6], both involved in high-order cognitive controls. Here, we hypothesized that the combined hyperactive and high-drinking phenotypes of Gpr88 knockout mice, together with their altered brain connectivity patterns in both cortical and striatal networks could also reveal/reflect an impulsive endophenotype in these animals. Our results indicate that both in an operant Go/No-Go task and a 5-choice serial reaction time (5-CSRT) task, Gpr88 knockout animals showed reduced inhibitory control, as demonstrated by increased premature responses and higher commission errors compared to control animals. We also detected an altered attentional performance in Gpr88 mutant mice as indicated by reduced choice accuracy in the 5-CSRT procedure. These findings suggest that GPR88 receptor function may contribute to cognitive control disorders, a trait implicated in the pathogenesis of addiction.
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2 Quintana, A. *et al. Nat Neurosci* 15, 1547-1555, doi:10.1038/nn.3239 (2012).
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6 Ben Hamida, S. *et al. Biol Psychiatry* 84, 202-212, doi:10.1016/j.biopsych.2018.01.026 (2018).

Disclosures: S. Ben Hamida: None. **M. McNicholas:** None. **E. Moroncini:** None. **E. Clarke:** None. **E. Darcq:** None. **B.L. Kieffer:** None.

Poster

783. Inhibitory Control

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 783.04/Z24

Topic: H.01. Animal Cognition and Behavior

Title: Impulsivity in a global cerebral ischemia rodent model: Optimization of a delay discounting task

Authors: *A. MORIN[1], H. PLAMONDON[2];
[1]Psychology, Univ. of Ottawa, Ottawa, ON, Canada; [2]Dept Psychol, Univ. Ottawa, Ottawa, ON, Canada

Abstract: Delay discounting (DD) tasks have been used to quantify impulsive behaviors in healthy animals and following various pathologies. To our knowledge, this task has not served to assess impulsive behavior in rat models of global cerebral ischemia. In this pilot study, rats were trained and tested on their ability to delay reward from the juvenile period to adulthood. Briefly, male Long Evans rats (n=8), maintained at 85% of normal body weight, were trained to lever-press using an autoshaping (AS) task. AS training was considered successful when the rat pressed a minimum of 60 times on both levers combined for three consecutive sessions. Each lever press triggered the delivery of one sucrose pellet. Following shaping, rats performed 30 daily sessions of DD, each consisting of 5 blocks of 12 trials lasting 100 seconds each. Rats could choose between pressing a smaller-sooner (SS) lever that provided an immediate small reward (1 pellet) or a larger-later (LL) lever that provided a bigger reward (4 pellets) at an increasing delay between blocks (0, 5, 10, 20, and 45 seconds). Performances over time were measured by comparing choice ratio (CR - the ratio of LL lever presses to total lever presses) between blocks and 3-day clusters. Based on two essential criteria, our results support the validity of the DD paradigm. First, no significant differences in CR were observed between clusters, indicating that performance achieved stability over time. Second, CR was elevated in the initial blocks (involving shorter delays) compared to later ones, allowing to determine changes in impulsivity between animals. Notably, as the delay increased to obtain a maximal reward, the number of omissions also increased. Thus, while this DD task is properly acquired by healthy rats, subsequent testing involving sham and ischemic animals will consider the motivation factor in selecting proper delays to assess changes in impulsivity level and overall performance.

Disclosures: A. Morin: None. **H. Plamondon:** None.

Poster

783. Inhibitory Control

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Topic: H.01. Animal Cognition and Behavior

Support: MOST 107 2410-H-004-109 MY3, Taiwan

Title: Effects of lesions of orbital frontal cortex and medial prefrontal cortex on the acquisition and extinction of DRL operant behavior in the rat

Authors: *R.-M. LIAO[1,2], S.-F. CHEN[2], Y.-H. YANG[2], Y.-J. YANG[1], C.-Y. CHUANG[2]; [1]Dept. Psychology, [2]Instit. Neurosci., Natl. Cheng-Chi Univ., Taipei, Taiwan

Abstract: Prefrontal cortex (PFC) is known to be critically involved in the execution of high-level cognitive functions including behavioral inhibition and timing process. These two are thought to be required for the operant response on differential reinforcement of low-rate response (DRL) schedules, and yet the role of PFC in DRL schedule-controlled behavior remains poorly understood. With the hypothesis of functional heterogeneity of PFC, the present study investigated the lesion effects of orbital frontal cortex (OFC) and medial prefrontal cortex (mPFC) on a DRL behavioral task in the rat. The lesion was made by using ibotenic acid before behavioral experiments. The rat received a basic training of lever press to obtain a water reinforcer before being subjected to a DRL 10 sec (DRL 10-s) for 18 days and then a DRL 15-s for 10 days in terms of acquisition. Subsequently, a 4-day extinction protocol was conducted and followed by a recovery test, where the reinforcer contingency resumed, on DRL 15-s task given four times intermittently over 12 days. The efficiency ratio, the number of reinforced responses divided by the number of total responses, was used in measuring behavioral response. The results showed the rats with OFC or mPFC lesion did not differ to those of sham controls in acquiring basic lever-pressing, neither for DRL 10-s response. When shifting to DRL 15-s task, a significant lesion effect of OFC was detected, but no such effect observed for that of the mPFC. During the extinction, the sham control rats significantly decreased responses across 4 test days. There was a significant lesion effect of mPFC, but no such effect for the OFC manipulation. For the recovery test, the results show that the lesion of OFC, but not mPFC, differed significantly from its sham control. Together, these data indicate that both the OFC and mPFC may contribute to the acquisition and extinction of DRL behavior in rats, but in different profiles. Specifically, OFC lesion yielded behavioral changes in DRL task with interval upward shifting and the recovery test, whereas the mPFC lesion affected responding in the extinction phase.

Disclosures: R. Liao: None. **S. Chen:** None. **Y. Yang:** None. **Y. Yang:** None. **C. Chuang:** None.

Poster

783. Inhibitory Control

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 783.06/Z26

Topic: H.01. Animal Cognition and Behavior

Support: Elsa-Neumann-Scholarship

Title: A high-throughput mouse stop signal task (SST)

Authors: *A. CAGLAYAN, K. STUMPENHORST, Y. WINTER;
Humboldt Univ. - Inst. Biologie, Berlin, Germany

Abstract: Behavioural inhibition is broadly defined as inhibiting a pre-potent response allowing animals to behave adaptively. It has multiple facets, one of which - namely action cancellation - consists of ceasing an ongoing motor response. The stop signal task (SST) has commonly been used to measure action cancellation (Logan, Cowan, & Davis, 1984; Eagle & Robbins, 2003; Humby, et al., 2013). Here we describe how a sorting system based on ID chips (ID sorter, PhenoSys) enabled the development of a quick and less labor intensive stop signal task for mice. In a stop signal task, subjects are first trained to quickly respond to the presentation of a go signal (go response). Once the go response is established, a stop signal is introduced to a proportion of trials. This stop signal is presented after the go signal but before the estimated time of completion of the go response (individual subject´s mean reaction time). The shorter the time interval that remains from presenting the stop signal to the completion of the go response, the more difficult it is for a subject to successfully stop the go response. Longer delays between the go signal and the stop signal thus decrease the percentage trials with successful action cancellation (stopping). Thus, by giving various stop signal delays (SSD), the subjects` ability for action cancellation is estimated. Several neurobiological disorders such as attention-deficit/hyperactivity disorder (ADHD), schizophrenia, and obsessive-compulsive disorder are associated with decreased action cancelation abilities. To better understand the nature of action cancelation and to develop potential treatment options requires analysing action cancelation in different rodent models. However, existing tasks for mice and rats require long training periods (~40 days before introducing SSDs) and are labour intensive. In this study we used a sorting system based on an ID chip gating system to allow group housed mice to individually enter the operant chamber in a self-determined manner. Female C57BL/6 mice were gradually trained to perform a quick go response upon initiating trials by themselves through an initiation response. After the go response was established, a stop signal (4.5 kHz, 65 dB tone) was introduced to 20% of the trials. Initially the stop signal coincided with trial initiation and mice learned to stop upon hearing the stop signal. Afterwards, delays (SSDs) were introduced between trial initiation and stop signal. It was observed that with increasing delay, stopping success decreased. The results

suggest that our current automated task delivers hallmarks of SST while greatly decreasing experimenter labour and the time required for training.

Disclosures: **A. Caglayan:** None. **K. Stumpenhorst:** None. **Y. Winter:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); YW owns PhenoSys equity..

Poster

783. Inhibitory Control

Location: Hall A

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Program #/Poster #: 783.07/Z27

Topic: H.01. Animal Cognition and Behavior

Support: AG046580

Title: Behavioral disinhibition as a cognitive endophenotype for early detection of Alzheimer's disease

Authors: T. PETERSON[1], Z. STEINBERG[1], M. R. DUGGAN[1], I. ASCI[1], *V. V. PARIKH[2]; [1]Psychology and Neurosci. Program, [2]Temple Univ., Philadelphia, PA

Abstract: Alzheimer's Disease (AD) is a neurodegenerative disorder effecting predominately older populations, and there is currently no means to accurately diagnose the disease before its progression has become severe. The existence of an effective behavioral biomarker for early detection of AD would improve diagnosis and encourage the implementation of a mechanism-based intervention for the initial stages of disease progression. Here, we utilized triple transgenic (3xTg) mice that harbors three mutations (APP Swedish, MAPT P301L, and PSEN1 M146V) associated with AD to delineate behavioral endophenotype at an early stage when neuropathological features are not visible. Wild type (WT) and 3xTg AD mice of both sexes were trained and tested in an automated operant go/no-go visual discrimination task that was designed to assess attention as well as behavioral inhibition under conditions of response conflict in mice. In the longitudinal study, animals started training at 2-3 months of age and were tested for behavioral performance until 9 months. Although 3xTg AD mice did not display decision-making deficits under 50%go/50%no-go condition at any age, higher false alarms were observed when the proportion of go trials was unpredictably reduced to 20%. These behavioral changes were visible in 3xTg-AD mice as early as 3 months of age. In general, AD mutants exhibited faster response times vs. WTs, which may indicate alterations in behavioral inhibition and their utilization of a more impulsive decision-making strategy under conflicting conditions. In the crossectional study, we compared the performance of young (3 months) and aged (9-10 months) old WT and AD mice. No differences in performance were noted in the 80%go/20%no-go condition. However, when the proportion of no-go trials was increased to 80%, older 3xTg-AD

mice exhibited reduced response latencies for both go-trials and false alarms, indicating strategy differences in response inhibition. Thus, regardless of the study design, behavioral disinhibition emerged as a possible cognitive endophenotype that was visible in the 3xTg-AD mutants before the onset of neuropathology. Provided that the integrity of the prefrontal cortex is critical for a wide range of executive processes, including behavioral inhibition, it is possible that early alterations in prefrontal networks may predict AD pathology, and that these networks may be targeted for early intervention.

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Poster

783. Inhibitory Control

Location: Hall A

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Program #/Poster #: 783.08/Z28

Topic: H.01. Animal Cognition and Behavior

Support: CIHR

Title: Pharmacological and behavioral modulation of impulsivity in the touchscreen-based mouse 5-choice serial reaction time test

Authors: *A. RAHBARNIA[1], A. R. ABELA[2], P. J. FLETCHER[3];
[1]Univ. of Toronto, Toronto, ON, Canada; [3]Section of Biopsychology, [2]Ctr. For Addiction and Mental Hlth., Toronto, ON, Canada

Abstract: In humans, impulsive behavior is a common feature of several neuropsychiatric disorders. Animal models have proven to be critical in understanding the neurobiology of impulsivity. An established test of impulsivity is premature responding in the rat five-choice serial reaction time test (5CSRTT). Recently, a touchscreen version of the 5CSRTT has been developed for mice. While premature responding in the 5CSRTT is well established as a test of impulsivity in rats, its transferability to mice and touchscreens is less documented. We evaluated whether task parameter and pharmacological manipulations that influence premature responding in the rat 5CSRTT exert similar influences in the touchscreen mouse 5CSRTT. Mice were trained to detect and respond to the presentation of a visual stimulus in one of five spatial locations for milkshake reward. Responses made prior to stimulus presentation were scored as premature and used as an index of impulsive responding. Impulsivity was then evaluated in three conditions. First, we investigated whether increasing the inter-trial interval (ITI) from 5s to 9s would enhance premature responding. Secondly, we assessed whether premature responding could be enhanced by drugs known to increase impulsivity in rats. Mice were tested with cocaine (7.5, 15 mg/kg i.p.), the selective 5-HT_{2C} receptor antagonist SB242,084 (0.125, 0.25 mg/kg

i.p.), and the alpha-2 adrenoreceptor antagonist yohimbine (0.313, 0.625 mg/kg i.p.). Thirdly, we assessed whether premature responding could be reduced by drugs known to decrease impulsivity in rats. Mice were tested on the 9s ITI version of the 5CSRTT following treatment with the 5-HT_{2C} receptor agonist lorcaserin (0.05, 0.1, 0.2 mg/kg s.c.), the selective norepinephrine reuptake inhibitor atomoxetine (0.5, 1 mg/kg i.p.), and the selective serotonin reuptake inhibitor citalopram (5, 10 mg/kg i.p.). Increasing the ITI to 9s reliably enhanced premature responding, an effect that was maintained over repeated tests. Cocaine, and to a lesser extent, SB242,084 increased premature responding. Yohimbine had no effect. Lastly, lorcaserin, atomoxetine, and citalopram significantly decreased premature responding. These results indicate that the touchscreen version of the 5CSRTT can reliably be used to measure impulsive action, and that there is some correspondence between the effects of pharmacological and behavioural manipulations on the 5CSRTT in rats and mice.

Disclosures: A. Rahbarnia: None. **A.R. Abela:** None. **P.J. Fletcher:** None.

Poster

783. Inhibitory Control

Location: Hall A

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Program #/Poster #: 783.09/Z29

Topic: H.01. Animal Cognition and Behavior

Title: Serotonin impairs social avoidance

Authors: *H. B. WEINBERG-WOLF, N. A. FAGAN, S. W. CHANG;
Yale Univ., New Haven, CT

Abstract: Many primates, including humans and rhesus macaques, must gather information about the social intention of conspecifics and select appropriate social behaviors in response. In macaques, threatening expressions and directed eye contact generally communicate dominance and an intent to aggress. On the other hand, lipsmacks generally communicate affiliation, subordinancy, and intention to submit. By monitoring these, and other facial expressions, individuals are able to learn and maintain their dominance status.
Recently, we have shown that i.m. injections of the serotonin precursor l-5-hydroxytryptophan (5-HTP) effectively increases central concentrations of serotonin in CSF and modulates looking duration to social images in rhesus macaques (Weinberg-Wolf et. al 2018), suggesting a role of the serotonergic system in social monitoring. However, successful social monitoring also requires balancing the needs to approach appetitive stimuli and avoid threatening stimuli (Weinberg-Wolf and Chang, 2019). Here, we tested whether the serotonergic system is also implicated in approaching or avoiding affiliative and threatening social stimuli. Monkeys were cued to look to (approach), or look away from (avoid), faces of unfamiliar conspecifics displaying threatening expressions, affiliative expressions, or luminance-matched scrambled

versions of these images. In this task, we examined how 5-HTP, compared to saline baseline, impacts approach and avoid behaviors using a repeated, within-subject, study design.
At baseline, monkeys approached the to-be-approached stimuli nearly perfectly. However, individuals varied in their avoidance behaviors and erroneously approached to-be-avoided stimuli frequently, indicating an overall prepotency for approaching stimuli. While enhancing central serotonin with 5-HTP generally shifted performance downward in the task, it especially impaired monkey's ability to avoid social stimuli depicting either threatening or affiliative expression. Our results suggest that approach and avoidance behaviors are regulated by the serotonergic system, especially when these stimuli contain social information about the intention of conspecifics. These findings are consistent with the view that the serotonergic system is implicated in adaptive regulation of social approach and avoidance, ultimately contributing to adaptive social monitoring.

Disclosures: H.B. Weinberg-Wolf: None. **N.A. Fagan:** None. **S.W. Chang:** None.

Poster

783. Inhibitory Control

Location: Hall A

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Program #/Poster #: 783.10/Z30

Topic: H.01. Animal Cognition and Behavior

Support: R01 DA038209

Title: Midbrain dopamine neuron activity predicts impulsive actions in mice

Authors: *T. P. PINKHASOV[1,2], S. STAROSTA[1], A. KEPECS[1];
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Abstract: Impulsivity, or acting without forethought or self-control despite negative consequences, increases the risk of suicidality, substance abuse, and violence. Dopamine (DA), the neuromodulator that is central to reward processing, has long been implicated in this behavior. While there is overwhelming evidence that DA drives conditioned behavior, pharmacological manipulations of DA have been found to both increase and decrease the ability to suppress conditioned responses that are maladaptive. Here, we study this issue and investigate how ventral tegmental area (VTA) DA activity reflects the ability to withhold prepotent responses during reward expectation. We developed a novel cued-reward lick-withholding task in which head-fixed, water deprived mice must suppress anticipatory licking during reward predicting cues. The task accomplishes the following: 1. It places Pavlovian cue responses in conflict with self-restraint, enabling us to study the neural substrates of action impulsivity. 2. It manipulates the degree of impulsivity by randomly interleaving three different auditory cues that

predict three different reward sizes. 3. It provides a quantitative, trial-by-trial measure of action impulsivity that can be precisely related to neural activity in real-time. The neural recordings were obtained using fiber photometry. Our behavioral results show that mice can discriminate between the three trial types and learn to exhibit self-restraint. In addition, mice behave more impulsively in anticipation of the larger reward, despite it resulting in a reduced rate of reward receipt. Neural recordings show that DA dynamically encodes for the failure to suppress conditioned responses. First, cue-induced phasic DA activity is predictive of impulsivity level, independent of reward expectancy. Second, changes in phasic DA cue responding may explain trial-to-trial variability in impulsivity. Third, DA ramping predicts the onset of impulsive actions. Lastly, impulsive actions lead to greater DA reward responses, suggesting a mechanism for the persistence of this maladaptive behavior. These data imply that phasic cue-induced DA activity drives action impulsivity.

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Poster

783. Inhibitory Control

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Topic: H.02. Human Cognition and Behavior

Support: R01NS100996
RO1NS095291

Title: Effects of dorsal and ventral STN stimulation on stopping performance

Authors: N. C. VAN WOUWE[1], S. A. WYLIE[2], P. M. KASKAN[3], E. B. BRADLEY[5], A. M. GIFFORD[2], S. SELVAM[2], S. HUGHES[5], A. LOPEZ[5], J. D. SCHALL[6], F. T. PHIBBS[5], B. M. DAWANT[7], J. S. NEIMAT[4];
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Abstract: Objective: Patients with frontal-basal ganglia dysfunction, like Parkinson's disease (PD), often experience problems with controlling their actions, for example, they have difficulty stopping a voluntary action. The PD motor symptoms can be effectively treated with deep brain stimulation (DBS) of the Subthalamic nucleus (STN). However, the precise role of the STN in cognitive functions like stopping control is unclear. The STN consists of functional sub-territories linked to dissociable cortical networks although the boundaries of the subregions is still under debate. The corticostriatal circuitry linking preSMA and right IFC with central STN has recently been associated to stopping control. We investigated whether stimulating subregions of the STN, and stimulation of left versus right STN would show dissociable effects on the

ability to stop. Methods: In experiment 1, we studied 11 PD patients with STN DBS. Patients with two adjacent contacts positioned within the bounds of the dorsal and ventral STN completed two testing sessions (off medication) with low amplitude stimulation (0.4mA) of either the dorsal or ventral contact. Patients performed a stop task with both stimulation settings. The second experiment (prelim data) included two groups of PD patients, receiving stimulation at either dorsal (n=7) or ventral STN (n=5) contacts with 4 different DBS settings: OFF stimulation, right lead DBS only, left DBS only, both left and right DBS. Both groups performed the stop task with each of the 4 DBS settings. Results: In the first experiment, ventral but not dorsal DBS improved stopping latencies ($p<.01$). Go reaction times were similar between dorsal and ventral DBS STN. Preliminary results from experiment 2 indicate that stopping tended to be faster with right ventral DBS STN, whereas stopping was slower with right dorsal STN DBS in comparison to OFF stimulation ($p=.09$). Neither bilateral nor left side stimulation settings modulated stopping and going speed in dorsal and ventral STN subregions. Conclusions: DBS in ventral (but not dorsal) subregion of the STN improved stopping speed. In contrast, previous work by our lab had shown improved conflict control with dorsal stimulation. Current study confirms the involvement of the STN in stopping control and provides support for STN functional subregions. More specifically, ameliorated stopping with right ventral DBS suggest a right lateralized network of inhibition of voluntary action.

Disclosures: N.C. van Wouwe: None. **S.A. Wylie:** None. **P.M. Kaskan:** None. **A.M. Gifford:** None. **A. Lopez:** None. **E.B. Bradley:** None. **F.T. Phibbs:** F. Consulting Fees (e.g., advisory boards); Boston scientific, Teva, Medtronic. **B.M. Dawant:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neurotargeting LLC. **J.S. Neimat:** None. **J.D. Schall:** None. **S. Hughes:** None. **S. Selvam:** None.

Poster

783. Inhibitory Control

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 783.12/Z32

Topic: H.02. Human Cognition and Behavior

Title: Individual differences in impulsivity correlate with weight-gain following DBS for the treatment of Parkinson's disease

Authors: *P. M. KASKAN[1], N. VAN WOUWE[1], W. BURKE[1], J. CHON[2], R. ALI[4], F. PHIBBS[3], P. KONRAD[2], J. NEIMAT[1];
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Abstract: Deep brain stimulation (DSB) of the subthalamic nucleus (STN) is intended to treat the motor symptoms of Parkinson's disease (PD) yet can produce a number of non-motor related side-effects. STN stimulation can elicit impulsive or frequent and erroneous responding, increase autonomic responses to affective stimuli, and alter subjective value. Side-effects like weight-gain, common following DBS for the treatment of PD, may be due to altered inhibitory control. We retrospectively reviewed a database which included body mass (BMI), neuropsychological measures, and cognitive data before and after surgery in a population of patients undergoing DBS for the treatment of PD at the Vanderbilt Movement Disorders Clinic (2012-2017). Pre- and post-surgical changes in BMI were calculated, and pre-surgical impulsivity was measured by the Questionnaire for Impulsive Compulsive Disorders Rating Scale (QUIP-RS). Pre-surgical performance on the Simon conflict task provided an additional objective measure of impulsivity. Post-surgical coordinates of active electrode contacts in STN and globus pallidus internus (GPi) were included. Seventy-nine patients were included (STN = 51, GPi = 28). The mean age at surgery was 61.7 years with male:female ratio of 2.5:1. There was a significant increase in weight following DBS (BMI-Pre = 27.4, BMI-Post = 28.8, p <0.001). Performance on the Simon task (STN = 30, GPi = 14) indicated that fast impulsive errors on Simon conflict trials (r = -0.381, p = 0.038), and faster reaction times with those errors (r = -0.368, p = 0.045) correlated with weight-gain in patients with STN targets (but not GPi). Of patients that gained weight (n = 66), patients with STN implants gained more weight than those with GPi implants (weight-gain x DBS target, p = 0.043), especially in patients with impulse control disorder (ICD) (weight-gain x impulse control disorder x DBS target, p = 0.028), corroborating findings on the Simon task. Our current study suggests patients with STN implants could experience a greater increase in BMI compared to patients with GPi implants, particularly when diagnosed with ICD pre-operatively. Future work will investigate the role of active contact location in STN (i.e. limbic, motor, and associative sub-regions), subjective reward sensitivity, response inhibition, and changes in activity in relation to post-surgery weight changes.

Disclosures: P.M. Kaskan: None. **N. van Wouwe:** None. **W. Burke:** None. **J. Chon:** None. **R. Ali:** None. **F. Phibbs:** None. **P. Konrad:** None. **J. Neimat:** None.

Poster

783. Inhibitory Control

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 783.13/Z33

Topic: H.01. Animal Cognition and Behavior

Support: University of Toledo DeArce-Koch Award (FSH)

Title: Decision-making, impulsivity, and attentional performance in heterozygous dopamine transporter knockout mice

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Abstract: Introduction: Dopamine is a neurotransmitter that has major roles in attention, working memory, reward, motivation, and motor activity. Dopamine signaling perturbations have been implicated in several developmental psychological disorders including attention deficit hyperactivity disorder (ADHD), schizophrenia, and obsessive-compulsive disorder. The dopamine transporter (DAT) has a critical role in regulating dopamine release dynamics. Consequently, during development dopamine activity influences prefrontal cortex maturation, with potential consequences on response inhibition, attention and decision making. DAT +/- mice have reduced DAT expression compared with DAT +/+ mice that produces behavioral and anatomical alterations that have been suggested to model aspects of ADHD. To further evaluate this model, decision-making and attentions were assessed in the 5-choice continuous performance test (5CCPT) and a mouse version of the Iowa gambling task (IGT). Methods: Separate groups of adult male DAT +/+ and DAT +/- mice were tested in the 5CCPT and the IGT. All mice were socially housed throughout testing and mildly food-deprived. The effects of amphetamine (0, 0.3, 0.66, 1.5 mg/kg) were also examined in the 5CCPT. Training in the 5CCPT was modified to accelerate training and testing so that the procedure could be completed in 10 days, to allow testing during the adolescent period in a separate group of mice. Results: In adolescence, DAT +/- mice had a lower sensitivity index (SI), but this was not observed in adult DAT +/- mice. This lower SI resulted primarily from poor response inhibition during no-go trials. Adult DAT +/- mice had more premature errors and incorrect response, and these impairments were reduced by amphetamine. Amphetamine also increased the SI in DAT +/+ mice. In the IGT, adult DAT +/- mice had an impaired ability to switch away from the disadvantageous choices to the advantageous ones. Conclusion: In the present study, adolescent DAT +/- mice showed deficits in response inhibition that impaired performance in the 5CCPT. In adulthood performance was again impaired on other measures, and these deficits could be ameliorated by amphetamine. Adult mice also showed impairments in decision making in the IGT, having difficulty switching from less advantageous choices to more advantageous choices. These cognitive impairments, deficits in decision making and impulsivity are all symptoms of ADHD, and further support the suggestion that DAT KO mice model aspects of ADHD. Moreover, these data suggest that heterozygous DAT deletion, that has more validity for human variation in DAT function, also models cognitive changes that underlie ADHD.

Disclosures: F.S. Hall: None. **Y.H. Saber:** None. **O. Chaker:** None.

Poster

783. Inhibitory Control

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 783.14/Z34

Topic: H.01. Animal Cognition and Behavior

Support: HR0011-17-2-0019

Title: Vagus nerve stimulation attenuates impulsivity in a 5-choice serial reaction time task

Authors: *J. F. DESLAURIERS[1], M. M. BRUNER[6], L. ALTIDOR[2], T. S. GARMAN[1], S. RAMIREZ[1], E. W. DIRR[1], K. OLCZAK[7], A. P. MAURER[3], K. J. OTTO[1], S. N. BURKE[2], D. G. LAMB[4], B. SETLOW[5], J. L. BIZON[8];
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Abstract: Impulsivity is a neurobehavioral phenotype that associates with a number of psychiatric disorders, including attention-deficit hyperactivity disorder and substance use disorder. Impulsivity can be assessed in rodent models using a 5-choice serial reaction time task in which rats must wait for presentation of a brief visual cue, the location of which indicates where a response will earn a food reward. Drugs modulating norepinephrine can attenuate premature responses in this task but these drugs also can also have off-target effects. Electrical stimulation of the vagus nerve (VNS) is approved for treatment of epilepsy and several other neuropsychiatric disorders and many of these beneficial effects are attributed to modulation of noradrenergic neurons in locus coeruleus. The current study evaluated whether VNS can inhibit premature responses on the 5-choice task. Adult male Brown Norway rats were trained in operant chambers, in which stimuli are projected on a touch-sensitive video screen. Under baseline conditions, individual differences in performance were observed such that some rats reliably made a high number of premature responses per session (i.e,10-50, “high impulsive”) and others made very few (<5, “low impulsive”). “High impulsive” rats showed worse attentional accuracy and a trend toward fewer omissions compared to “low impulsive” rats. Rats were then tested using a randomized, within-subjects design in which VNS (50 Hz, 60 µs pulse width, 500 µA, 0.8 s train duration) was delivered upon correct responses. These VNS parameters decreased premature responses in high impulsive rats, in the absence of effects on either attentional accuracy or trial omissions. Several additional VNS parameters (30 Hz, 120 µs pulse width, 700 µA, 0.8 s train duration, or 12.5 Hz, 100 µs pulse width, 400 µA, 1.25 s train duration) had no effects on performance. For comparison, a separate group of rats was tested in the 5-choice task following acute administration of the noradrenergic reuptake inhibitor atomoxetine (0, 0.3, 1.0, 3.0 mg/kg), using a randomized, within-subjects design. As has been previously reported, atomoxetine reduced premature responses, but also impaired attentional accuracy and increased trial omissions. Considered together, the data show that VNS is efficacious for reducing motor impulsivity, in the absence of off-target effects evident in pharmacological approaches. The findings suggest that VNS might be useful in conditions characterized by elevated impulsivity.

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Poster

783. Inhibitory Control

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 783.15/Z35

Topic: H.02. Human Cognition and Behavior

Support: NIJ 2017-R2-CX-0034

Title: Symptoms of post traumatic stress disorder in police officers are related to ERP measures of cognitive control in a Go/NoGo task

Authors: *J. L. SHUCARD[1], X. WANG[1], M. EVANS[1], T. J. COVEY[1], J. M. VIOLANTI[2], D. W. SHUCARD[1];
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Abstract: Police officers are frequently exposed to traumatic events and are at high risk for the development of Posttraumatic Stress Disorder (PTSD). This study examined the effects of PTSD symptoms on the ability of active duty police officers to make rapid and critical decisions. Dense electrode (256 channels) electroencephalography (EEG) was used to extract event-related brain potentials (ERPs) from the scalp-recorded EEG obtained while trauma-exposed police officers and non-trauma exposed civilians performed two visual A-X CPT Go/NoGo tasks (each approximately 10 minutes in length). Participants had to respond (Go) with a button press to an "X" when it followed an "A", and inhibit their response (NoGo) when a letter other than "X" followed the "A." The first task had normal letter stimuli and the second had visually degraded stimuli, which increased the difficulty of stimulus discrimination. The tasks provide behavioral and neural measures of target detection (Go), response inhibition (NoGo), and ability to screen irrelevant stimuli. ERPs are uniquely able to measure the timing (in msec) of neuronal decision-making events that require cognitive control mechanisms necessary to respond or inhibit a response. The N2 and P3 components are thought to reflect different aspects of cognitive/response control, with the NoGo N2 being related to conflict monitoring and the NoGo P3 to inhibition of a response. We hypothesized that conflict monitoring, as measured by N2, and inhibitory control, as measured by the NoGo P3, would be affected by the level of PTSD symptoms in police. Degraded stimuli were hypothesized to increase conflict and demand on inhibitory processes, thereby enhancing the ability to detect deficits in cognitive control. Preliminary examination of ERPs components for high PTSD symptom police, low symptom police, and controls (32 officers and 14 controls) from an ongoing large-scale study showed that all three groups had the expected Go/NoGo effects for N2 and P3, with greater fronto-central amplitude NoGo compared to Go for the regular stimuli. However, differences were present in the waveforms, particularly for the degraded stimuli, that were dependent on the degree of PTSD

symptoms. For example, the high PTSD symptom police group had the greatest fronto-central P3 amplitude to NoGo stimuli, and an attenuated fronto-central N2 for the NoGo degraded stimuli. These findings may reflect reduced cognitive control and increased activation of response inhibition in high symptom police relative to the other two groups.

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Poster

784. Social Memory and Cognition I

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 784.01/Z36

Topic: H.01. Animal Cognition and Behavior

Support: H2020-ERC-2018-SyG 810580-BrainPlay

Title: Rats play hide & seek, an elaborate role-play game

Authors: *A. S. REINHOLD, J. I. SANGUINETTI SCHECK, K. HARTMANN, M. BRECHT;
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Abstract: Evolutionary, cognitive and neural underpinnings of mammalian play are not yet fully elucidated. We played 'Hide & Seek' – an elaborate role-play-game – with rats. We did not offer food-rewards, but engaged in playful interactions with rats after finding or being found. All rats quickly acquired the game and learnt to switch roles. During 'Seek', rats systematically searched a large $30m^2$-room and guided searches by visual cues and memories of past hiding locations. Hiding strategies included preferences for non-transparent over transparent hiding enclosures and frequent changing of hiding locations.
Rats emitted complex ultrasonic vocalizations during 'Hide & Seek' that varied with game-events and trial types. Vocalization rates peaked at the beginning of the game, when finding the experimenter, during playful interactions and when being returned. Rats called very little when searching, when hiding and when being found. Hence, ultrasonic calls might coordinate rat role-play. The game of 'Hide & Seek' affords rules. Rats played by these rules and showed highly distinct behavior between 'Hide' and 'Seek' trials.
'Hide & Seek' has found little attention in science, but our findings confirm pet-owner-reports that animals enjoy playing 'Hide & Seek'. Fast acquisition, strategic behavior and game-adequate vocalization patterns – traits, which emerged without specific conditioning – point to an innate preparedness for role-play and elaborate cognitive and neural capacities for 'Hide & Seek' in rats. We suggest that role-play in general and 'Hide & Seek' in particular might be very old.

The paradigm established here offers a playful approach to the mammalian mind and the comparative study of social role-play behavior.

Disclosures: A.S. Reinhold: None. **J.I. Sanguinetti Scheck:** None. **K. Hartmann:** None. **M. Brecht:** None.

Poster

784. Social Memory and Cognition I

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 784.02/Z37

Topic: H.01. Animal Cognition and Behavior

Support: H202-ERC-2018-SyG810580-BrainPlay

Title: Neural correlates of 'hide and seek' in medial prefrontal cortex

Authors: *J. I. SANGUINETTI-SCHECK[1], M. CONCHA-MIRANDA[2], A. S. REINHOLD[1], K. HARTMANN[1], M. BRECHT[1];
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Abstract: Rats have elaborate cognitive capacities for playing 'Hide & Seek' (accompanying poster Reinhold et al, 2019). Rats are able to switch roles, they use strategies for successful play and develop differential game-related vocal patterns. The brain is rarely studied during such rich unrestricted behavior. We investigated the neural correlates of 'Hide & Seek' by performing tetrode recordings of single neurons (n=177) in rat medial prefrontal cortex, a brain area previously associated to decision making, social proximity and task rules. A data logger system allowed us to record from untethered freely playing animals in a 30 m^2 room. We assessed if medial prefrontal cortex neurons are engaged with 'Hide & Seek'. Our recordings revealed intense prefrontal cortex activity that varied with game-events (initiation, finding, being-found, interaction, etc.) and trial-types ('Hide' vs. 'Seek') and might thus coordinate role-play behavior. Our results indicated that medial prefrontal cortex follows closely the narrative of the game. We then also asked, what happens in rat medial prefrontal cortex, when the animal observes others playing vs when the animal plays 'Hide & Seek' itself? We again found prefrontal cortex activity (n=110) that was sharply locked to game-events, when the animal played itself. Observing play, however, did not lead to a comparable activation of rat medial prefrontal cortex. Average firing rates during observing play were lower than during real play and neural responses during observing game-events did not mirror event responses during play. We conclude that even though rat medial prefrontal cortex is highly engaged during 'Hide and Seek', it's activity does not mirror play-events under our experimental conditions. We wonder if the lack of prefrontal

activity while observing play points to the necessity of a ‘play brain state’ for engaging prefrontal cortex.

Disclosures: J.I. Sanguinetti-Scheck: None. **M. Concha-Miranda:** None. **A.S. Reinhold:** None. **K. Hartmann:** None. **M. Brecht:** None.

Poster

784. Social Memory and Cognition I

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 784.03/Z38

Topic: H.01. Animal Cognition and Behavior

Support: MH100318
P50MH100023

Title: Basolateral amygdala and recognition memory for social odors

Authors: *Z. SONG[1], S. SWARNA[2], J. MANNS[1];
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Abstract: The amygdala, a key component of the neural circuitry that supports adaptive affective behavior, is implicated in a variety of behavioral disorders including autism, PTSD, and psychopathy. It is essential for learning and leveraging the affective salience of stimuli, including not only associating tones with fear responses, but also including processing stimuli with particular relevance to social interactions. The present project examined the extent to which the basolateral complex of the amygdala (BLA) in female rats was involved in processing social cues and more specifically the recognition memory of social odors. Urine odors of female and male rats were used as stimuli, as conspecific urine is a potent social cue that conveys a range of socially-relevant information such as health, sex, social status, and reproductive status. Household aromatherapy scents were used as nonsocial control stimuli and were presumed to not bear any biological significance. All the social odors and aromatherapy scents were novel to the rats prior to each experiment. Recognition memory was tested using a spontaneous preference for novel odors paradigm, and one question was whether differences in baseline preference for social versus nonsocial odors might impact the results. In general, female rats showed preference for male urine as compared to female urine and nonsocial odors. In addition, inactivation of the BLA via infusion of muscimol, as compared to infusion of saline, appeared to impact both baseline preference and recognition memory of male urine more than for female urine. The results suggested that the role of the BLA in spontaneous preference for novel social odors might differ for same-sex versus opposite-sex urine, perhaps indicating a role for the BLA in modulating both preference and memory.

Disclosures: **Z. Song:** None. **S. Swarna:** None. **J. Manns:** None.

Poster

784. Social Memory and Cognition I

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 784.04/Z39

Topic: H.01. Animal Cognition and Behavior

Support: FRQnt

Title: New model to assess prosocial behaviours in juvenile rats: An operant box sharing task

Authors: *V. CHARRON, J. TALBOT, H. PLAMONDON;
Sch. of Psychology, Dept. of Neurosci., Univ. of Ottawa, Ottawa, ON, Canada

Abstract: Altruism is characterized by a behaviour associated with a cost to the animal while granting a beneficial outcome for others. Prosocial behaviours have been studied in primates and other animals, including rodents. The majority of models used is pain or fear related, but positive prosocial behaviours are not as much studied in rodent models. Existing literature supports that rodents can exhibit prosocial behaviours, although research on altruistic behaviours is sparse and limited. This pilot study aims to establish a novel method measuring prosocial behaviours in rats. Long-Evans adolescent male rats (PND 28- *n*=8) were housed in pairs. During the test, one rat was assigned an observer's role while its cagemate could engage in prosocial behavior. A modified operant box unit with two levers was used. The box was divided by a plexiglass wall were rats could see, smell and hear each other. The task was designed so that the actor could choose to press an easy lever (35 g of pressure needed), which dispenses one single pellet to the actor, or push a harder lever (75 g of pressure needed), dispensing one pellet to the actor and one pellet to the observer. Our findings showed that the actors pressed more frequently the hard lever compared to the easy one. This method could help assess different social behaviours, including altruism, cooperation and prosocial choices, helping to understand prosociality in rodents. It could also help determine bio/behavioural responses underlying mental health disorders, including autism, depressive and anxiety-like behaviours.

Disclosures: **V. Charron:** None. **J. Talbot:** None. **H. Plamondon:** None.

Poster

784. Social Memory and Cognition I

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 784.05/Z40

Topic: H.01. Animal Cognition and Behavior

Support: FRQnt

Title: Prior relationship as a mediator in prosocial behaviours in rats: A stranger rat operant box task model

Authors: *J. TALBOT, V. CHARRON, H. PLAMONDON;
Sch. of Psychology, Dept. of Neurosci., Univ. of Ottawa, Ottawa, ON, Canada

Abstract: Previous research investigated animals' ability to display prosocial behaviour under aversive conditions or constraints. As a result, current literature is sparse and limited when it comes to altruistic behaviour testing using a stranger rat scenario. This study aims to compare a prosocial behaviour in a sharing scenario where the rat is either a stranger versus a cagemate. Based on findings from previous research on the same theme, we speculate that faced with a concrete reward in form of pellets, actors will be more prone to display a prosocial behaviour towards cagemates versus stranger rats (i.e., making a greater effort in order to give a reward to the other rat). Male Long-Evans late adolescent through early adulthood rats (PND 28- *n*=8) were used. The task consisted of an actor and an observer, where the observer was either a cagemate or a stranger rat. The actor has a choice of two levers, one of which dispenses one sucrose pellet only to himself (defined as the easy lever, 35 g of pressure needed), while the hard lever (75 g of pressure needed) dispenses one pellet to both rats. Preliminary results show that the actors tend to prefer pressing the harder prosocial behaviour lever over the more selfish approach, when facing their cagemate. At present, the second phase using a stranger rat is still ongoing. Once acquired, the data will help create a solid anchor and could help direct future studies in prosocial behaviour observation in rodent models.

Disclosures: J. Talbot: None. **V. Charron:** None. **H. Plamondon:** None.

Poster

784. Social Memory and Cognition I

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 784.06/Z41

Topic: H.01. Animal Cognition and Behavior

Support: MH104602

Title: VIP neurons support CA2 input-timing dependent plasticity and social memory

Authors: *F. LEROY, C. A. DESOLIS, A. ASOK, S. A. SIEGELBAUM;
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Abstract: CA2 pyramidal neurons receive strong excitatory input from entorhinal cortex (EC) that is capable of triggering CA2 spike output. CA3 pyramidal neurons also receive excitatory input from the CA3 Schaffer collaterals (SC). However, the SC input to CA2 is dominated by strong feedforward inhibition mediated by PV^+ interneurons (INs). In contrast to the well-known ability of SC inputs to CA1 to support long-term synaptic potentiation, the SC inputs to CA2 are highly resistant to LTP induction. As CA2 neurons are important for social memory, one important goal is to identify the cellular and molecular mechanisms that may contribute to CA2 memory storage. In previous work we found that CA2 pyramidal neurons undergo input timing-dependent plasticity (ITDP), a heterosynaptic, circuit-based form of plasticity in feedforward inhibition first described in CA1. Pairing of the direct entorhinal cortical (EC) inputs to CA2 with the CA2 SC inputs at a 20 ms delay interval (EC before SC) produced a δ-opioid receptor-dependent long-term depression of PV^+ IN feedforward inhibition. Social interactions with a novel mouse reduced the magnitude of ITDP, suggesting that social memory storage may recruit CA2 ITDP. Finally, we found that infusion of the δ-opioid receptor (DOR) antagonist naltrindole through a cannula into CA2 impaired social memory, suggesting that ITDP may provide CA2 with a mnemonic plasticity mechanism. To further explore the mechanism of CA2 ITDP and its link to social memory, we searched for the source of enkephalin (ENK), the principal DOR agonist, released during CA2 ITDP. Consistent with previous studies, we found that ENK and VIP expression overlap extensively in CA2/CA3. Using a VIP-cre mouse line to selectively identify or target VIP^+ INs, we activated or silenced these cells using optogenetic tools in acute dorsal hippocampal slices. We found that VIP^+ INs in the CA2 region received excitatory input from both EC and CA3, suggesting that they could integrate these distinct inputs during paired stimulation. Importantly, optogenetic stimulation or inhibition of the VIP^+ INs, respectively, triggered or blocked CA2 ITDP. Moreover, activation of VIP^+ INs failed to elicit ITDP when naltrindole was present in the bath to block DORs. Finally, using viral injections to express the inhibitory DREADD (iDREADD) in VIP^+ INs in CA2 and neighboring hippocampal regions, we found that silencing hippocampal VIP^+ INs *in vivo* with systemic injection of the DREADD ligand CNO was sufficient to impair social memory. Overall, our results support the hypothesis that enkephalin release from VIP^+ INs during social interactions triggers CA2 ITDP and allows the formation of social memory.

Disclosures: F. Leroy: None. **C.A. DeSolis:** None. **A. Asok:** None. **S.A. Siegelbaum:** None.

Poster

784. Social Memory and Cognition I

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 784.07/Z42

Topic: H.01. Animal Cognition and Behavior

Support: T32 GM736743

Title: Regulation of social behavior along the dorsoventral axis of the hippocampal subregion CA2

Authors: *L. M. BOYLE[1], F. LEROY[1], R. B. SAHAI[1], S. IRFAN[2], S. A. SIEGELBAUM[3]; [1]Columbia Univ., New York, NY; [2]Barnard Col., New York, NY; [3]Dept of Neurosci., Columbia Univ. Coll P & S, New York, NY

Abstract: Altered social behavior is a prominent feature of psychiatric and neurological disorders including autism spectrum disorder (ASD), depression, and schizophrenia. The neuropeptide vasopressin has emerged as one essential signaling molecule for social cognition and behavior. Polymorphisms in the AVPR1b vasopressin receptor subtype are associated with ASD, and knockout of this receptor in mice results in decreased sociability, social recognition memory (SRM), and social aggression. In the hippocampus, AVPR1b is exclusively expressed in the CA2 region. Recently, activation of vasopressin inputs from the paraventricular nucleus (PVN) to the CA2 region in dorsal hippocampus was shown to enhance SRM in mice, while inhibition of dorsal CA2 (dCA2), and in particular the projections of dCA2 to ventral hippocampus, results in an impairment in the encoding, consolidation and recall of SRM. Multiple studies demonstrate that while the dorsal hippocampus primarily regulates contextual memory and spatial navigation, ventral hippocampus plays an important role in anxiety, emotional processing and social memory. Here, we explore the hypothesis that, whereas dorsal CA2 may influence SRM, ventral CA2 may influence other aspects of social behavior. As the dorsal-ventral extent of CA2 remains relatively unexplored, we first examined the expression of several molecular markers that are characteristic of dorsal CA2. We find that whereas the expression of some CA2 markers is restricted to more dorsal regions of hippocampus, a population of AVPR1b-expressing cells, defined using an AVPR1b-Cre line, extends along the entire extent of the dorsoventral axis of CA2. Moreover, the ventral CA2 region receives dense vasopressin inputs from the PVN. Anterograde tracing reveals that dorsal and ventral CA2 project topographically to output regions, providing a potential mechanism for a differential functional role. We are therefore using a pharmacogenetic approach to compare how selective manipulations of dorsal versus ventral CA2 affect different aspects of social behavior.

Disclosures: L.M. Boyle: None. **F. Leroy:** None. **R.B. Sahai:** None. **S. Irfan:** None. **S.A. Siegelbaum:** None.

Poster

784. Social Memory and Cognition I

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 784.08/AA1

Topic: H.01. Animal Cognition and Behavior

Support: NIH-NINDS Training Grant 5 T32 NS 064928-08
NIH 1 R01 NS106983-01
NIH R21 NS093991

Title: The role of hippocampal area CA2 in the pilocarpine mouse model of mesial temporal lobe epilepsy

Authors: *A. C. WHITEBIRCH, K. VADDURI, B. SANTORO, S. SIEGELBAUM; Neurosci., Columbia Univ., New York, NY

Abstract: Mesial temporal lobe epilepsy (MTLE) is a drug-resistant form of epilepsy associated with a pattern of pathology termed mesial temporal sclerosis, in which there is extensive cell loss in the hippocampal CA1 and CA3 areas while the dentate gyrus and CA2 remain relatively intact. The fact that the hippocampus is a major site of seizure activity in MTLE, despite the degeneration in CA1 and CA3, suggests that epileptiform activity may be generated in or conveyed through surviving CA2 circuitry. Accumulating evidence also suggests that CA2 may have a key role controlling hippocampal network excitability in the healthy brain. However, relatively little is known about CA2 circuitry under either physiological or pathological conditions. To explore whether changes to CA2 excitability or functional synaptic connectivity may contribute to seizure activity in MTLE we utilized the pilocarpine mouse model of temporal lobe epilepsy, in which a single dose of pilocarpine (PILO) induces acute *status epilepticus* and ultimately causes recurring spontaneous seizures. We used optogenetic and chemogenetic excitation and inhibition to selectively manipulate CA2 using Cre-dependent viral expression in the *Amigo2-Cre* mouse line and obtained electrophysiological recordings from CA2 pyramidal neurons (PNs) in acute hippocampal slices from control and PILO-treated mice. We found that in normal brain tissue, CA2, like CA3, forms an auto-associative excitatory network. Thus, CA2 PNs send longitudinal projections that excite other CA2 neurons. However, normally this recurrent excitation is small and dominated by feedforward inhibition. Similarly powerful feedforward inhibition is also recruited by CA3 Schaffer collateral input to CA2 and by CA2 PN back-projections to CA3. Preliminary recordings in slices from PILO mice revealed a significant reduction in feedforward inhibition recruited by excitatory inputs to CA2 PNs, including the CA3 Schaffer collateral inputs and CA2 recurrent collateral inputs. Notably, fast inhibition mediated by $GABA_A$ receptors shows a greater reduction than slow $GABA_B$-mediated inhibition. In addition we found an increase in the intrinsic excitability of CA2 PNs, largely as a result of

increased input resistance. Taken together, these data suggest a shift in the inhibitory-excitatory balance of the CA2 network and provide support for the hypothesis that CA2 may contribute to the generation of epileptiform activity in the hippocampus.

Disclosures: A.C. Whitebirch: None. **K. Vadduri:** None. **B. Santoro:** None. **S. Siegelbaum:** None.

Poster

784. Social Memory and Cognition I

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 784.09/AA2

Topic: H.01. Animal Cognition and Behavior

Support: NIH MH104602
NIH MH106629
EMBO ALT-120-2017

Title: Ca2 ripples regulate social memory

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Abstract: Sharp-wave ripples (SWRs) represent a synchronous pattern of population activity in the hippocampus during slow wave sleep that are necessary for spatial memory consolidation. This mnemonic function likely results from the sequential reactivation of place cells that replay spatial trajectories recently experienced by the animal. Although the role of SWRs in spatial memory is well established, it is not known if they are also involved in other types of hippocampal-dependent memory. Here we explore the role of SWRs in social memory, the ability of an animal to recognize and remember a conspecific. Recent evidence suggests that social memory encoding, consolidation and recall require the participation of the hippocampal CA2 region *and* that CA2 acts as a local source of SWR generation. These separate findings led us to investigate the role of SWRs and CA2 in social memory. We found that CA2 and CA1 ensembles that were more active during social exploration of a novel animal were reactivated during SWRs during sleep. Moreover, specific optogenetic silencing of CA2 pyramidal cells during social exploration impaired memory performance and SWR reactivation during sleep. In addition, closed-loop interference with spontaneous SWRs, using strong brief pulses of optogenetic stimulation of CA2 pyramidal neurons, suppressed the formation of social memory. Furthermore, promoting SWR firing during consolidation using weak shaped light pulse activation of CA2 pyramidal cells enhanced social memory duration. We are currently investigating the computational capabilities by which the hippocampus represents such social

episodes. Social memory deficits associated with mental disorders, such as schizophrenia, are recapitulated in a genetic mouse model (Df(16)A+/-) of the human 22q11.2 deletion syndrome that has intrinsic and synaptic alterations in CA2. Most SWRs in these mice had abnormally high frequency components, with a minority of physiological SWRs showing normal physiological parameters. By combining optogenetic closed-loop SWR disruption and generation we were able to interfere with aberrant SWRs and promote normal SWRs using appropriate light pulses during consolidation. Remarkably, this manipulation was sufficient to rescue social memory deficits to a level comparable to wild-type animals. Our results demonstrate that SWRs and CA2 reactivation are both necessary for the consolidation of social memory, a non-spatial, complex form of information storage, and sufficient to enhance social memory performance in wild-type mice and restore social memory in a neuropsychiatric disease model.

Disclosures: A. Oliva: None. **S.A. Siegelbaum:** None.

Poster

784. Social Memory and Cognition I

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Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 784.10/AA3

Topic: H.01. Animal Cognition and Behavior

Support: NARSAD Young Investigator Grant

Title: Population dynamics during olfactory discrimination of hippocampal area CA2 in mice

Authors: *S. HASSAN[1], S. A. SIEGELBAUM[2];
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Abstract: Social cognition is one of the key features that underlie an animal's sense of a stable community and allows formation of lasting social relationships. It refers to the psychological and neural processes that are involved in the perception, encoding, storage, retrieval and regulation of information about conspecifics in relation to an individual, including the process of social memory, the ability to recognize and remember an individual conspecific. Despite a growing body of research aimed at resolving the underlying mechanisms of social cognitive processes, a detailed understanding about the brain regions involved and especially their specific population activity dynamics in the context of social behavior is still lacking.
Recent work in our lab identified a crucial role of the CA2 subregion of the hippocampus in social recognition memory in rodents. Silencing of excitatory output from CA2 resulted in the loss of the encoding, consolidation and recall of social recognition memory and also suppressed social aggression between a resident male and an intruder. An important next step is the characterization of the underlying dynamics and processing of sensory cues that take place

during social recognition in CA2, ideally employing a high resolution approach that allows the identification of population dynamics during social recognition and memory recruitment. Olfactory stimuli, and in particular olfactory social stimuli such as urine, are one candidate salient cue that may enable mice to recognize conspecifics. We are using an olfactory discrimination task involving both social and non-social odors in awake, head-fixed mice while using 2-photon imaging of CA2 neuron activity based on GCaMP6s fluorescence signals. Our preliminary results indicate that mice are able to discriminate social odors from distinct male conspecifics and that these odors trigger robust CA2 activation. Experiments in progress explore whether CA2 activity can distinguish social from non-social odor cues.

Disclosures: S.A. Siegelbaum: None.

Poster

784. Social Memory and Cognition I

Location: Hall A

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Program #/Poster #: 784.11/AA4

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant R01MH095894
NIH Grant R01MH108627
NIH Grant R37MH109728
SFARI Grant 304935 MLP

Title: Humans and monkeys playing an interactive chicken game with an option to cooperate

Authors: *W. S. ONG, M. L. PLATT;
Univ. of Pennsylvania, Philadelphia, PA

Abstract: Competitive opponents today might be cooperative allies tomorrow. Navigating social environments requires understanding the strategies of others, and how their actions may change across different situations. The neurobiological mechanisms that mediate dynamic social interactions remain poorly understood. To address this gap, we devised a variant of the “chicken” game that alternates between competitive and cooperative scenarios that can be played iteratively, by pairs of players, either monkey or human, thus opening up the possibility of studying the underlying neurobiology at multiple levels.
Two individuals (S1&S2) faced each other across screen(s) showing 2 colored annuli and 4 response targets. On some trials, the larger reward (denoted by visual tokens) was opposite S1 behind S2’s annulus and smaller rewards were on the left (see figure). S1 is tempted to choose straight, but if S2 also chooses straight the annuli collide and neither player receives reward. On some trials, a “cooperation bar” allows both players to unlock larger rewards if and only if they both choose to swerve; if only one swerves he receives a smaller reward and the other player

receives the larger reward for going straight.
To understand the underlying process, we created a model in which S1 uses his beliefs about S2's strategy to predict his behavior on each trial. S1's beliefs about S2's strategy are represented as a logistic regression relating the potential payoffs on a trial to the probability of S2 swerving or going straight. S1 learns S2's strategy by updating his beliefs using a strategic prediction error, computed as the mismatch between his expectation of S2's choice and what S2 actually did.
Most human players (181 pairs) preferentially played cooperative strategies irrespective of the payoffs on the current trial, consistent with the simplest model. By contrast, monkeys (4 pairs) were much more attentive to payoffs for self and other, consistent with the belief updating model. We also collected eye-tracking data (n=75) and EEGs (n=20) on a subset of pairs of human players. Humans rarely looked at their opponents, unlike monkeys, although both species preferentially looked at their opponents after they made selfish choices.

Disclosures: W.S. Ong: None. **M.L. Platt:** None.

Poster

784. Social Memory and Cognition I

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 784.12/AA5

Topic: H.01. Animal Cognition and Behavior

Support: KAKENHI (26293261)
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KAKENHI (JP15H05917)
Ministry of Education, Culture, Sports, Science and Technology (156180-510210)
AMED (JP18dm0107146)

Title: Neural activity in the macaque medial prefrontal cortex plays a causal role in false-belief attribution

Authors: *R. AKIKAWA[1,2], T. HAYASHI[2,3], K. KAWASAKI[2], J. EGAWA[3], T. MINAMIMOTO[4], K. KOBAYASHI[5], S. KATO[5], Y. HORI[4], Y. NAGAI[4], A. IIJIMA[1,6,7], T. SOMEYA[3], I. HASEGAWA[2];
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Engineering, Assistive Technology, and Art and Sports Sciences, Fac. of Engineering, Niigata Univ., Niigata, Japan

Abstract: The ability to guess other's mental states, such as beliefs or desires driving their behavior, is fundamental to social interactions among individuals. Acquisition of this function, called "theory of mind (ToM)", is critically evaluated by testing whether one predicts others' actions according to their beliefs, even when those beliefs are different from reality. Human neuroimaging studies using various false-belief (FB) attribution tasks have revealed the relationship between ToM and brain networks including the medial prefrontal cortex (mPFC). However, whether the mPFC plays a causal role in ToM remains unsettled due to the lack of interventional studies to manipulate neuronal activity using appropriate animal models of FB attribution. In the present study, we initially used an anticipatory looking FB paradigm in eight macaque monkeys and found spontaneous gaze bias of the monkeys implicitly anticipating others' FB-driven actions. We next examined whether there is causation between the neuronal activity of the mPFC and the animals' spontaneous gaze bias to the FB targets. A lentiviral vector incorporating hM4Di, an inhibitory DREADD (designer receptor exclusively activated by designer drugs) was injected into the mPFC in five monkeys. Six weeks following viral injection, we chemogenetically inactivated the mPFC by intramuscular injection of clozapine N-oxide (CNO), a specific ligand to hM4Di. Within 60 to 80 minutes after CNO injection, neuronal activity in the mPFC was significantly inhibited. We found that chemogenetic deactivation of the mPFC by CNO injection in hM4Di-expressing monkeys specifically altered the gaze bias to the FB target. If CNO was injected into animals without hM4Di expression, or saline was injected into hM4Di-expressing animals, the gaze bias remained significant. Thus, hM4Di induction or CNO application alone did not alter, but their combination did alter FB comprehension in macaques. Therefore, FB attribution-like behaviors underpinned by shared neural circuits with humans are demonstrated in non-human animals, suggesting that the mPFC would have evolved as a crucial hub of the brain network causally linked to mental attribution in the primate lineage.

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Poster

784. Social Memory and Cognition I

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Program #/Poster #: 784.13/AA6

Topic: H.01. Animal Cognition and Behavior

Support: NIMH Intramural Research Program (ZIAMH002887)

Title: Effect of anterior cingulate cortex damage on live social interactions in rhesus monkeys

Authors: *B. M. BASILE, J. SCHAFROTH, C. KARASKIEWICZ, E. A. MURRAY;
Lab. of Neuropsychology, Natl. Inst. of Mental Health, NIH, Bethesda, MD

Abstract: The anterior cingulate cortex (ACC) has been implicated in social cognition. Previous work from our lab has shown that rhesus monkeys with selective ACC damage do not acquire the species-typical preference for giving juice to a familiar conspecific over giving juice to nobody. This suggests a deficit in social valuation. However, it is less clear the degree to which ACC lesions affect more natural social relationships. To fill this gap, we assessed the dominance relationships of monkeys before and after selective, bilateral, ibotenic acid lesions of the ACC. We tested nine monkey dyads in total. First, individuals sat opposite each other in chairs while we video recorded them. To assess dominance, we coded the time gazing at the other monkey, the number of looks at the other monkeys, affiliative lipsmacks, aggressive yawns, and stress yawns. Next, we tested each dyad on a food competition task in which individual grapes were sequentially placed between the two monkeys. Finally, we solicited subjective ratings of which individual seemed most dominant from the monkeys' primary handler and a monkey expert who viewed the videotapes but did not know these monkeys. Three individuals, representing six of the nine dyads, were then given bilateral ACC lesions, the remaining three dyads were left intact as controls, and we re-ran our tests. Preliminary results suggest one dominance reversal and subtle changes in viewing pattern of monkeys with ACC damage, but no robust social dysregulation. These data help characterize the role of the ACC in live social interactions.

Disclosures: B.M. Basile: None. **J. Schafroth:** None. **C. Karaskiewicz:** None. **E.A. Murray:** None.

Poster

784. Social Memory and Cognition I

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Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 784.14/AA7

Topic: H.01. Animal Cognition and Behavior

Support: ERC Grant 648734-HUMO

Title: Agent related activity in area 10 of macaque monkeys during a social interactive task

Authors: *L. FERRUCCI[1], S. NOUGARET[1], V. FASCIANELLI[1], R. C. SAUNDERS[2], A. GENOVESIO[1];
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Abstract: The most anterior part of the frontal cortex in primates is represented by the Frontal Pole (FP), also known as Broadmann's area 10, and contributes in many aspects of cognition.

Human imaging studies suggest that the FP mainly contributes to complex reasoning and problem-solving and that its position among the neighboring prefrontal regions enables a flexible control of decision-making. To date, the only electrophysiological study available highlights the importance of the FP in the encoding of monkey's decision at feedback time. The present work aims to study the contribution of the FP in the monitoring and the evaluation of goals achieved through self-generated decisions and other agent's decisions. With this purpose, we recorded the activity from three 96-channels arrays implanted on the FP of two monkeys while they performed two different variants of a Non-Match-To-Goal task. The task's rule required the monkeys to discard the stimulus selected in the previous trial and to select the other one. Following the same Non-Match-To-Goal rule, the monkeys performed the task in two different conditions, interacting in a subset of trials with a human or a computer agent, alternating their roles as actor or observer. Both monkeys showed high performance in both conditions. They were able to keep in mind not only their own previous choice but also the human's or the computer's choice to select the stimulus accordingly in their following trial. We recorded the single-unit activity of 319 cells to investigate whether and how FP neurons encoded the agent identity. As reported before, the greatest modulation was found around feedback time. Of 319 cells, 109 (34%) cells were modulated at feedback time depending on who performed the trial, either the monkey or the human partner. In the same way but to a less extent, 62/319 cells (19%) showed a significant difference in their activity at feedback time between monkey and computer trials. This finding indicates that the FP distinguishes agents, monitoring differently self-generated and others agent's behaviors. The higher number of cells encoding the agent in the human interaction condition compared to the computer interaction condition (34% vs 19%, $p < .001$) indicates that the FP also differentiates real physical agent from computer and plays a key role in social cognition.

Disclosures: L. Ferrucci: None. **S. Nougaret:** None. **V. Fascianelli:** None. **R.C. Saunders:** None. **A. Genovesio:** None.

Poster

784. Social Memory and Cognition I

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Support: NIH Grant R01MH095894
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NIH Grant R37MH109728
SFARI 304935 MLP
Wharton Postdoctoral Dean's Fellowship

Title: Superior temporal sulcus (STS) neurons integrate social cognition with economic value in monkeys trading in a simulated stock market

Authors: *A. W. HUTTUNEN[1], M. L. PLATT[1,2,3];
[1]Wharton Marketing, [2]Dept. of Med., [3]Dept. of Psychology, Univ. of Pennsylvania, Philadelphia, PA

Abstract: In social environments, information gleaned from others' movements, facial expressions, or gaze often serves as an important factor in our own decision-making calculations. Evolutionarily, the ability to make inferences about the intent behind others' behavior (i.e. Theory of Mind, ToM) leads to improved chances of foraging success and escape from predation. However, individuals in stochastic financial markets often maladaptively employ ToM when forecasting others' value estimations, leading to 'bubble' markets and market crashes. Prior research supports the hypothesis that connections between brain areas associated with value judgements (e.g. ventromedial prefrontal cortex; vmPFC) and those associated with ToM (e.g. temporal parietal junction; TPJ) underlie suboptimal decision making due to artificial inflation of stock values (De Martino et al., 2013). Current work in our lab demonstrates that macaque middle superior temporal sulcus (mSTS), the putative homolog of human TPJ, is engaged during strategic social decision making, highlighting a potential role for mSTS in social biasing of decisions in financial markets. In order to further explore the evolutionary roots and neural circuit mechanisms underlying these behaviors, we developed a rudimentary 'stock market' task for rhesus macaques (Macaca mulatta; N=2), which was also validated in humans (N=350). Multichannel electrodes recorded electrophysiological activity from mSTS while monkeys made investment decisions on a touchscreen computer for juice reward in 4 conditions: 1) computer opponent, 2) replay opponent, 3) decoy opponent, and 4) live opponent. We speculated that willingness-to-pay would be biased by other monkeys' choices in the social condition, but not by the computer's choices in the non-social condition. We then intranasally delivered the social neuropeptide oxytocin (or saline) prior to performing the task to determine its effect on behavior and neural activity. Our behavioral results indicate that both humans and macaques are willing to pay more per share when playing with a conspecific compared to a computer. In monkeys, mSTS differentially signals the value of M1 actions in social and non-social contexts, and firing rates are modulated by M2 choices in the social condition only. We also observed an overall increase in engagement of mSTS as well as increased 'herding' behavior under oxytocin conditions compared to saline controls. This research suggests that mSTS encodes a social information signal that is likely integrated into downstream valuation computations (e.g. in vmPFC), which biases choices toward suboptimal decisions in bubble markets.

Disclosures: A.W. Huttunen: None. **M.L. Platt:** None.

Poster

784. Social Memory and Cognition I

Location: Hall A

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Program #/Poster #: 784.16/AA9

Topic: H.01. Animal Cognition and Behavior

Support: CNPq (455532/2014-1)

Title: Effects of the CB1 receptor antagonism on social interaction in capuchin monkeys

Authors: *R. S. MAIOR, N. GONCZAROWSKA, F. V. CAIXETA, C. TOMAZ;
Univ. of Brasilia, Brasilia, Brazil

Abstract: University of Brasilia, Brazil. The Endocannabinoid System (ES) is an important modulator of different neural functions, including memory and emotions. Changes in the ES's activity is known to play a role in several neurological disorders, such as autism spectrum disorders (ASD). In the present study, we evaluated the ES's role in social interaction in *Sapajus* spp. by blocking the CB1 receptor with the antagonist AM251. Social and non-social behaviors of five adult males were observed after administration of AM251 at the doses of 0.3, 1.0 and 3.0 mg/kg, i.m. All behavioral sessions were carried out in the animals' home cage. AM251 administration increased self-directed behaviors while it decreased social behaviors at the highest dose. No changes were observed in vigilance and locomotion. These preliminary results corroborate findings of studies with rodents, implicating an important role for CB1 receptor in social interaction. Taken together, the results indicate that the CB1 receptor may be involved in social deficits observed in (ASD). Supported by CNPq (455532/2014-1) from Brazil.

Disclosures: R.S. Maior: None. **N. Gonczarowska:** None. **F.V. Caixeta:** None. **C. Tomaz:** None.

Poster

784. Social Memory and Cognition I

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Program #/Poster #: 784.17/AA10

Topic: D.07. Vision

Support: the National Natural Science Foundation of China (Grants No. 31771209)

Title: Decoding others' intention to interact in the human parietal lobule

Authors: *M. HAN[1], Q. LIANG[1], S. KUAI[1,2];
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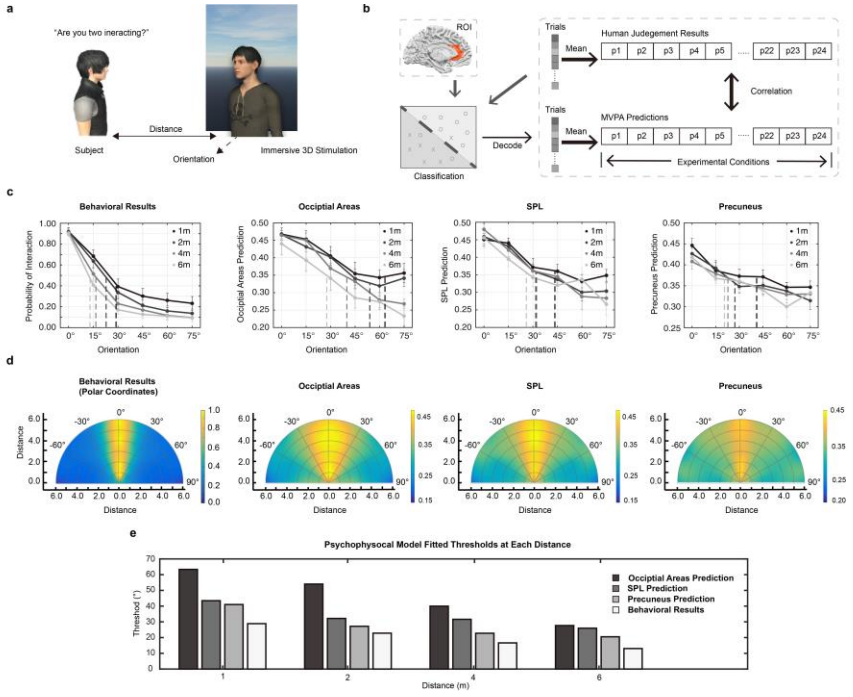
Abstract: It is essential for human beings to understand others' intention to interact with him/her in a social environment. Previous studies have indicated other people's heading direction and distance are critical cues for judging their social interaction. However, there has been little quantitative analysis of these cues. In this study, we asked participants to report whether a virtual avatar was intended to interact with him/her while their brain activation was recorded in an MRI scanner. In an event-related run, a virtual avatar was presented at a distance of 1m, 2m, 4m, or 6m. The heading of avatars varied from -75° and 75° at a step of 15°. Our behavioral results showed that the probability of interaction significantly decreased as a shift of heading direction and an increase of distance. We used a psychophysical model to fit the probability of interaction and defined 50% as the threshold. The thresholds were 28.83°, 22.79°, 16.60° and 13.03° at the distance of 1m, 2m, 4m, and 6m respectively. In the fMRI data analysis, we selected the occipital area, superior parietal lobule (SPL) and the precuneus as the region of interest (ROI). In each ROI, we trained support vector machine classifiers to predict whether the avatar intended to interact with participants in each stimulus trial. We found that thresholds of the occipital area (mean threshold = 46.24°) were significantly higher than that of behavioral data (mean threshold = 20.31°). The mean threshold decreased to 33.29° in SPL and 27.85° in the precuneus, which was comparative with that of behavioral threshold. The results indicate that the human brain analyzes the heading direction and distance of others in the occipital regions, and then interprets the others' intention to interact with him/her in the high-level parietal area, such as precuneus.



Disclosures: **M. Han:** None. **Q. Liang:** None. **S. Kuai:** None.

Poster

784. Social Memory and Cognition I

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Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 784.18/AA11

Topic: H.01. Animal Cognition and Behavior

Support: ZIA-MH-002498-24

Title: CA2 neurons recapitulate sniffing behavior exhibited by mice for conspecifics

Authors: *A. CYMERBLIT-SABBA[1], M. STACKMANN[2], S. K. WILLIAMS AVRAM[1], M. C. GRANOVETTER[3], A. S. SMITH[4], H.-J. LEE[5], J. SONG[1], S. YOUNG[6];
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Abstract: Recognitions of others may occur at different levels: social hierarchical status, health (e.g., parasitic load), emotions (e.g., stress-empathy), genetic relatedness (kin recognition) familiarity (have I met you before?) and individual identity (yes, you are Alma). To maintain successful complex social behaviors, the neural network must allow dynamic acquisition, representation and retrieval of the social cues. The involvement of the CA2 subfield of the hippocampus in social memory have been well established[(1-4)]. Still, the way these memories are encoded by it remains, for the most part, unknown. We created a transgenic mouse line expressing Cre driven by the vasopressin 1b receptor (Avpr1b) promoter that allows us to target the viral delivery of a Cre-dependent calcium sensor (GCaMP6s) into the pyramidal neurons of CA2 hippocampal subfield. We found a unique scheme of neural encoding in the dCA2 for social memories that is different from that for inanimate object memory encoding. These results provide insight into the neural correlates of social memory and will promote more studies of its architecture.References: 1. Young, W. S., J. Li, S. R. Wersinger, and M. Palkovits. The vasopressin 1b receptor is prominent in the hippocampal area CA2 where it is unaffected by restraint stress or adrenalectomy.*Neuroscience* **143**, 1031-9 (2006)2. Hitti, F. L. and S. A. Siegelbaum. The hippocampal CA2 region is essential for social memory.*Nature* **508**, 88-92 (2014).3. Smith, A. S., et al. Targeted activation of the hippocampal CA2 area strongly enhances social memory.*Mol Psychiatry* **21**, 1137-44 (2016).4. Wersinger, S. R., et al. Vasopressin V1b receptor knockout reduces aggressive behavior in male mice. Mol Psychiatry 7, 975-84 (2002).

Disclosures: **A. Cymerblit-sabba:** None. **M. Stackmann:** None. **S.K. Williams Avram:** None. **M.C. Granovetter:** None. **A.S. Smith:** None. **H. Lee:** None. **J. Song:** None. **S. Young:** None.

Poster

784. Social Memory and Cognition I

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 784.19/AA12

Topic: H.01. Animal Cognition and Behavior

Support: R01MH095894
R01MH108627
R37MH109728
Simons Foundation (SFARI 304935, MLP)

Title: Cross brain neural signatures of strategic pairwise interaction in humans and monkeys

Authors: *Y. JIANG, M. L. PLATT;
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Abstract: Animals and humans alike compete with conspecifics for various resources. Even though social competition involves at least two agents with opposing goals dynamically interacting and continuously updating their expectations about each other, so far most studies have only focused on examining the behavior and underlying neurobiology of a single agent making reiterated two alternative forced choices. Here pairs of humans and rhesus macaques played a zero-sum competitive soccer game, in which one player (the kicker) tried to continuously circumnavigate the other player (the goalie) to win a point. Simultaneously, neural recordings were obtained using EEG in humans and single unit electrophysiology in monkeys. Behavioral analyses and computational modeling with Gaussian Processes revealed that the interactions between human and monkey players were similarly complex. Both species utilized comparable strategies and were equally sensitive to their opponents'. In monkeys, we found that firing rates of neurons in mid-superior temporal sulcus (mSTS), a potential homologue to human temporo-parietal junction (TPJ), encoded various aspects of the game including strategy, behavioral context, and game outcome. Most importantly, there were two distinctive populations of mSTS neurons and they retained different types of information regarding local trial history. Silencing these neurons with the GABA agonist muscimol critically impaired performance, demonstrating these neurons contribute functionally to strategic gameplay. On a single trial, behavioral strategies and accompanying neural activity from two players interlinked and co-evolved; ultimately it was the joint firing rate patterns across two brains that determined game outcome. Over much longer periods of time, local field potentials in monkeys and EEG recordings in humans indicated that slower changes in brain states predicted game performance.

These findings confirm that our computerized soccer game captures the essence of real life competition cross species. The observation that mSTS in monkeys functionally contributes to strategic gameplay endorses the hypothesis this area is the homologue of human TPJ. Finally, examining TPJ activity across different time scales offers us great insight as to how interacting agents effectively and flexibly select strategies in an ever changing environment.

Disclosures: Y. Jiang: None. **M.L. Platt:** None.

Poster

785. Social Memory and Cognition II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 785.01/AA13

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant R01NS092216

Title: Mechanical differences in social deficit process are revealed between two mouse models of autism, BTBR T+tf/J and BALB/cJ

Authors: *H. ARAKAWA;
Anat. and Neurobio., Univ. of Maryland Baltimore, Baltimore, MD

Abstract: Autism is a complex spectrum of disorders characterized by core behavioral deficits in social communicative behavior. Social behaviors are governed by multiple processes including motivated approach to social signals for assessment and appropriate expression of specific responses to would-be social partners, which are essential for exhaustive analysis of preclinical mouse models. Two inbred strains, BTBR T+tf/J (BTBR) and BALB/cJ (BALB), both of which have been used as an animal model of core behavioral deficit in autism, were compared to standard strain C57BL/6J (B6) in a variety of social factors and situations. All three strains (all female subjects) were capable of recognizing differences in inanimate objects and social features (strain, sex, and familiarity) of the opponents. However, BTBR and BALB mice poorly expressed approach to stimulus mice, while BTBR mice exhibited avoidance to BTBR stimuli, in the 3-chamber test situation, in which mice mainly express approach, but not contact, behavior to assess the social (olfactory) cues. When allowed direct contact, all three strains displayed similar patterns of social approach/contact to either strain of stimulus mouse, although they exhibited the highest amount of approach/contact to BALB and the lowest to BTBR stimulus mice. In addition, BALB mice displayed more facial investigation (approach) compared to other strains. The brain serotonin plays a role in facilitating social behavior. An injection of buspirone, serotonin 1A partial agonist, enhanced social approach in the 3-chamber test and increased social contacts during direct social interaction in B6 and BTBR mice, but not in BALB mice. A sequential analysis of social interaction revealed that buspirone injected into the subject mice

substantially facilitated social approach in the stimulus mice that were not given the injection. The stimulus dependency was confirmed by the 3-chamber test, in which B6 mice increased approach to buspirone-injected stimulus mice (but not in BALB stimulus mice). Social deficits shown in BTBR mice likely stem from odorant communication, while those in BALB mice would be associated with a defect of serotonergic system.

Disclosures: H. Arakawa: None.

Poster

785. Social Memory and Cognition II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 785.02/AA14

Topic: H.01. Animal Cognition and Behavior

Support: NRF-2017M3C7A1048089 (JWK)
19-BR-04-03 (JWK)
NRF-2017R1A6A3A01076049 (TYC)

Title: Physiological and molecular differences in specific medial prefrontal cortex subpopulations mediate social hierarchy

Authors: *T.-Y. CHOI[1], B. KANG[2], Y. JEONG[1], J. KIM[1,3], H. JEON[4], S. JEONG[1], M. CHOI[4], J. KOO[1,3];
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Abstract: Social hierarchy is a universal phenomenon observed in many animal species including mice and humans and it is essential for individuals' life and survival. Although it was recently revealed that the medial prefrontal cortex (mPFC) is a hub brain region of social hierarchy, we still do not know about the relevant neural circuits and molecular mechanisms in detail. To address this question, we compared physiological and molecular differences in mPFC subpopulation neurons that project to other brain regions that has been implicated in social behaviors - nucleus accumbens (NAc), ventral tegmental area (VTA), and amygdala (AMY) - from social dominant and subordinate mice, which were determined by tube dominance test. Neuronal excitability of social dominants was increased in mPFC-NAc, but decreased in mPFC-VTA, compared to social subordinates. However, neuronal excitability in mPFC-AMY was not different between social dominants and subordinates. We next measured in vivo neural activity of mPFC-NAc and mPFC-VTA using fiber photometry during tube dominance test. We finally conducted single-cell RNA sequencing (scRNA-seq) of mPFC regions from social dominant and

subordinate mice to compare molecular differences of social hierarchy in mPFC subpopulation neurons. Collectively, these results suggest that specific physiological and molecular changes in mPFC subpopulations mediate social hierarchy.

Disclosures: T. Choi: None. **B. Kang:** None. **Y. Jeong:** None. **J. Kim:** None. **H. Jeon:** None. **S. Jeong:** None. **M. Choi:** None. **J. Koo:** None.

Poster

785. Social Memory and Cognition II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 785.03/AA15

Topic: H.01. Animal Cognition and Behavior

Title: Behavioral evaluation of the impact of different types of bedding in laboratory rat

Authors: *L. D. PANTALEON[1], J. Z. MAGALHÃES[3], J. R. CAMUSSO[2], A. ARNOLD[2], M. O. RIBEIRO[2], E. L. RICCI[4];
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Abstract: Recently there is a crescent concern for the welfare of laboratory animals, to increase their comfort and to ensure reliable experimental results. Despite this concern, there is still few studies that address this issue. Scientific literature describe the influence of the microenvironment in animals behavior and physiology. The type of bedding used in animals cages is an important factor that can influence their behavior. This study aimed to evaluate the impact of three types of bedding material in rats behavior. Twenty seven male Wistar rats were separated into groups and habituated for two weeks in different types of bedding materials: group A - *Pinus sp* wood ships; group B - *Pinus sp* wood flakes; group C - corn cob (n=9 animals/group). After this period the behavioral evaluation were performed as follow: 1st day - open field; 2nd day - elevated plus maze; 3rd-5th days - social interaction; 6th day - preference test. For the open field test it was evaluated the frequencies of locomotion, rearing and grooming, and time of immobility. In the elevated plus maze it was measure the frequencies of entry in the open and close arms, head-dipping and risk assessment, and total time in the open and close arms. The parameters evaluated in the social interaction were the frequencies of sniff, chase and pass over the othe animal. In the preference test it was evaluated the time spend in each zone of the test during the three periods of the day (morning, afternoon and night) and the total time spend in each zone. The analysis of the behavior of male rats in the open field, elevated plus mazes and social interaction did not showed alterations in any parameter evaluated, indicating that all animals behave accordingly, regardless of the bedding material they were in. Regarding the preference test, the analysis showed that 1) the animals from the wood chips cages stayed

longer in the corn cob zone compared to the wood flakes in the total time ($p<0,01$); 2) the rats from the corn cob cages stayed longer in the wood chips zone compared to the corn cob zone and the wood flakes zone in the total time ($p<0,0001$); 3) the animals from the wood flakes cages stayed longer in the wood chips zone compared to the wood flakes zone at night and stayed longer in the wood chips zone compared to the corn cob ($p<0,001$) and the wood flakes ($p<0,0001$) zones in the total time. This results indicate, althought all rats presented the expected behavior for the species, there is a clear preference for the bedding material, suggesting that this material could reflect in other kinds of alterations in this animals. Therefore, future studies needs to be done in order to elucidate the influence of these materials on physiological and biochemical parameters.

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Poster

785. Social Memory and Cognition II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 785.04/AA16

Topic: H.01. Animal Cognition and Behavior

Support: NSFC Grant 81801355

Title: NMDA receptor dysfunction in the medial prefrontal cortex of NL3 R451C knock-in mice

Authors: *W. CAO, Q. XIA, J. XU, J. LUO;
Zhejiang Univ., Hangzhou, China

Abstract: Neuroligins (NLs) are critical for synapse formation and function. NL3 R451C is an autism-associated mutation. NL3 R451C knock-in (KI) mice exhibit autistic behavioral abnormalities, including social novelty deficits. Our previous paper reported that gamma oscillation dysfunction in the medial prefrontal cortex (mPFC) led to social deficits in KI mice, and manipulating mPFC parvalbumin (PV) interneurons could reverse the deficits. However, the underlying mechanism is not clearly understood. Glutamate N-methyl-D-aspartate receptors (NMDARs) dysfunction exists in some ASD mouse models. NMDARs disruption in specific brain regions or on PV-containing interneurons lead to autism-like phenotypes. Thus, we focused on the NMDARs function in both pyramidal neurons and interneurons in the mPFC, which may play a vital role in social defects. We found decreased NMDAR function in both pyramidal neurons and fast-spiking (FS) interneurons in the KI mice. We also found that GluN2A and GluN2B density decreased in cultured cortical neurons of KI mice. A partial agonist of NMDARs, D-cycloserine (DCS), restored the NMDAR function,FS interneuron excitability and

social novelty deficits in the KI mice. Together, our findings suggest that declined NMDARs function may contribute to the development of ASD-like phenotypes in the KI mice.

Disclosures: W. Cao: None. **Q. Xia:** None. **J. Xu:** None. **J. Luo:** None.

Poster

785. Social Memory and Cognition II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 785.05/AA17

Topic: H.01. Animal Cognition and Behavior

Support: UMN AHC seed grant

Title: Effects of oxytocin administration on social behaviors in felids

Authors: *J. C. BURKHART[1], N. D. BORREGO[1], S. R. HEILBRONNER[2], E. R. DE KOCK[4], C. PACKER[3];
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Abstract: Felids of the genus Panthera form a monophyletic clade, yet exhibit a divergence of social structures. The African lion is highly social, forming life long bonds, while the leopard is completely solitary. Male cheetahs are semi-social, whereas female cheetahs are considered solitary. It is uncommon to find a system so closely related with such divergent social organization, making Panthera a good model for neurological comparisons. In other such systems, such as voles, sociality is mediated by the neuropeptide oxytocin, although this has largely been studied in the context of reproductive social behavior. We hypothesized that behavioral responses to oxytocin in felids would be different according to whether the behaviors are social or non-social in nature, and according to the social organization of the species. Using a DeVilbiss Atomizer, 10 IUs of oxytocin were administered to semi-free-ranging African lions, leopards, and cheetahs during a variety of social and non-social tasks. A significant increase in affiliative behaviors, as well as a decrease in vigilance, was observed in African lions post oxytocin administration as compared to baseline and saline trials. These results indicate that administration of oxytocin modulates social behavior in African lions. Responses of leopards and cheetahs will be analyzed and compared. We anticipate that oxytocin's ability to modulate social behavior in these less social animals will be decreased. These results have important implications for our understanding of the evolution of social circuitry, as well as for conservation (reintroduction) efforts.

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Poster

785. Social Memory and Cognition II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 785.06/AA18

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant R01MH112504

Title: Learning vicariously - Role of anterior cingulate cortex in social cognition

Authors: ***K. N. SCHNEIDER**[1], X. SCIARILLO[2], J. NUDELMAN[2], J. F. CHEER[3], M. R. ROESCH[4];
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Abstract: Socially-derived cues help us navigate social interactions and continuously provide information about the environment, allowing us to learn without risking an adverse personal experience. In psychiatric disorders such as autism or psychopathy our ability to perceive these social cues is impaired, resulting in maladaptive behavior. However, the circuits underlying social cognition and how they influence learning remain unclear. Previous research has shown that the anterior cingulate cortex (ACC), a region of interest for social cognition, may engage deeply with the reward system. In order to examine how social cues modulate learning, and investigate the role of ACC in these processes, we recorded single-unit activity from observer (‘self’) rats undergoing a novel Pavlovian Social Outcome Task with a conspecific (‘other’). In the task, both rats were separated in a chamber by a see-through grate while four blocks of trials were used, alternated between two sequences, during which three cues were either appetitive (sugar pellets), aversive (foot-shock) or neutral (no outcome). Based on the block type, rats underwent conditioning or extinction, together or separately, leading to congruent or contrasting learning contexts. As a social control, training included sessions where 'self' rats were alone in the chamber, while 'other' outcomes were delivered to an empty side. Preliminary results showed that the relative conditioning context of other rats modulated appetitive and aversive performance of self rats undergoing extinction, suggesting social cues influence this form of learning. Moreover, neural recordings revealed differences in the firing rate of ACC neurons between learning contexts (e.g., simultaneous extinction vs incongruent extinction) in response to outcomes to both the 'self' and the 'other.' Our preliminary findings suggest that rats utilize social cues to update their predictions about the environment, influencing both their appetitive and aversive strategies. Further, the profile of ACC activation observed, during either appetitive or aversive outcomes delivered to both the 'self' and the 'other,' would suggest that the ACC

plays a broader role in processing social cues that is regardless of valence, and relevant to outcome prediction errors. We continue to examine ACC responses to the different transitioning social contexts in the task, as well as its influences on classical associative learning paradigms, in comparison to social controls (alone).

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Poster

785. Social Memory and Cognition II

Location: Hall A

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Program #/Poster #: 785.07/AA19

Topic: H.01. Animal Cognition and Behavior

Support: NARSAD Grant 27202
NSF NRT UtB: Neurophotonics
Boston University Undergraduate Research Opportunities Program

Title: Dissecting the role of VIP interneurons within the anterior cingulate cortex in a social cognitive task

Authors: *W. W. YEN[1], R. LIU[2], A. O. THOMAS[3], C. JOHNSON[4], L. N. KRETSGE[5,6], D. P. LEMAN[4], F. S. HAUSMANN[4], M. MINNIG[9], E. FUCHS[4], T. P. H. NGUYEN[7], A. CRUZ-MARTIN[1,6,8];
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Abstract: As converging evidence implicates the anterior cingulate cortex (ACC) as a critical area for social cognition and emotional responses, there is an increasing need for a better understanding of the underlying circuitry and regulation of this area. Vasoactive intestinal polypeptide-expressing (VIP) interneurons are a subtype of cortical interneurons that drive strong cortical disinhibition, placing them in a key position to regulate the overall activity of the ACC. Here, we investigate the role of VIP interneurons located within the ACC of mice during a cognitive task that assess social memory and novelty. Using miniaturized, head-mounted fluorescence microscopes (“miniscopes”) in combination with genetically encoded calcium indicators (GECIs), we were able to study the activity patterns of this sub-population within ACC in freely moving, behaving mice. The use of miniscopes in lieu of other head-fixed techniques, such as 2-photon microscopy, allow our experiments to occur in a more naturalistic setting as the mice are free to explore their environments with little to no physical impedance. We first injected viral vectors containing flex-GCaMP6f, a GECI, into the ACC of VIP-IRES-

Cre mice in order to selectively target VIP interneurons in this area. This was then followed by a surgical implantation of a gradient-index (GRIN) lens to allow for optical imaging via miniscopes. The miniscopes used in these experiments were a custom-designed variant of the open-source FinchScope that were modified to allow for the removal of the miniscope in between experiments. This allowed us to co-house all experimental animals. Finally, in order to characterize the response of VIP interneurons to social versus non-social environments, mice were put through a battery of social and analogous object recognition tasks that occurred within a large acrylic chamber. Our data suggests that VIP interneurons in the ACC preferentially activate to social stimuli relative to objects.

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Poster

785. Social Memory and Cognition II

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Program #/Poster #: 785.08/AA20

Topic: H.01. Animal Cognition and Behavior

Support: Human Frontier Science Program
Children Tumor Foundation
R01 MH084315

Title: Post-natal immune activation in a mouse model of tuberous sclerosis results in sexual dimorphic microglia dependent deficits underlying social memory impairments

Authors: *M. F. LOPEZ-ARANDA[1], I. CHATTOPADHYAY[2], T. SILVA[1], C. THADANI[1], S. TALOMA[1], E. LUGO[1], A. RZHETSKY[3], A. SILVA[1];
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Abstract: There is evidence for differences between females and males in the prevalence of certain neuropsychiatric disorders, such as autism spectrum disorder (ASD). Additionally, there is growing evidence that environmental factors, such as immune activation, contribute to the severity and range of cognitive phenotypes in neuropsychiatric disorders. We found that early post-natal immune activation triggers long lasting social memory deficits in male but not female mice with a mutation in the tuberous sclerosis 2 gene ($Tsc2^{+/-}$). Approximately half of the patients with tuberous sclerosis are diagnosed with ASD. We have multiple lines of evidence that immune activation during a critical phase of early post-natal development triggers an mTOR-

dependent, self-perpetuating cycle of increased interferon (IFN) production in microglia that is responsible for social memory deficits in $Tsc2^{+/-}$ male mice. Previous results implicated microglia in behavioral phenotypes associated with animal models of autism. Our studies showed that deletion followed by repopulation of this cell type in the adult brain reversed the social memory deficits of $Tsc2^{+/-}$ male mice with early post-natal immune activation. Importantly, this procedure opened a window of susceptibility in adult $Tsc2^{+/-}$ female mice, such that immune activation during microglia repopulation triggered lasting social memory deficits in these female mice. Importantly, our human epidemiological studies show a strong correlation between the prevalence of infections during early childhood in male (but not in females), and a future diagnose of neuropsychiatric disorders, suggesting that our results in mice are mirrored by human findings. These results open new therapeutical opportunities for neuropsychiatric disorders, and demonstrate the critical importance of microglia development for cognitive phenotypes associated with neuropsychiatric conditions.

Disclosures: **M.F. Lopez-Aranda:** None. **I. Chattopadhyay:** None. **T. Silva:** None. **C. Thadani:** None. **S. Taloma:** None. **E. Lugo:** None. **A. Rzhetsky:** None. **A. Silva:** None.

Poster

785. Social Memory and Cognition II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 785.09/AA21

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant T32MH065214
NIH Grant MH117459-01

Title: Axons, dendritic spines, glia, and perineuronal nets are atypical in the CA2 and CA3 regions of the hippocampus in a mouse strain with deficient social and object memory

Authors: *E. C. COPE, A. D. ZYCH, N. J. KATCHUR, B. J. LAHAM, C. Y. PARK, C. G. DIAS, R. C. WATERS, K. A. PAGLIAI, M. J. LOTITO, E. GOULD;
Princeton Univ., Princeton, NJ

Abstract: Several studies suggest that the CA2 and dorsal CA3 (dCA3) regions of the hippocampus are important for social memory as well as for spatial and contextual processing (Hitti and Siegelbaum, 2014; Stevenson and Caldwell, 2014; Chiang et al., 2018). Recent work suggests that synaptic function involves presynaptic and postsynaptic neurons, along with glial cells and the extracellular matrix (ECM), which together comprise the tetrapartite synapse (Dityatev and Rusakov, 2011; Cope and Gould, 2019). We examined these synaptic components in the CA2 and dCA3 of a mouse strain with deficient social and contextual processing, the BTBR mouse. First, we verified that BTBR mice have deficits in social recognition and object

location memory compared to control C57BL/6J mice. Then, we explored a neuronal population known to innervate both the CA2 and dCA3 regions, the granule cells of the dentate gyrus. We specifically examined adult-generated granule cells and their mossy fiber axons in these target regions, using the immature neuron marker 3R-tau, and found reduced numbers of new neurons, and diminished mossy fiber projections, in BTBR compared to control mice. Examination of postsynaptic sites revealed that BTBR mice have reduced numbers of dendritic spines, sites of excitatory synapses, on DiI labeled pyramidal neurons of the CA2 and dCA3. We next examined whether there were changes in glial cell numbers in areas of synapse loss. Compared to controls, BTBR mice had robust decreases in iba1-labeled microglia in the CA2 and dCA3, as well as decreases in GFAP-labeled astrocytes in the CA2. We also found perineuronal nets (PNNs), specialized ECM structures that surround certain types of neurons and limit brain plasticity, to be increased in volume and intensity in the CA2 as well as increased in PNN+ cell number in the dCA3. Ongoing studies will determine the potential role these differences in CA2 and dCA3 play in mediating social recognition and object location deficits in BTBR mice.

Disclosures: E.C. Cope: None. **A.D. Zych:** None. **N.J. Katchur:** None. **B.J. Laham:** None. **C.Y. Park:** None. **C.G. Dias:** None. **R.C. Waters:** None. **K.A. Pagliai:** None. **M.J. Lotito:** None. **E. Gould:** None.

Poster

785. Social Memory and Cognition II

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Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 785.10/AA22

Topic: H.01. Animal Cognition and Behavior

Support: IBS-R001-D1

Title: Neuronal dynamics of social representation in the hippocampus

Authors: *K.-H. LEE[1], Y.-B. LEE[1], J. DO[1,2], E. KONG[1,2], J. KIM[1,2], D. LEE[1];
[1]Inst. for Basic Sci., Taejon-City, Korea, Republic of; [2]Korea Advanced Inst. of Sci. and Technol., Taejon-City, Korea, Republic of

Abstract: Animals engage in various forms of social interactions in daily life such as aggression, avoidance, cooperation, mating as well as forming a hierarchy. It has been challenging to understand neural underpinnings of such social behaviors due to their inherent complexity. One of the most critical cognitive elements shared by different social behaviors is an ability to recognize the social counterpart and retrieve associated information in order to exhibit appropriate behavioral responses during social interactions. We developed a novel social discrimination paradigm that requires a subject mouse to distinguish between two familiar mice presented in random order and associate each with either a reward or a punishment. This

paradigm utilizes head-restrained mice repetitively engaged in simplified and stereotyped social interactions and thus allows us to quantitatively measure behavioral performance and to precisely correlate behaviors with neuronal activities. Most mice could perform the task with a higher than 80% accuracy within 2 weeks of training. The performance was dropped to a chance level when dorsal hippocampus was inactivated by injecting muscimol. Behavioral results showed that the subject mice can recognize a conspecific within a second and the established social memory lasted for at least more than a week even in single housing conditions. *In vivo* two-photon calcium imaging revealed that dorsal CA1 neurons show various responses to different task variables. By imaging the same neuronal population over multiple days up to three months while repeatedly reversing the reward contingency, we could identify neurons whose activities selectively code for different social identities. Our results suggest that activities of the dorsal CA1 neurons are critical for associative social memory formation.

Disclosures: **K. Lee:** None. **Y. Lee:** None. **E. Kong:** None. **J. Kim:** None. **D. Lee:** None.

Poster

785. Social Memory and Cognition II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 785.11/AA23

Topic: H.01. Animal Cognition and Behavior

Support: EU FP7 217148
EU FP7 ICT Grant 270108
European Union's Horizon 2020 Framework Programme for Research and Innovation under the Specific Grant Agreement No. 785907 (Human Brain Project)

Title: Hippocampal coding of self versus other in the absence of mirror-like place cell responses

Authors: *C. M. A. PENNARTZ[1], M. VINCK[3], P. MARCHESI[2], A. KEESTRA[2], L. A. VAN MOURIK-DONGA[2], J. C. JACKSON[4], P. F. VERSCHURE[5], J. J. BOS[2];
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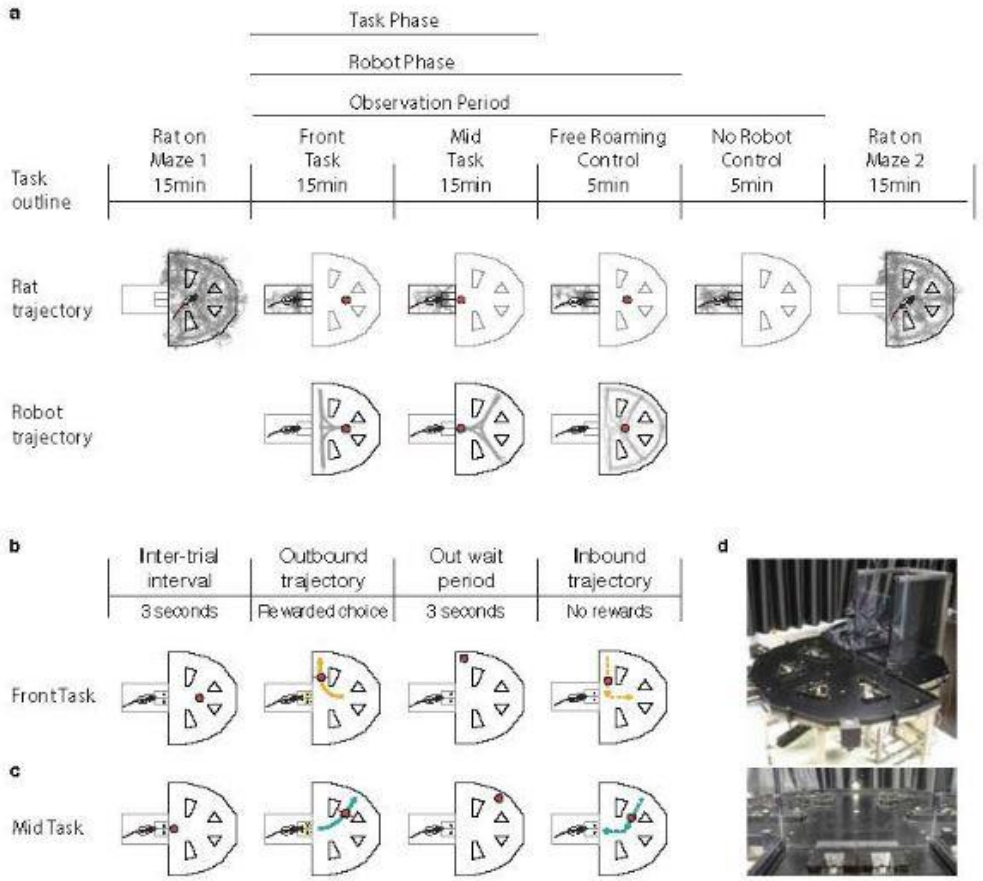
Abstract: The hippocampus is essential for spatial navigation and memory and harbors place cells, coding an animal's location in space. The hippocampus has also been suggested to code "social" information, such as about the spatial position of conspecifics. "Social place cells" have been reported for tasks where an observer mimics the behavior of a demonstrator. We examined whether hippocampal neurons may encode the behavior of a minirobot, however without requiring the animal to mimic it. Rather than finding "social place cells" we observed that place

cells were modulated by the robot's behavioral patterns. During task performance, the rat's own positions correlated with robot movements. Hippocampal ensemble activity coded information about robot movement patterns, even when correcting for changes in rat position. Interneurons were more informative on robot movements than principal cells. In conclusion, when the animal's own behavior is conditional on external agents, the hippocampus multiplexes information about self and others.



Disclosures: **C.M.A. Pennartz:** None. **M. Vinck:** None. **P. Marchesi:** None. **A. Keestra:** None. **L.A. van Mourik-Donga:** None. **J.C. Jackson:** None. **P.F. Verschure:** None. **J.J. Bos:** None.

Poster

785. Social Memory and Cognition II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 785.12/AA24

Topic: H.01. Animal Cognition and Behavior

Support: Champalimaud Foundation
ZonMw Vidi
ERC
FCT

Title: Neural correlates of competitive social interaction in the anterior cingulate cortex

Authors: *I. M. MARCELO[1,2], R. M. COSTA[3,1], S. A. KUSHNER[2];
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Abstract: Social behavior and cognition are ubiquitous in the animal kingdom, crucial for both individual fitness and species survival. Behavioral repertoires like pair bonding, parental care, prosocial or aggressive displays, are especially important for group fitness and cohesion. Fundamental to all is the animal's dynamic capabilities of perceiving and deploying correct action to important aspects of its surrounding, in particular cues arising from conspecifics that make up its social environment.
Previous results from our laboratory, using an automated version of the Lindzey Tube Test, have shown that groups of mice are able to establish and maintain stable long-term social hierarchies, based on dyadic interactions in which hierarchy is operationally defined by advancing or retreating against defined conspecific opponents.
Given that recent literature has suggested a crucial role for the Anterior Cingulate Cortex (ACC) in social cognition, with particular relevance in building models of perseverance and others' intentions, we have investigated the function of the ACC in the context of competitive social interactions in the Lindzey Tube. For this purpose, we adapted the classical version of the task to permit simultaneous GCaMP6f-enabled *in vivo* 1-photon calcium imaging of all pairwise matches among 3 groups of 4 interacting male conspecifics. Mice were imaged during individual tube crossings, pairwise matches and pseudo-matches with a dummy mouse. Our results suggest the importance of ACC neural activity during social interactions, notably in a pairwise competitive setting. In particular, we find that ACC neurons robustly predict impending conflict and outcome resolution of socially competitive interactions.

Disclosures: I.M. Marcelo: None. **R.M. Costa:** None. **S.A. Kushner:** None.

Poster

785. Social Memory and Cognition II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 785.13/AA25

Topic: H.01. Animal Cognition and Behavior

Support: NSERC

Title: Sex difference in the way dorsal hippocampal D2-type dopamine receptors interact with gonadal sex hormones to mediate social learning in mice

Authors: *N. BASS[1], S. CRASTO[1], C. CRAWFORD[1], E. CHOLERIS[2];
[2]Psychology, [1]Univ. of Guelph, Guelph, ON, Canada

Abstract: Social learning, the process by which learning occurs via the interaction with, or the observation of, a conspecific (Galef, 1988) is poorly understood, and in animals may be tested using a social transmission of food preference (STFP) paradigm. During the STFP, the preference for a novel flavored food diet is acquired during social interaction with a recently fed conspecific. The catecholamine dopamine (DA) modulates many forms of cognition including feeding, reward and social behavior. By antagonizing D2-type DA receptors in the dorsal HPC, the STFP was blocked in female but not male mice suggesting an interaction between these receptors and sex hormones (Matta et al., 2017). Both estrogens and androgens modulate DA action. Indeed, estrogens have been directly implicated in social learning whereas the role of androgens has not been investigated. Collectively, these findings suggest that D2-type DA receptors interplay with sex hormones to modulate social learning. Here, we bilaterally infused D2-type DA receptor antagonist raclopride (18 μg/μL, 20 μg/μL, or saline) into the dorsal HPC (0.5 μL per hemisphere) of gonadally intact and gonadectomized 2-3-month old CD1 male and female "observer" mice 10 minutes prior to a 30-minute social interaction with a recently fed same-sex familiar "demonstrator". Immediately following the social interaction, the "observer" mice began an 8-hour flavored food choice test between 2 novel flavored food diets, one of which their respective "demonstrator" mice had consumed earlier. Food intakes were taken at 2, 4, 6, and 8 hours. Findings revealed that raclopride shortened the duration of a socially acquired food preference in gonadally intact females whereas it prolonged the food preference in ovariectomized mice. Notably, ovariectomy alone significantly reduced the duration of a socially acquired food preference. Lastly, raclopride prolonged the duration of a socially acquired food preference in gonadally intact males whereas castration prevented the prolonging effects of raclopride. These results suggest that gonadal female sex hormones interact with D2-type DA receptors in the dorsal HPC during the STFP in female mice, and that gonadal male sex hormones modulate social learning in male mice. Thus, there appears to be a sex difference in the way that D2-type DA receptors in the dorsal HPC interact with gonadal sex hormones to mediate social learning.

Disclosures: **N. Bass:** None. **S. Crasto:** None. **C. Crawford:** None. **E. Choleris:** None.

Poster

785. Social Memory and Cognition II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 785.14/AA26

Topic: H.01. Animal Cognition and Behavior

Support: ICMR Grant

Title: Neuropathological examination of fetal rat brain in valproic acid induced cognitive deficits autistic rats: A protective effect of granulocyte colony stimulating factor (GCSF)

Authors: *A. MISHRA[1], R. SINGLA[1], R. RAJPOOT[1], P. SARMA[1], B. MEDHI[2];
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Abstract: Introduction
Autism is a group of complex neurodevelopmental disorder of unknown etiology which manifests with problems like social interaction, language, communication and behaviour deficits like stereotypic and repetitive behaviour. Granulocyte-Colony Stimulating Factor (GCSF) is a glycoprotein that stimulates the bone marrow to produce granulocyte and release them into the blood stream. It has well known neuro-protectant, anti-inflammatory, anti-apoptotic, neurogenesis and excitoprotective properties in both human and rodent models of CNS disorders. The present study is designed to the evaluate the neuroprotective effect of GCSF in VPA induced autistic rats.
Method
Animals were divided into six groups. Group 1 (Control, received only Normal saline 0.9%), Group 2 (VPA 600mg/kg on PND 12.5), Group 3 (Pups, Risperidone 2.5 mg/kg, PND 23 to 43) and group 4-6(GCSF 10, 35,70 µg/kgPND 23 to 43).All the groups were subjected to different behaviour (Three chamber sociability test,Morris water maze) and histopathological examination using 0.1% Cresylviolet(for Nisslstaining).
Result
Treatment group showed significant improvement in the behavioural parameters.The histopathological evaluation implied extensive neuronal loss in the CA1 region of the hippocampus in the VPA treated groups. Decrease in the neuronal score was seen with GCSF treatment. Maximum effect was seen with GCSF dose of 70 µg/kg.
Key words: Autism, Valproic acid, Granulocyte Colony Stimulating Factor, Hippocampus

Disclosures: A. Mishra: None. **R. Singla:** None. **R. Rajpoot:** None. **P. Sarma:** None. **B. Medhi:** None.

Poster

785. Social Memory and Cognition II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 785.15/AA27

Topic: H.01. Animal Cognition and Behavior

Title: Neuroprotective effect of homotaurine in modulation of GABAergic signaling in VPA-treated rat model of autism: Role of GAD67

Authors: *R. SINGLA[1], A. MISHRA[2], R. RAJPUT[2], B. MEDHI[2];
[1]Pharmacol., [2]Post Grad. Inst. of Med. Educ. & Res., Chandigarh, India

Abstract: Introduction
Autism is a heterogeneous neurodevelopmental and neurobehavioral disorder of unknown etiology which manifests difficulties in social interaction, communication and usually behavior deficit like stereotype and repetitive behavior. Homotaurine is demonstrated to have a neuroprotective effect and also has a GABAergic activity. Based on previous literature glutamate and GABA -related abnormalities are found in the autistic brain.The present study is designed to investigate the role homotaurine in VPA induced autistic rat via GABAergic signalling.
Method
Animals were divided into six groups. Group 1 (Control, received only Normal saline 0.9%), Group 2 (VPA 600mg/kg on PND 12.5), Group 3 (Pups, Risperidone 2.5 mg/kg, PND 23 to 43) and group 4-6(Homotaurine 10,25,50 mg/kg PND 23 to 43). All the groups were subjected to different behaviour (Three chamber sociability test,Morris water maze) and expression of GAD 67 protein by immunohistochemistry (IHC) in different brain region (Prefrontal cortex , Hippocampus , Cerebellum).
Result
Significant improvement in the behavioral parameters were seen at 50 mg/kg dose of homotaurine. IHC staining of brain sections indicated the homotaurine treated rats exhibited significantly higher expression of GAD 67 in prefrontal cortex and hippocampus. However, no differences were observed in GAD67 expression in the cerebellum.
Key words: Autism, Valproic acid, Homotaurine, GABAergic

Disclosures: R. Singla: None. **A. Mishra:** None. **R. Rajput:** None. **B. Medhi:** None.

Poster

785. Social Memory and Cognition II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 785.16/AA28

Topic: H.01. Animal Cognition and Behavior

Support: Novo Nordisk Foundation Grant 112441
NIH Grant 1U19NS107616-01

Title: Automatic tracking and classification of mouse social behavior by 3D videography

Authors: *C. L. EBBESEN[1], R. C. FROEMKE[2];
[2]Otolaryngology, [1]New York Univ., New York, NY

Abstract: Measuring mouse social behavior is difficult. Mice are small, their movements are fast, and mice move in 3 dimensions (during mounting, for example). Currently, most studies of social behavior rely on labor-intensive methods, such as manual annotation of individual video frames. These methods are susceptible to experimenter bias and have a very limited throughput. We present an experimental setup and a robust calibration and tracking method that allows us to measure the behavior of multiple freely moving mice in 3 dimensions with high spatial and temporal precision (90 frames/s). In addition to this 3D data, we collect accelerometer data and record ultrasonic vocalizations (which are classified into call types using unsupervised clustering methods). These data allow us to construct a matrix representation of the 3D postures and movements (within and between mice) and patterns of ongoing ultrasound vocalizations - a kind of "social state space". This representation gives us a fine-grained read-out of social behaviors and how they change with circuit manipulations. Because our system uses the third dimension, the method is robust and tracks the identity of individual mice, even in unmarked animals that overlap in individual images.

Disclosures: C.L. Ebbesen: None. **R.C. Froemke:** None.

Poster

785. Social Memory and Cognition II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 785.17/AA29

Topic: H.01. Animal Cognition and Behavior

Support: Kresge Endowment
Troyer Research Fellowship
Harris Endowment

Title: Social learning and social behavior of the triple-transgenic mouse model of Alzheimer's disease

Authors: B. A. SULKOWSKI[1], H. R. LEBLANC[2], A. C. WILLIAMSON[3], B. V. ROHR[4], B. G. GENTRY[3], ***C. C. WRENN**[1];
[1]Pharmaceut. and Administrative Sci., Drake Univ. Col. of Pharm. and Heath Sci., Des Moines, IA; [2]Psychology and Neurosci., [3]Pharmaceut. and Administrative Sci., [4]Pharm. and Hlth. Sci., Drake Univ., Des Moines, IA

Abstract: The pathology of Alzheimer's disease (AD) results in behavioral problems which include memory deficits and impaired social behavior. The present study assessed social learning

and social behavior in a transgenic mouse model of AD (3xTg-AD). In the first study, WT (B6/129 hybrids) and 3xTg mice were compared in their performance in the social transmission of food preference (STFP) task, an olfactory memory test that depends on social behavior. The effect of daily ingestion of the soy phytoestrogen genistein on STFP performance in both WT and 3xTG mice was also assessed. In the second study, sociability and social recognition was assessed in WT and 3xTg mice using the three-chamber social interaction task. In this task, sociability was measured by the subject's preference for investigating a conspecific over a novel object. Social recognition was measured by the subject's preference for a novel conspecific over a familiar conspecific. Further, we tested the utility of the three-chamber task as a test of social memory persistence by varying the delay (0, 20, 120, and 240 min) between initial exposure to the familiar conspecific and the exposure to the familiar versus novel conspecific. In the STFP experiment we found that both WT and 3xTg mice had unimpaired olfactory, social-dependent memory, and social behavior in the task did not differ between the genotypes. Daily ingested genistein impaired olfactory memory in the STFP, and this impairment occurred in both genotypes. In the three-chamber task, we found that both WT and 3xTG mice had a preference for a conspecific over a novel object. In the social recognition test, WT mice preferred the novel conspecific, but 3xTg showed no preference indicating an impairment in social recognition. Neither genotype preferred the novel conspecific when the delay was increased to 20, 120, or 240 minutes showing that even in WT mice, social memory is disrupted by a short delay. These studies show that compared to WT mice, the 3xTg mouse has similar baseline sociability, similar socially-dependent olfactory memory, and similar memory sensitivity to genistein. Social recognition was impaired in the 3xTg mice. Current studies are testing whether this impaired recognition phenotype is specific to differences in the social domain, generalizable to other stimuli, or due to an anxiety-like response to novel stimuli.

Disclosures: B.A. Sulkowski: None. **H.R. LeBlanc:** None. **A.C. Williamson:** None. **B.V. Rohr:** None. **B.G. Gentry:** None. **C.C. Wrenn:** None.

Poster

785. Social Memory and Cognition II

Location: Hall A

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Program #/Poster #: 785.18/AA30

Topic: H.01. Animal Cognition and Behavior

Support: NIH BRAIN Initiative grant U01NS108680

Title: Large scale recording of population activity during social cognition in freely moving non-human primate

Authors: *M. FRANCH[1], A. WRIGHT[1], B. AAZHANG[2], V. DRAGOI[1];
[1]Neurobio. & Anat., UTHealth - McGovern Med. Sch., Houston, TX; [2]ECE, Rice Univ., Houston, TX

Abstract: Social interactions, a ubiquitous aspect of our everyday life, are critical to the health and survival of the species, but little is known about their underlying neural computations. The major limitation preventing our understanding of the neural underpinnings of social cognition is the lack of a suitable framework to allow us to study how it emerges in real time from interactions among brain networks. Indeed, examining the neural bases of complex social interactions has been traditionally performed by studying the brain of nonhuman primates (NHP) in a laboratory environment in which the head and body are restrained. However, it has become increasingly understood that studying the brain in spatially confined, artificial laboratory rigs poses severe limits on our capacity to understand the function of brain circuits. To overcome these limitations, we propose a novel approach using high-yield (up to 200 channels) wireless electrical recordings and eye tracking to study the cortical dynamics of social interactions in visual and prefrontal cortex while animals learn to simultaneously push and hold buttons to cooperate for food reward. Over time, animals developed a cooperative strategy, with one animal's actions leading cooperation. Furthermore, we found that reward value influences social behavior, and animals learn to cooperate faster for low reward across sessions. Neural activity in prefrontal and visual cortex is modulated by reward anticipation and the animals' choices. Population activity in prefrontal cortex is sensitive to reward value, and the motivation to cooperate increases on trials with larger reward. This new approach will enable us to uncover the dynamics of neuronal network activity that drives social interactions in an ethologically relevant behavioral task that involves sensory integration, memory, and complex decision-making. Furthermore, our proposed research has the potential to constitute a paradigm shift by moving social neuroscience from simply observing animal behavior and recording the responses of single cells to a quantitative understanding of the distributed neuronal network encoding during social behavior in freely moving NHPs performing naturalistic tasks.

Disclosures: M. Franch: None. **A. Wright:** None. **B. Aazhang:** None. **V. Dragoi:** None.

Poster

785. Social Memory and Cognition II

Location: Hall A

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Program #/Poster #: 785.19/AA31

Topic: H.01. Animal Cognition and Behavior

Support: Chicago Biomedical Consortium and Loyola University CVRI Equipment Grant

Title: Prenatal stress results in molecular and behavioral deficits associated with abnormal function of the hippocampus

Authors: *B. E. POWERS, M. SODHI;
Loyola Univ. Chicago, Maywood, IL

Abstract: A post-transcriptional process known as RNA editing regulates the trafficking and function of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid glutamate receptors (AMPARs), which are critical for synaptic plasticity, learning and memory. RNA editing of AMPARs has been associated with stress, anxiety, schizophrenia, mood disorders and suicide. Prenatal stress results in abnormal brain development and is a risk factor for several psychiatric disorders. We have tested the hypothesis that the long term effects of prenatal stress are mediated by altered RNA editing. We analyzed prenatal restraint stress (PRS)-induced effects on behavior and RNA editing in the hippocampus of C57BL/6J mice. Pregnant dams were subjected to PRS from gestation day 7 until birth. In adulthood, offspring were assessed for social interaction behavior, locomotor activity, and spatial learning and memory. The hippocampus of each mouse was analyzed for the expression of the RNA editing enzymes (ADARs 1-3) in addition to analysis of the RNA editing levels of the AMPAR subunits. PRS reduced social interaction behavior and reduced hippocampal RNA editing of the AMPAR subunits GluA2, GluA3 and GluA4. Social interaction deficits and alterations of GluA2 RNA editing were normalized by treatment with the antipsychotic drug clozapine. Additional experiments using a reduced intensity of PRS failed to produce behavioral deficits. Our data show that PRS produces long-term changes in behavior that may be due to abnormal development of the hippocampus. Therefore the long-term behavioral deficits resulting from severe PRS may be mediated through a molecular pathway involving AMPAR RNA editing.

Disclosures: B.E. Powers: None. **M. Sodhi:** None.

Poster

785. Social Memory and Cognition II

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Topic: H.01. Animal Cognition and Behavior

Support: CV Starr Fellowship, Princeton Neuroscience Institute
NIH R01 NS045193
NIH R01 MH115750

Title: Brain-wide mapping of neural activity during observational learning

Authors: *K. M. SEAGRAVES[1], T. J. PISANO[1,2,3], Z. DHANERAWALA[1], S. S.-H. WANG[1,2];
[1]Princeton Neurosci. Inst., [2]Dept. of Mol. Biol., Princeton Univ., Princeton, NJ; [3]Robert Wood Johnson Med. Sch., Rutgers Univ., New Brunswick, NJ

Abstract: During observational learning animals acquire new information by observing a social partner's response to a stimulus. This form of social learning is thought to be a primary way humans learn social norms, and also serves as an adaptive mechanism for avoiding potentially harmful situations. Despite the clear importance of observational learning in the development of mental models of the world, the long-range neural circuits that control this social learning phenomenon remain poorly understood. To address this, we used whole-brain clearing, antibody labeling, and light-sheet microscopy to image brain-wide c-Fos protein expression following a fear-based observational learning paradigm. In this paradigm an observer animal witnesses the fear of a social partner (the demonstrator) while that animal undergoes classical delay fear conditioning. The imaged brain volumes were registered to the Allen Brain Atlas, and c-Fos+ cells were identified using a custom algorithm. The c-Fos pattern of observers was compared to that of demonstrators, and to control animals that experienced the same paradigm without the fear-inducing stimulus. As expected from previous work, brain areas typically associated with direct fear conditioning, such as various amygdalar nuclei, show elevated c-Fos levels compared with controls. Furthermore, observers show elevated c-Fos in the anterior cingulate cortex, a region known to be involved in observational learning, compared with demonstrators. Surprisingly, the parabrachial nucleus, which is strongly activated in demonstrator animals, did not show elevated c-Fos expression during observational learning, despite previous work showing that it responds to other types of perceived threats. This suggests differential involvement of the parabrachial nucleus in the acquisition of socially-learned fear. Overall, this study has generated a comprehensive activation map of the brain areas that may be coordinating both direct and indirect fear learning, and provides insight into the areas that are specifically involved in the social aspect of observational learning.

Disclosures: K.M. Seagraves: None. **T.J. Pisano:** None. **Z. Dhanerawala:** None. **S.S. Wang:** None.

Poster

785. Social Memory and Cognition II

Location: Hall A

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Program #/Poster #: 785.21/AA33

Topic: H.01. Animal Cognition and Behavior

Support: Start up funding to Y.M.Y.

Title: Chemogenetic inhibition of Purkinje cells in the anterior cerebellum disrupts motor coordination, social recognition and interaction

Authors: *O. Y.-H. CHAO, Y.-M. YANG;
Biomed. Sci., Univ. of Minnesota Med. Sch., Duluth, MN

Abstract: The posterior cerebellum has been implicated in social cognition, while the involvement of the anterior cerebellum, evidenced for sensorimotor processes, remains enigmatic in social behaviors. To address this issue, we applied NMDA lesions, and chemogenetic inhibition of Purkinje cells with AAV-L7-hM4Di-mCherry or a control AAV-hSyn-EGFP, into the cerebellar lobules IV/V of male C57BL/6 mice. Three weeks after the surgery, clozapine-*N*-oxide (1 mg/kg, i.p.) was injected to activate chemogenetic receptors 30-40 minutes before each behavioral test. In the open field, the lesioned and hM4Di groups travelled longer distance than the control group, and their performance on a rotarod was impaired. The control and hM4Di groups showed intact object recognition memory, while the lesioned group showed low amount of object exploration. In the social recognition test, the control group, but not the lesioned and hM4Di groups, sniffed the novel stranger more than the familiar one. In the free social interaction test, the lesioned and hM4Di groups exhibited less interaction than the control group. Subsequent *c-fos* imaging indicated that the functional connectivity required for free social interaction was disorganized in the lesioned and hM4Di groups. Collectively, chemogenetic inhibition of Purkinje cells of the cerebellar lobules IV/V or lesions of the region impaired motor coordination, along with social recognition and interaction. These findings suggest that the anterior cerebellum is critically involved in social behaviors although being masked by its sensorimotor role.

Disclosures: O.Y. Chao: None. **Y. Yang:** None.

Poster

785. Social Memory and Cognition II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 785.22/AA34

Topic: H.01. Animal Cognition and Behavior

Title: Observational learning in a working memory, food-reward task in rats

Authors: *R. TROHA[1], T. SHAO[1], N. HERNANDEZ[1], A. BUZZANCA[2], J. WANG[1], E. J. MARKUS[3];
[1]Univ. of Connecticut, Storrs, CT; [2]Univ. of Connecticut, Storrs, IN; [3]Univ. of Connecticut, Storrs Manfld, CT

Abstract: Observational learning allows an animal to indirectly learn the outcome of an action by watching a conspecific. Seminal work by Bandura (1961) illustrated how children imitate the behavior of adults. Although this behavior can be seen in humans, animal models have only recently been developed to study the neural circuitry involved in this behavior. The bulk of these experiments rely on social fear conditioning and fewer experiments examine observational learning of a reward-based behavior. Such a task would allow comparison of the brain areas involved in these two contrasting scenarios. We have shown that rats can learn the location of a

food reward on a T-maze by watching another rat. However, this task is limited by a limited number of daily trials, proximity of the two rats, and that only the first trial per session requires observation. The current task includes two attached operant chambers with the observer and demonstrator at close proximity. The demonstrator responds randomly at one of two nose-poke locations in order to receive a food reward. The observer must continuously monitor the behavior of the demonstrator to correctly respond in its own chamber. The issue of local enhancement is addressed by using a light cue to indicate whether the correct choice is either the same or opposite the performer. This within-animal design provides a way to test the same animal using many different manipulations and provides a powerful method for studying observational learning in a reward-based task. This could lead to a better understanding of disorders in which social learning deficits are seen, such as Autism Spectrum Disorder and Schizophrenia.

Disclosures: R. Troha: None. **E.J. Markus:** None. **N. Hernandez:** None. **T. Shao:** None. **J. Wang:** None. **A. Buzzanca:** None.

Poster

785. Social Memory and Cognition II

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Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 785.23/AA35

Topic: H.01. Animal Cognition and Behavior

Support: NSERC
CIHR

Title: Neural correlates of gaze direction in basolateral amygdala

Authors: *B. MAHMOUDIAN[1], B. W. CORRIGAN[2], J. LAU[3], W. W. PETTINE[4], J. MARTINEZ-TRUJILLO[5];
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Abstract: Social communication in primates relies heavily on visual cues. Head and eye orientation can signal one's gaze direction and provide cues for directing attention (Ghazanfar & Santos, 2004). the amygdala, a subcortical structure in the anterior temporal lobe, has been shown to respond to elements of a face such as eyes (Mosher et al. 2015). One possibility is that the amygdala contains circuits that encode gaze direction. However, evidence in favor of this hypothesis is scarce. Amygdala lesions impair performance of individuals in spatial cueing tasks utilizing social cues (eye) but not in case of arrow (non-social) cues (Akiyama 2007). Although fMRI studies provide evidence for differences in basolateral amygdala nuclei (BLA) activation in viewing static images of direct vs averted gaze (Hoffman 2007, Mormann 2015, Tazumi

2010), there exists little evidence of how the local amygdala circuitry might encode gaze direction. To address this gap we have designed a spatial cueing task in which the animal must utilize gaze direction cues to locate the rewarded target while single unit activity of BLA is monitored.Hypothesis: We hypothesize that different populations of neurons in primate BLA are tuned for gaze cues of head and eye orientation. Two Rhesus Macaques will be placed in front of a computer screen and head fixed while their eye positions on the screen are recorded during experiment. In a four-alternative choice task, the animal must utilize the presented direction of social or non-social cue to attend the location of the rewarded target. Social conditions include avatar monkey models cueing the target location using different combinations of head and eye rotations. Non-social conditions will employ a variety of non-biological cues (e.g. an arrow) to indicate the position of the target. Recordings from single neurons in the BLA amygdala will be conducted using 64 microwire electrode. Eye movements will be recorded to determine the animal's gaze position. We have recorded behaviorally data from two animals. In the social (avatar) condition the animals quickly learned to make gaze saccades towards the cued location (in the direction of the avatar's gaze). They also follow the avatars gaze when it deviates from the usual target locations suggesting that the animals indeed interpret gaze cues. Preliminary recordings show that neurons in the amygdala are responsive to gaze cues.

Disclosures: B. Mahmoudian: None. **B.W. Corrigan:** None. **J. Lau:** None. **W.W. Pettine:** None. **J. Martinez-Trujillo:** A. Employment/Salary (full or part-time):; Western University.

Poster

785. Social Memory and Cognition II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 785.24/AA36

Topic: H.01. Animal Cognition and Behavior

Support: Autism Science Foundation
Harvard Program for Research in Science and Engineering
NIH 1R01MH112846
NIH 1R01NS091390

Title: Neuronal encoding of prosocial helping behavior in the mouse prefrontal cortex

Authors: *P. B. GABRIELI, S. W. LI, J. L. DEMAREE, J. CAI, Z. WILLIAMS; Massachusetts Gen. Hosp., Boston, MA

Abstract: Prosocial behaviors, typically defined as voluntary actions that benefit others, are a cornerstone of both human and animal societies. Unlike other sensorimotor processes, however, the act of helping others is also complex, requiring individuals to not only perceive the need of others but also select behaviors that can provide specific help. Further, abnormal prosocial

behavior is a major characteristic of several psychosocial conditions, including autism spectrum disorders (ASD), schizophrenia, and antisocial personality disorder. Here, we discover neurons in the mouse dorsomedial prefrontal cortex (dmPFC) that encoded the aversive experiences of others as well as a distinct group of neurons that reflected specific selection of helping behavior. To investigate prosocial behavior in an animal model, we developed a novel prosocial assay based on a modified real-time place preference (RTPP) task, in which the position of a subject mouse controlled the aversive experience of a nearby conspecific partner. Interestingly, we find that wild-type C57BL/6J males demonstrated helping behavior that reduced their partner's aversive experience when their partner was familiar but not when they were unfamiliar. Male mice with ASD-related *Shank3*$^{+/-}$ mutation, by contrast, did not demonstrate helping behavior under any condition. By further recording from the dmPFC, we identified specific subsets of neurons that encoded the demonstrator's aversive experiences, changing their activity when their partner received a brief shock. Other neurons, by comparison, encoded the act of helping the other, displaying changes in their activity prior to selecting the area that did not shock their familiar partner. Taken together, these findings suggest a neuronal mechanism in the mouse dmPFC for enacting helping behavior and an early cellular substrate for pro-sociability.

Disclosures: P.B. Gabrieli: None. **S.W. Li:** None. **J.L. Demaree:** None. **J. Cai:** None. **Z. Williams:** None.

Poster

785. Social Memory and Cognition II

Location: Hall A

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Topic: H.01. Animal Cognition and Behavior

Support: Autism Science Foundation
NIH 1R01MH112846
NIH 1R01NS091390

Title: Dorsomedial prefrontal cortex encodes collective behavioral states in groups of mice

Authors: *S. W. LI, Z. WILLIAMS;
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Abstract: Social interactions among individuals within a group are remarkably complex, often involving the simultaneous actions of numerous individuals. Unlike many other forms of behavior, intragroup interactions are highly multi-dimensional, meaning that they require group members to consider factors such as their partners' identities, behavioral strategies, past decisions and the dynamic relation between them. Although prior behavioral observations have provided important insight into how individuals within groups interact or how they may

represent the behavior of others, the basic cellular mechanisms that underlie group behavior are largely unknown. In this study, we aimed to examine whether and how group behavioral states and the interaction between animals may be encoded by individual neurons in freely behaving groups of mice. Nests of three or six familiar mice were allowed to freely interact in a large open arena while we telemetrically recorded single neuronal activity from the dorsomedial prefrontal cortex (dmPFC) in one individual from the group. Using dimensionality reduction and unsupervised clustering algorithms, we characterized collective group behavioral states and their evolution over time. We further classified and ordered specific group level measurements (e.g. group velocity, group polarization, group spread) that are most relevant for determining these behavioral states by using a regression tree analysis. Lastly, we identified subsets of dmPFC neurons that differentially encoded group level measurements, collective behavioral states of the group, and dynamical relationships between self and group. Interestingly, we found that dmPFC neurons exhibited temporally modulated and divergent roles specific to self-group versus others-group interactions, and that these neurons were modulated by the behavioral state of the group. Taken together, data from this study reveals a remarkably rich neuronal process in the mouse prefrontal cortex for representing the collective behavior of social groups and the complex interactions within them.

Disclosures: S.W. Li: None. **Z. Williams:** None.

Poster

785. Social Memory and Cognition II

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Topic: H.01. Animal Cognition and Behavior

Support: Autism Science Foundation
Summer Scholars Independent Research Fellowship
NIH 1R01MH112846
NIH 1R01NS091390

Title: Single-neuronal differences in social encoding between males and females during social competition

Authors: *L. STRAHS, S. W. LI, Z. WILLIAMS;
Massachusetts Gen. Hosp., Boston, MA

Abstract: Males and females perceive and respond to social information differently, a property that plays a powerful role in the behavior of both animals and humans. Whether or how social information is encoded differently in males and females at the single-cell level, however, is largely unknown. A common example of sexual dimorphism manifests in the way individuals

interact within groups or how they compete for resources. Significantly, these processes are dysfunctional in psychosocial disorders such as Autism Spectrum Disorders (ASD), which also presents differently in males and females. Here, we investigated the single-neuronal encoding mechanisms by which males and females may differ by using a mouse model of group competition. Behaviorally, we show that males display a highly positive correlation between competitive success and hierarchical rank when competing for resources within groups. Females, by contrast, demonstrate little relation between social rank and competitive success. We also demonstrate that males and female utilize differing social strategies to obtain a limited resource in a competitive environment. Building on these behavioral findings, we next performed single-neuronal recordings in the animal's dorsomedial prefrontal cortex (dmPFC), an area thought to be involved in social behavior. We find that dmPFC neurons are able to track not only the hierarchical standing of particular individuals within a group, but also their competitive success by predicting competitive outcomes based on information about competitors. Preliminary data further suggests that information encoded in the dmPFC about hierarchical standing, success and competitors are encoded differently between males and females. Taken together, this study provides a functional framework to decode the neuronal mechanisms governing sexually dimorphic behaviors between males and females.

Disclosures: **L. Strahs:** None. **S.W. Li:** None. **Z. Williams:** None.

Poster

786. Learning and Memory: Subcortical-Hippocampal Interactions

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 786.01/AA39

Topic: H.01. Animal Cognition and Behavior

Support: National Natural Science Foundation of China Grant 31661143038
Israel Science Foundation Grant 2523/16
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Title: Theta state related septal cholinergic neurons disrupt hippocampal sharp wave-ripples via muscarinic receptors

Authors: X. MA[1], Y. ZHANG[1], L. WANG[1], N. LI[1], E. BARKAI[2], X. ZHANG[3], ***J. XU**[1], L. LIN[1];
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Abstract: The septo-hippocampal cholinergic system is critical for hippocampal function. However, a quantitative description of the *in vivo* firing patterns and physiological function of

medial septal (MS) cholinergic neurons are yet to be shown. Combining optogenetics with multi-channel *in vivo* recording, we were able to continuously record MS cholinergic neurons' firings in freely behaving mice for 5.5 - 72 hours and found that their firings were highly correlated with hippocampal theta states. MS cholinergic neurons were highly active during theta-dominant epochs, such as active exploration and rapid eye movement sleep, and almost inactive during non-theta epochs, such as slow wave sleep (SWS). Interestingly, optogenetically activating these MS cholinergic neurons during SWS suppressed CA1 sharp wave-ripples. This suppression could be rescued by muscarinic M2 or M4 receptor antagonists. These results suggest an important physiological function of MS cholinergic neurons: maintaining high hippocampal acetylcholine level by persistent firing during theta epochs, consequently suppressing ripples and allowing theta oscillations to dominate.

Disclosures: X. Ma: None. **Y. Zhang:** None. **L. Wang:** None. **N. Li:** None. **E. Barkai:** None. **X. Zhang:** None. **J. Xu:** None. **L. Lin:** None.

Poster

786. Learning and Memory: Subcortical-Hippocampal Interactions

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 786.02/AA40

Topic: H.01. Animal Cognition and Behavior

Support: 2T32MH067564
MH078064
MH108837

Title: A sexually dimorphic role of dentate gyrus oxytocin receptor expressing neurons in social and memory related behaviors

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Abstract: The neuropeptide oxytocin and its receptor have a well-established role in modulating social behaviors, including parental behavior, pair bonding, and social memory. Due to the body of literature supporting the role of the oxytocin system in social behavior, oxytocin has been proposed as a therapeutic target for psychiatric disorders involving social behavior, such as autism spectrum disorder. Importantly, the oxytocin system often regulates sex-specific social behaviors, which may be due to known sex differences in synthesis and receptor expression. Therefore, clinical strategies should consider that oxytocin may have differential treatment effects in males and females. Given the well-established role of the hippocampus in social behavior and memory, we set out to investigate the role of hilar oxytocin neurons in social and

non-social memory-related behaviors in mice of both sexes. We first performed a detailed cellular characterization of oxytocin receptor-expressing neurons and their connectivity, followed by chemogenetic and circuit inactivation approaches to test the functional role of these neurons. Our findings demonstrated that hilar oxytocin receptor-expressing neurons affect behavior in a sexually-dimorphic manner, with a predominant role in social behavior in males, and a predominant role in memory-related behavior in females. These studies begin to elucidate a cellular population of oxytocin neurons that differentially regulate behaviors between sexes. Identifying sexual dimorphisms in oxytocin system function is important for developing practical treatment strategies for patients, of both sexes, who suffer from psychiatric disorders involving social behavior.

Disclosures: **M. Meyer:** None. **K. Nishimori:** None. **J.M. Radulovic:** None.

Poster

786. Learning and Memory: Subcortical-Hippocampal Interactions

Location: Hall A

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Title: The role of subcortical hippocampal inputs in contextual memory formation

Authors: *V. S. GRAYSON[1], Y. HAN[3], A. L. GUEDEA[1], V. JOVASEVIC[1], C. GAO[4], A. APKARIAN[2], J. M. RADULOVIC[1];
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Abstract: The role of cortical efferents to the hippocampus in the formation of episodic-like memory is well established, however, less is known about the contribution of subcortical memory circuits to memory. In the present study, we studied the roles of several subcortical inputs into the dorsal hippocampus in mouse models of contextual fear conditioning, extinction, and reinstatement. Fear conditioning was induced by a single exposure of mice to a context followed by foot shock. Subsequently, mice were exposed to daily extinction trials. After significant reduction of freezing, indicating successful extinction, mice were exposed to a brief reminder shock and re-tested in the conditioning context. Circuit manipulations were performed

by chemogenetic silencing with the inhibitory designer receptor exclusively activated by designer drugs (DREADD) hM4(Gi) or targeted cholinergic depletion induced by 192 IgG-saporin, at different stages of fear conditioning, extinction, and reinstatement. We identified projection- and neurotransmitter-specific roles of discrete circuits, indicating complex regulation of fear-inducing memories by subcortical afferents.

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Poster

786. Learning and Memory: Subcortical-Hippocampal Interactions

Location: Hall A

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Program #/Poster #: 786.04/AA42

Topic: H.01. Animal Cognition and Behavior

Support: Department of Anatomy, AIIMS, New Delhi, India

Title: Effects of arsenic trioxide-induced oxidative stress on basal forebrain of mice

Authors: *B. KAUR, K. MEHTA, K. K. PANDEY, P. DHAR;
Anat., All India Inst. of Med. Sciences, New Delhi, New Delhi, India

Abstract: Background: Arsenic trioxide (As_2O_3) has been considered for therapeutic purposes over a long period and presently is in use as chemotherapeutic agent for treatment of acute promyelocytic leukemia (APL). As_2O_3-induced oxidative stress is considered as the major mechanism for its chemotherapeutic action as well as for associated toxic effects on various organ systems including cholinergic system in central nervous system which is responsible for cognitive functioning. Basal forebrain (BF) region of brain houses the majority of cholinergic neuronal population projecting to different regions of brain such as hippocampus and prefrontal cortex. Any insult to BF area or to its projection fibres may result in cognitive deficits. Thus, the present study was undertaken to investigate the effect of arsenic trioxide induced-oxidative stress on the cognitive functions and neuronal population of basal forebrain.
Material & methods: Adult male mice were divided into control group (I) and experimental group (II). The experimental group received increasing dosage of As_2O_3 (2, 4 & 8 mg/kg) via oral route for a period of 45 days. Open field test (OFT) and Morris Water Maze (MWM) test were carried out during the experimental period. On day 46, perfusion fixed and freshly obtained brain tissue from animals was processed for immunohistochemical localization of various proteins and estimation of oxidative stress markers and western blot analysis respectively.
Results: The animals receiving higher dose of As_2O_3 spent significantly less time in central zone of open field as compared to control group. In MWM, during acquisition phase As_2O_3 treated mice showed prolonged escape latency and travelled longer distance to find the platform whereas

in probe trial, these animals showed less number of platform crossing. Decreased levels of glutathione and antioxidant enzymes (superoxide dismutase and catalase) were recorded in BF of As_2O_3 treated groups. Immunoexpression of ChAT and AChE was significantly downregulated while that of SCGN was upregulated in As_2O_3 alone treated animals as compared to controls. **Conclusion:** These preliminary observations do suggest increase in oxidative stress markers and alterations in behavioral parameters alongwith changes in neuronal population of BF in mice exposed to increasing concentration of As_2O_3.

Disclosures: B. Kaur: None. **K. Mehta:** None. **K.K. Pandey:** None. **P. Dhar:** None.

Poster

786. Learning and Memory: Subcortical-Hippocampal Interactions

Location: Hall A

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Topic: H.01. Animal Cognition and Behavior

Support: Atención a Mexican Science and Technology Council (Consejo Nacional de Ciencia y Tecnología) Grant 273553
Problemas Nacionales Grant 464
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Title: Electrophysiological recording on basolateral amygdala and ventral hippocampus during memory tasks induced by high fat diet during adolescence

Authors: *C. I. PEREZ[1,3], A. I. HERNANDEZ-COSS[2], M. G. MORENO[1], G. FERREIRA[4], G. PACHECO-LOPEZ[3], F. BERMUDEZ-RATTONI[5], R. GUTIERREZ[1];
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Abstract: The prevalence of obesity in adolescents has become a major challenge for public health. This is particularly worrisome since this period is crucial for the maturation of some brain structures like amygdala and hippocampus, areas that are involved in learning and memory process. Previous studies demonstrated that high-fat diets (HFD) impair hippocampal-dependent memory and hippocampal glutamatergic neurotransmission, also enhances emotion-induced neuronal activation of the basolateral complex amygdala. However, the link between obesity during adolescence and cognitive dysfunction in rodents remains poorly characterized, and more studies at the neural level are important to identify the functional circuits involved in emotional and spatial memory. To address this issue, we characterized the influence of HFD given to juvenile rat upon memory performance. Wistar rats have *ad libitum* access to either regular diet

(2.9 Kcal/g; A04, Safe) or HFD (4.7 Kcal/g; D12451, Research Diet) starting at weaning until 12 weeks old (adulthood). After this period, rats were implanted with an electrode that consisted of 8 filaments of tungsten wires targeting the basolateral amygdala and 8 more the ventral hippocampus. Neuronal activity was recorded in both structures simultaneously during the acquisition and test of object recognition memory (ORM) and then, during a conditioned odor aversion (COA). Our results confirm that rats that started to consume HFD during the adolescence were less efficient than their control Chow feeds counterparts in performing spatial ORM task and enhances long-term emotional memories as assessed by odor-malaise association (COA). The analysis of neuronal recordings will be presented at the conference. Nevertheless, we hypothesize that juvenile obese rats will show enhanced neuronal activity in the amygdala, while hippocampus has the opposite effect on the retrieval during object recognition memory and odor memory. This study has the goal of revealing the participation of both ventral hippocampus and basolateral amygdala on memory impairment induced by consumption of HFD during adolescence.

Disclosures: C.I. Perez: None. **A.I. Hernandez-Coss:** None. **M.G. Moreno:** None. **G. Ferreira:** None. **G. Pacheco-Lopez:** None. **F. Bermudez-Rattoni:** None. **R. Gutierrez:** None.

Poster

786. Learning and Memory: Subcortical-Hippocampal Interactions

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

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Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant DA037255

Title: Signals in hippocampus (CA1) and dorsomedial striatum (DMS) predict response in a visuomotor conditional association task

Authors: *K. GURLEY[1], T. G. WEYAND[2];
[1]Cell Biol. and Anat., LSU Hlth. Sci. Ctr., New Orleans, LA; [2]Louisiana State Univ. Med. Ctr., New Orleans, LA

Abstract: The hippocampus and striatum are associated with two broad types of learning thought to drive competing behavioral strategies. The hippocampus is central to context learning, in which behavior is driven by associations between contiguous cues in the environment, and the striatum is central to habit learning, in which behavior is driven by subconscious recall of a cued motor response. While many studies have focused on dissociating the functions of these structures, here we focus on potential cooperativity. Rats performed an operant visuomotor conditional association task, in which they must nose-poke a left or right port based on one of two visual stimuli. A correct nose-poke was reinforced with a drop of 25% sucrose solution.

Naive Bayesian decoding of multiunit spike activity show decision-related signals in both regions emerging ~75 msec prior to the nose-poke, with decoding accuracy increasing to significant levels in the hippocampus prior to the striatum. Furthermore, gamma coherence of the local field potentials in CA1 and DMS increase prior to nose-poke, suggesting the potential for synchronized communication between the regions. Collectively these data support the idea that both CA1 and DMS simultaneously facilitate context-dependent decision-making.

Disclosures: K. Gurley: None. **T.G. Weyand:** None.

Poster

786. Learning and Memory: Subcortical-Hippocampal Interactions

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 786.07/BB1

Topic: H.01. Animal Cognition and Behavior

Support: FONCICYT-DADC OBTEEN 273553

Title: Metabolic changes induced by high-fat diet intake during adolescence affect spatial and aversive long-term memories

Authors: *P. SALCEDO-TELLO[1], S. HERNANDEZ RAMIREZ[2], A. HERNANDEZ-MATIAS[1], D. OSORIO-GÓMEZ[1], C. I. PEREZ[3], R. GUTIERREZ[3], F. BERMUDEZ-RATTONI[1], K. GUZMAN-RAMOS[4];
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Abstract: The obesity epidemic is increasing at an alarming rate. According to the World Health Organization, the global prevalence of obesity has almost tripled between 1975 and 2016. The prevalence of overweight and obesity is also increasing dramatically in children and adolescents. Mexico and USA are today the countries amongst most childhood/youth obesity in the world. In addition to being associated with diseases such as hypertension, cancer and diabetes, obesity affects neurocognitive features including learning and memory. Adolescence is a crucial period for maturation of limbic brain structures like hippocampus and amygdala. Recent studies have shown a particular vulnerability of juvenile individuals to the effects of the early onset of obesity in memory function. To assess the effects of obesity in adolescence on hippocampal and amygdala function, we use a model of diet induced obesity in male Wistar rats. Rats were exposed to a regular diet (control group, 2.9Kcal/g) or a high-fat diet (HFD group,4.7Kcal/g) after weaning for 3 months thus covering adolescence. After exposure to the diet, rats were trained in the hippocampal dependent Morris water maze (WM) or amygdala-dependent

conditioned odor aversion (COA). We also measure metabolic parameters. The individuals who received HFD showed an increase in body weight with respect to control diet animals. The HFD group also exhibited an increase in basal glucose blood levels, diminished glucose tolerance and insulin sensitivity. The cognitive tasks showed that HFD rats have an impaired performance in WM´s long term memory. This is consistent with previous findings indicating a functional deterioration of the hippocampus due to a high fat and/or high sugar induced obesity. Regarding amygdala-dependent long-term memory performance, we found that the consumption of HFD increases the aversive response in COA. This could be due to catecholaminergic deregulation since tyrosine hydroxylase (TH) levels in the amygdala were affected in the HFD group, while in the hippocampus TH levels remained equal within the groups The specificity of changes in the amygdala could explain the increase in the aversive response while interrupting spatial memory.

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Poster

786. Learning and Memory: Subcortical-Hippocampal Interactions

Location: Hall A

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Program #/Poster #: 786.08/BB2

Topic: H.01. Animal Cognition and Behavior

Support: MINECO (SPAIN) PSI2014-57643-P
MINECO (SPAIN) PSI2017-86381-P
MECD (SPAIN) FPU14/01531

Title: Auditory context-modulation of taste recognition memory relies on the accumbens hippocampus dopaminergic circuit

Authors: *A. B. GRAU-PERALES[1], E. R. LEVY[2], A. A. FENTON[2], M. GALLO[1]; [1]Dept. of Psychobiology. Inst. of Neurosciences, Univ. of Granada, Granada, Spain; [2]Ctr. for Neural Sci., New York Univ., New York, NY

Abstract: Rodents exhibit neophobia to novel tastes which attenuates across days if consumption is not followed by visceral negative consequences, indicating safe taste recognition memory. This attenuation of taste neophobia (AN) is context-dependent because the attenuation is disrupted when contextual cues change. A dopaminergic circuit involving the dorsal hippocampus (HC) has proven to be involved in spatial context-dependent AN. Whether non-spatial auditory contexts might also modulate AN and whether the hippocampus has a role has been largely unexplored. We confirmed that a change in the auditory context disrupted AN in adult male mice. This effect was lost following NMDA excitotoxic lesions targeted to dorsal

CA1 hippocampus. A similar disruption of the context-dependent AN was induced by intracerebral administration of 6-OHDA targeted to ventral CA1 hippocampus in rats. Moreover, systemic administration of the D1 dopamine receptor (D1DR) antagonist SCH-23390 resulted in a delayed AN in mice whether or not the auditory context changed, even if the drug was given a day after the context change. Finally, we used DREADD chemogenetics by combining intracerebral injection of two viral vectors to identify the crucial dopaminergic-hippocampal circuit. The retrograde Cre-recombinase expressing CAV-Cre was targeted to ventral CA1, and the DREADD pAAV-hSyn-DIO-hM4D(Gi)-mCherry was targeted to the nucleus accumbens shell. Intraperitoneal injection of clozapine-N-Oxide hydrochloride (CNO: 2mg/kg of body weight) 2 hours before the taste session interrupted AN similar to the previously observed D1DR antagonist, causing delayed AN when the context remained constant. Administering CNO a day after changing the auditory context also altered context-dependent AN. We conclude that the ability of changes in the auditory context to modulate taste recognition memory requires the activity of a dopaminergic nucleus accumbens shell-hippocampal circuit involving D1DRs that might be crucial for acquiring the taste-context association which is relevant for taste learning and memory. Supported by PSI2014-57643-P and PSI2017-86381-P (MINECO, Spain) and FPU14/01531 (MECD, Spain).

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Poster

786. Learning and Memory: Subcortical-Hippocampal Interactions

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Topic: H.01. Animal Cognition and Behavior

Support: NSERC 298475
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CIHR MOP-324941

Title: Intracellular dynamics of midline thalamic neurons during ripple-slow wave coupling in anesthetized mice

Authors: *D. BASHA[1,2], I. TIMOFEEV[3,1];
[1]CERVO Brain Res. Ctr., Quebec, QC, Canada; [3]CRIUSMQ, [2]Univ. Laval, Quebec, QC, Canada

Abstract: **Background:** Increased cortico-hippocampal synchrony during slow wave sleep is closely linked to sleep-mediated consolidation of memory. Specifically, the coupling of hippocampal high frequency oscillations **(*ripples; 100-300 Hz*)** to the phase of the neocortical slow oscillation ***(< 1 Hz)*** results in a selective increase in the recall and consolidation of spatial

memory. **However, the pathways that coordinate *ripple-SW coupling* in the sleeping brain remain unknown.** The midline thalamus has major reciprocal connections with the cortex and hippocampal structures, constituting a central node in cortico-hippocampal communication. Yet, little is known about the intracellular activity of the midline thalamus during cortico-hippocampal synchrony. **Methods:** Using sharp glass micropipettes and tungsten microelectrodes, we obtained intracellular recordings of 13 identified neurons of the midline thalamus together with local field potential recordings of the hippocampus and EEG in mice anesthetized with ketamine-xylazine. **Results:** All recorded midline thalamic neurons revealed membrane potential depolarization during the active phase of the EEG slow oscillation. Phase analysis revealed a propensity for hippocampal ripples to occur during thalamic silent states with a significant decrease in ripple incidence during the active state. This pattern was also observed in first order neurons of the ventromedial nucleus although the active state in these cells corresponded to a marked hyperpolarization. **Conclusions:** Given the anatomical connections of the midline thalamus with hippocampal and parahippocampal structures, the results suggests a role for the activate state of the thalamic slow oscillation in biasing the timing of hippocampal ripples. The cortical drive to the midline thalamus is likely the main source of cortico-hippocampal feedback during slow oscillatory activity.

Disclosures: D. Basha: None. **I. Timofeev:** None.

Poster

786. Learning and Memory: Subcortical-Hippocampal Interactions

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 786.10/BB4

Topic: H.01. Animal Cognition and Behavior

Support: CIHR
NSERC
Vanier CGS

Title: Investigating the spatial coding properties of lateral septum GABAergic neurons in freely behaving mice using miniaturized microscopy

Authors: *S. VAN DER VELDT, G. ETTER, F. SOSA, B. RIVARD, S. WILLIAMS; McGil University, Douglas Inst., Montreal, QC, Canada

Abstract: There is little evidence on how the hippocampal spatial map is processed in downstream regions such as the lateral septum (LS) for spatial navigation. The GABAergic cells of the lateral septum receive dense, converging projections from the pyramidal neurons of CA3, CA1 and subiculum. The inputs from the anatomical subregions of the hippocampus to the lateral septum appear to be highly anatomically organized, with more caudal regions receiving

inputs from CA3, rostral areas receiving stronger projections from the CA1 area. Spatially tuned cells have been previously reported in the LS (Tingley & Buszaki, 2018; Zhou et al., 1999; Leutgeb and Mizumori, 2002; Takamura et al., 2006), yet how their firing characteristics relate to hippocampal inputs remains unknown. Using calcium imaging with miniaturized fluorescence microscopy in behaving animals, we characterized the spatial firing properties of cells in the LS based upon their anatomical connections and hypothesized functional relationship with the hippocampal formation. For this, we have identified that approximately 15% of LS GABAergic cells are spatially modulated. We observed a decrease in place field stability along the dorsal-ventral axis of the LS, but not along the anterior-posterior axis. We compared LS place cell stability, mutual information and in-field firing rate with hippocampal place cell firing in open field and linear track paradigms, finding that the LS carries a highly similar, yet degraded firing rate code for position. The LS has emerged as an important structure in context recognition, as suggested by its role in context induced cocaine reinstatement (McGlinchey & Aston-Jones, 2018) and contextual fear condition (Vetere et al., 2017). Using the unique advantage of the miniscope to reliably follow the activity of the same cells over the course of multiple days, we followed these LS GABAergic assemblies activity pattern over the course of multiple days in same and different open fields, to assess the stability and remapping properties of the LS spatial code as compared to its hippocampal inputs. In addition, we have characterized the LS firing dynamics and distribution of place field centroids in response to objects or reward zones to determine whether the LS firing rate carries a purely spatial code, or anchor to salient cues in the environment.

Disclosures: S. van der Veldt: None. **G. Etter:** None. **F. Sosa:** None. **B. Rivard:** None. **S. Williams:** None.

Poster

786. Learning and Memory: Subcortical-Hippocampal Interactions

Location: Hall A

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Program #/Poster #: 786.11/BB5

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant R01MH107886
Alzheimer's Association Grant SAGA-17-419092

Title: Role of the nucleus reuniens in object memory consolidation in mice

Authors: *M. R. SCHWABE, L. R. TAXIER, K. M. FRICK;
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Abstract: Coordinated activity between the hippocampus and medial prefrontal cortex (mPFC) is required for memory encoding and retrieval. Recently, (Tuscher et al., 2018) our laboratory

demonstrated that simultaneous subthreshold chemogenetic inactivation of the dorsal hippocampus (DH) and medial prefrontal cortex (mPFC) impairs the consolidation of object recognition (OR) and object placement (OP) memories in female mice, suggesting that these two brain regions work in concert to promote memory consolidation. However, direct anatomical connections between the DH and mPFC are relatively sparse, so the mechanisms through which these brain regions interact to promote memory consolidation remains poorly understood. A small cluster of cells in the midline thalamus known as the nucleus reuniens (RE) facilitates communication between the hippocampus and mPFC through bidirectional excitatory projections. Furthermore, recent work indicates that the RE is necessary for spatial working memory and fear extinction learning. Collectively, these data suggest that the RE may be a key element of a memory circuit including the DH and mPFC, in which the RE mediates interactions between these regions. However, much is unknown about the RE's contribution to memory, including its role in memory consolidation. The goal of this study was to determine whether activity in the RE is necessary for object recognition and object placement memory. Kappa-opioid receptor DREADD (KORD) virus activated by Salvinorin B was used to inactivate excitatory neurons in the RE. Mice infused with GFP virus or saline were used as controls. KORD virus, GFP virus, or saline was infused into the RE of 9-week old ovariectomized female mice and 3 weeks were given for recovery and optimal expression before training. During training, mice were allowed to explore 2 identical objects placed near the corners of a large white box, and then received a 10 mg/kg injection of Salvinorin B immediately afterwards to target effects to the consolidation phase of memory formation. During testing, a training object was moved (OP) or replaced with a novel object (OR). OP and OR testing was conducted 4 h or 24 h after training, respectively, timepoints at which control animals remember the identity and location of the training objects. Preliminary data indicate that, unlike controls, KORD-treated mice did not exhibit intact OP memory consolidation, supporting a key role for the RE in spatial memory consolidation. Ongoing studies are investigating the necessity for RE activity for OR memory consolidation and potential mechanisms for interaction with the mPFC and DH.

Disclosures: **M.R. Schwabe:** None. **L.R. Taxier:** None. **K.M. Frick:** None.

Poster

787. Hippocampus, Engrams, and Memory

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 787.01/BB6

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JSPS KAKENHI 16H04653
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JST CREST JPMJCR13W1
JSPS KAKENHI 23220009
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Title: Preconfigured ensembles are recruited into upcoming hippocampal engram

Authors: *K. GHANDOUR[1], N. OHKAWA[1], C. A. FUNG[2], H. ASAI[1], Y. SAITOH[1], T. TAKEKAWA[3], H. NISHIZONO[1], M. SATO[4], M. OHKURA[5], J. NAKAI[6], Y. HAYASHI[7], T. FUKAI[2], K. INOKUCHI[1];
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Abstract: The process of determining the allocation of information to particular neurons and synapses within a neural network is known as the theory of `Memory allocation`. These particular set of neurons are termed engram cells, in which activating these engram cells either by physiological or artificial input can drive the recall of that specific event. However, how memory is allocated to these specific subpopulations of neurons is still poorly understood. Here we show that spontaneously evoked “pre-configured” ensembles formed during pre-learning sleeping periods are highly correlated with those formed during novel experience only in engram cells. A compatible imaging system was established to observe the neuronal activity of CA1 neurons and the labelled engram cells; through a photoconvertible fluorescent protein Kikume Green Red (KikGR). The neuronal activity of hippocampal CA1 neurons was observed, through Ca^{2+} influx with G-CaMP7 in freely-moving animals by miniature head-mount fluorescent microscopy. Our advanced imaging system of engram cells and non-engram cells provides deeper insights into the dynamics of the neural activity across several memory processing stages. Using Non-negative Matrix Factorization (NMF) analysis, engram cells showed that sub-ensembles detected during learning were highly correlated with sub-ensembles found during pre- and post-learning sleep sessions as well as retrieval sessions, however these correlations were abolished upon exposure to a different context. In contrast, these features were not observed in the non-engram cells. These findings suggest that the hippocampal network is pre-configured into cellular sub-ensembles that could rapidly be used to encode the near future novel experience.

Disclosures: **K. Ghandour:** None. **N. Ohkawa:** None. **C.A. Fung:** None. **H. Asai:** None. **Y. Saitoh:** None. **T. Takekawa:** None. **H. Nishizono:** None. **M. Sato:** None. **M. Ohkura:** None. **J. Nakai:** None. **Y. Hayashi:** None. **T. Fukai:** None. **K. Inokuchi:** None.

Poster

787. Hippocampus, Engrams, and Memory

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Program #/Poster #: 787.02/BB7

Topic: H.01. Animal Cognition and Behavior

Support: Japan Society for the Promotion of Science KAKENHI: JP18H05213

Title: Pcdhs modulate synchronous activity in the hippocampus

Authors: *H. ASAI[1,2], N. OHKAWA[1,2,3], K. GHANDOUR[1,2,3], Y. SAITOH[1,2,3], M. MATSUO[1], H. NISHIZONO[1], T. HIRAYAMA[4,5], R. KANEKO[6], S.-I. MURAMATSU[7,8], T. YAGI[4], K. INOKUCHI[1,2];
[1]Univ. of Toyama, Toyama, Japan; [2]CREST, Toyama, Japan; [3]PRESTO, Toyama, Japan; [4]Osaka Univ., Suita, Japan; [5]Tokushima Univ., Tokushima, Japan; [6]Gunma Univ., Gunma, Japan; [7]Jichi Med. Univ., Tochigi, Japan; [8]The Univ. of Tokyo, Tokyo, Japan

Abstract: Clustered protocadherins (Pcdhs), a large subgroup of adhesion molecules, are important for neural morphology, such as axonal projection and dendrite spread. Pcdhs have two unique characteristics: diversity based on the complex combinations of expressing isoforms in each cells and highly specific interaction with each other. Therefore, Pcdhs are thought to have crucial roles in forming diverse neural circuits. However, little is known whether Pcdhs affect neural activity. Observation of neuronal activities with two methods, in vivo Ca^{2+} imaging and immunostaining with neural activity marker cFos in Pcdhs-mutant mice, demonstrates that Pcdhs modulate neuronal activities in cellular ensemble and hippocampal circuit levels. Ca^{2+} imaging showed that Pcdhβs-deletion remarkably reduced repetitive activity during novel context exploration, which was revealed by correlation matrix analysis, and that Pcdhβs-deletion increased the number of large ensembles, which were extracted with non-negative matrix factorization analysis based on synchronous activity. Majority of the large ensembles showed low frequent activity. In immunostaining, the expression of cFos, induced by novel context exploration, was slightly reduced in the hippocampus of Pcdhβs-deletion mice. Pcdhβs-deletion mice showed significant correlation in the number of cFos-positive cells between hippocampal subregions, suggesting that Pcdhβs modulate neural activities in the hippocampal circuit level. Together Pcdhβs play an important role in controlling neuronal activity in the hippocampus.

Disclosures: H. Asai: None. **N. Ohkawa:** None. **K. Ghandour:** None. **Y. Saitoh:** None. **M. Matsuo:** None. **H. Nishizono:** None. **T. Hirayama:** None. **R. Kaneko:** None. **S. Muramatsu:** None. **T. Yagi:** None. **K. Inokuchi:** None.

Poster

787. Hippocampus, Engrams, and Memory

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Program #/Poster #: 787.03/BB8

Topic: H.01. Animal Cognition and Behavior

Support: NIH-NINDS R01 NS109226
NSF grant CCF-1409422

Title: Sub second dynamics of theta gamma coupling in hippocampal CA1

Authors: *L. ZHANG[1], J. LEE[1], C. ROZELL[1], A. C. SINGER[2];
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Abstract: Oscillatory brain activity reflects different internal brain states including neurons' excitatory state and synchrony among neurons. However, characterizing these states is complicated by the fact that different oscillations are often coupled, such as gamma oscillations (30-120 Hz) nested in theta (6-12 Hz) in the hippocampus, and changes in cross-frequency coupling are thought to reflect distinct states. In CA1, at least three gamma oscillators have been described with distinct gamma frequencies and theta-phase coupling: high gamma (>100 Hz) thought to be generated within CA1; median gamma (60-120 Hz) and low gamma (30-80 Hz), thought to originate from CA3 and entorhinal cortex (EC) respectively. Previous characterization of these different gammas and their cross-frequency coupling was mainly based on methods that quantify signals over long time scales and therefore cannot detect short-timescale variations in gamma or theta-gamma coupling. Thus, how theta-gamma coupling varies in both frequency and theta-phase and how theta-gamma coupling changes over short timescales remains unclear. Here, we describe a new method to separate single oscillatory cycles into distinct states based on frequency and phase coupling. Using this method, we identified four theta-gamma coupling states in rat hippocampal CA1. These states differed in abundance across behaviors, phase synchrony with other hippocampal subregions, and neural coding properties suggesting that these states are functionally distinct. We captured cycle-to-cycle changes in oscillatory coupling states and found frequent switching between different theta-gamma states showing that the hippocampus rapidly shifts between different functional states. This method identify cross-frequency coupling states within single oscillatory cycles and track cycle-to-cycle changes in these states provides a new approach to investigate oscillatory brain dynamics broadly.

Disclosures: L. Zhang: None. **J. Lee:** None. **C. Rozell:** None. **A.C. Singer:** None.

Poster

787. Hippocampus, Engrams, and Memory

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Support: NSF GRFP Grant No. DGE-1444932
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Title: Inhibitory connections are disrupted during spatial navigation in the 5XFAD mouse model of Alzheimer's disease

Authors: *S. M. PRINCE[1], A. L. PAULSON[2], N. JEONG[1], S. M. AMIGUES[2], A. C. SINGER[2];
[1]Emory Univ., Atlanta, GA; [2]Coulter Dept. of Biomed. Engin., Georgia Inst. of Technol. and Emory Univ., Atlanta, GA

Abstract: Alzheimer’s disease (AD) is the most common form of dementia and is associated with protein accumulation and neurodegeneration, resulting in neural dysfunction from the level of synapses to networks. One of the best correlates of cognitive impairment in AD is synaptic loss, which suggests that synaptic dysfunction is important to the pathogenesis of AD. While synaptic dysfunction in AD has been well characterized *in vitro*, synaptic changes in awake, behaving animals have not been examined because it is technically very challenging to record such alterations in mice, the primary animal model of AD. Here, we use a virtual-reality behavioral task and an *in vivo* measurement of synaptic efficacy in order to overcome the challenges of recording and measuring synaptic dysfunction in behaving animals. We show *in vivo* deficits in the inhibitory connection strength of interneurons onto pyramidal cells in the 5XFAD mouse model of AD, a well-established AD model that expresses five familial AD mutations. Inhibitory activity in hippocampus is critical for sharp wave ripple activity, high frequency network oscillations that are important for memory consolidation and retrieval. Thus, these synaptic deficits could be related to previously reported lower sharp wave ripple rates in 5XFAD mice. Indeed, we found that these 5XFAD mice had not only fewer but also shorter sharp wave ripples and decreased place cell activation during sharp wave ripples. These results show that *in vivo* synaptic dysfunction occurs in the 5XFAD mouse model of AD during spatial navigation behavior, revealing a potential mechanism of the deficits in network oscillations observed in humans and animal models of AD. This work has broad implications for how neural

circuits for memory are disrupted in AD, and in bridging the gap between synapses, neural activity, and cognitive deficits.

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Poster

787. Hippocampus, Engrams, and Memory

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Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant R01MH102450
DoD CDMRP Grant W81XWH1810314

Title: Impaired CA2 place cell remapping in response to social olfactory stimuli in a rat model of fragile X syndrome

Authors: *E. ROBSON[1,2], A. J. MABLY[1,2], L. T. HEWITT[1,2], J. B. TRIMPER[1,2], L. L. COLGIN[1,2,3];
[1]Ctr. for Learning and Memory, Univ. of Texas At Austin, Austin, TX; [2]Dept. of Neurosci., [3]Inst. for Neurosci., Univ. of Texas at Austin, Austin, TX

Abstract: The CA2 region of the hippocampus has been implicated in social memory. A recent study showed that CA2 place cell firing patterns change ("remap") during social interactions, a response that is not apparent in CA1 place cells (Alexander et al., *Nature Communications* 2016). Our preliminary results show that CA2 place cells remap after a rat interacts with a familiar rat's empty homecage that contains only the rat's odors. On the contrary, CA2 place cells do not remap in response to interactions with an identical cage containing the rat, but with clean bedding and no familiar rat odors (Mably et al., SfN Abstracts, 2018). These results suggest that CA2 place cells remap in response to the olfactory content of social experiences. Interestingly, preliminary data using a rat model of Fragile X Syndrome (FMR1 knockout rats or "FXS rats") suggest that CA2 place cell remapping does not occur in FXS rats in response to olfactory social stimuli. Necessary control experiments (e.g., to assess whether CA2 place cells respond to non-social odors in control and FXS rats) will also be discussed.

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Poster

787. Hippocampus, Engrams, and Memory

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Topic: H.01. Animal Cognition and Behavior

Support: NIMH 5R01MH102450
NIMH 5T32MH106454

Title: Selective modification of hippocampal representations of a goal location after learning

Authors: *E. HWAUN[1], C. ZHENG[2], L. L. COLGIN[3];
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Abstract: Solving a goal-directed navigation task requires estimation of current position and a goal location. While many studies have shown that neurons in the hippocampus provide information about current position, the question of how goal information is processed in the hippocampus has received less experimental attention. To address this question, we recorded spiking activity of place cells in hippocampal subregion CA1 while rats learned a new goal location in a delayed match-to-sample task. We found that ensembles of place cells developed an over-representation of a goal location by recruiting new place cells to fire at the goal location. To balance excess activity near a goal location after learning, there was suppression of place cell activity that had already been present around a goal location before learning. In addition to changes in spatial representations upon learning of a new goal location, we also found that those place cells that emerged at a goal location after learning increased their firing rates during sharp wave–ripples more than other place cells. Moreover, replay trajectories decoded from ensemble activity of place cells during sharp wave-ripples developed biases to start or end near a goal location. Together, these results add to our understanding of how goal representations in the hippocampus are modified and reactivated following learning.

Disclosures: E. Hwaun: None. **C. Zheng:** None. **L.L. Colgin:** None.

Poster

787. Hippocampus, Engrams, and Memory

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Topic: H.01. Animal Cognition and Behavior

Support: NIH R01NS39600
NIH U01MH114829

Title: Estimating probabilities of potential synaptic connections by axonal-dendritic overlap in local hippocampal circuits

Authors: *C. TECUATL[1], D. W. WHEELER[2], G. A. ASCOLI[3];
[1]Ctr. for Neural Informatics and Bioengineering Dept., [2]Volgenau Sch. of Engin., [3]George Mason Univ., Fairfax, VA

Abstract: A quantitative description of the synaptic architecture in the hippocampal formation (dentate gyrus, CA3, CA2, CA1, subiculum, and entorhinal cortex) is essential for understanding the neural correlates of memory. Yet, the existing knowledge of connectivity statistics between different neuron types in the rodent hippocampus only captures a mere 5% of this circuitry. To supplement these scarce data, we present a systematic pipeline to produce first approximation estimates for the majority of the missing information. Leveraging Hippocampome.org, we derive the local connection probabilities between distinct pairs of morphologically identified neuron types from their axonal-dendritic overlap calculated from published illustrations in the peer-reviewed literature. Specifically, we start with 202 representative 2D reconstructions of characterized neuron types. Next, we adapt pixel-counting algorithms from modern image analysis technology to determine the axonal and dendritic lengths in each layer for every neuron type. We then compute the probabilities of axonal-dendritic connection using relevant anatomical volumes from the adult mouse brain Allen Reference Atlas and ultrastructurally-established interaction distances. Finally, we validate the results with the available subset of experimentally-quantified connections. With this approach, we estimate probabilities of connection for over 1800 neuron type pairs, increasing the available quantitative assessments more than 13-fold. Connectivity statistics thus remain unknown for only a minority of potential synapses in the hippocampal formation, including those involving long-range (23%) or perisomatic (4%) connections and neuron types with no available morphological tracings (9%). The described approach also yields approximate measurements of synaptic distances to/from the soma along the dendritic and axonal paths, which may affect signal attenuation and delay. In conclusion, this dataset fills a substantial gap in quantitatively describing the hippocampal synaptic circuits and provides useful model specifications for biologically realistic neural network simulations until direct experimental data become available.

Disclosures: C. Tecuatl: None. **D.W. Wheeler:** None. **G.A. Ascoli:** None.

Poster

787. Hippocampus, Engrams, and Memory

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Program #/Poster #: 787.08/BB13

Topic: H.01. Animal Cognition and Behavior

Support: NIH R01NS39600
NIH U01MH114829

Title: Towards hippocampome.org 2.0: A simulation-ready knowledge base of rodent hippocampal neuron types

Authors: *D. W. WHEELER[1], C. M. WHITE[1], A. O. KOMENDANTOV[1], D. J. HAMILTON[1], S. VENKADESH[2], K. MORADI[2], S. M. ATTILI[2], C. TECUATL[1], J. D. KOPSICK[2], G. A. ASCOLI[1];
[1]Volgenau Sch. of Engin., [2]Neurosci. Program, George Mason Univ., Fairfax, VA

Abstract: Hippocampome.org is an open-access knowledge base of the rodent hippocampus, which uses peer-reviewed literature to define over 120 neuron types by their main neurotransmitter and the patterns of their axonal and dendritic presence across the parcels of the rodent hippocampal formation: dentate gyrus, CA3, CA2, CA1, subiculum, and entorhinal cortex. For each neuron type, the knowledge base also encompasses information on molecular markers, which includes both direct and inferential evidence; known and potential connectivity; intrinsic electrophysiological parameters and corresponding experimental conditions; quantitative firing-pattern classification; and parametrically identified single- and multi-compartmental Izhikevich models. Additional accumulating information includes estimated counts of each of the neuron types, which are derived from multiple constraints including the cellular distributions in Nissl images from the Allen Brain Atlas; the quantification of the presence of the axons and dendrites across a given parcel, which enables the statistical estimation of the probability of potential connectivity between neuron types; data on the amplitude, kinetics and short-term plasticity of synapses; and information concerning the phase locking of neuronal firing to theta and gamma rhythms in the hippocampus. All data are linked to extracted publication excerpts and illustrations, which facilitate users' abilities to confirm all data interpretations. We are continuing to endeavor toward using the collated data in a computational simulation of the complete hippocampal formation. As we grow, we also expand the underlying foundations of Hippocampome.org by continually data mining the literature for new neuron types and neuronal properties while cross-linking and integrating new and prior data.

Disclosures: D.W. Wheeler: None. **C.M. White:** None. **A.O. Komendantov:** None. **D.J. Hamilton:** None. **S. Venkadesh:** None. **K. Moradi:** None. **S.M. Attili:** None. **C. Tecuatl:** None. **J.D. Kopsick:** None. **G.A. Ascoli:** None.

Poster

787. Hippocampus, Engrams, and Memory

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Program #/Poster #: 787.09/BB14

Topic: H.01. Animal Cognition and Behavior

Support: NINDS Grant NS088053
NIH T32 GM099608-07

Title: Contextual fear conditioning increases intrinsic excitability in activated neuronal ensembles in CA1 pyramidal neurons

Authors: *E. V. BARRAGAN[1], J. H. WILMOT[2], B. J. WILTGEN[1,2], J. A. GRAY[1,3];
[1]Ctr. for Neurosci., [2]Psychology, [3]Neurol., Univ. of California Davis, Davis, CA

Abstract: Learning induces long-lasting changes in synaptic strength that are required for memory formation. It also produces transient changes in intrinsic excitability, the function of which are not yet understood. In the hippocampus, learning increases the excitability of CA1 neurons for several days, a change that is thought to enhance replay and promote memory consolidation. If this is the case, then increases in intrinsic excitability should only be observed in neurons that were strongly activated during learning (e.g. memory cells). However, until recently, it was not possible to identify these neurons and perform *in vitro* whole-cell recordings after learning. To accomplish this, we used activity-dependent reporter mice (TetTag) to label active neurons in CA1 for several days. In these animals, activation of the c-Fos promoter leads to expression of the long-lasting protein H2B-GFP. To determine if intrinsic excitability changes occur specifically in neurons activated by learning, we trained these mice on a contextual fear conditioning task and prepared acute hippocampal slices 48 hours later. Consistent with our hypothesis, we found that tagged CA1 neurons (GFP+) exhibited increased firing rates compared to neighboring cells that were not labeled during learning (GFP-). This increase in excitability persisted for at least two days. In contrast to previous studies using trace eyeblink conditioning in rabbits, we found that changes in the medium afterhyperpolarization (mAHP) could not explain the different excitability observed in GFP+ neurons compared to GFP- cells. Therefore, a distinct mechanism may underlie the increases in CA1 excitability following context fear conditioning.

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Poster

787. Hippocampus, Engrams, and Memory

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Program #/Poster #: 787.10/BB15

Topic: H.01. Animal Cognition and Behavior

Support: NSERC

Title: Functional integration of adult-generated granule cells in the avian hippocampus

Authors: *D. F. MARRONE, C. C. DAMPHOUSSE;
Wilfrid Laurier Univ., Waterloo, ON, Canada

Abstract: Adult neurogenesis of granule cells (GCs) is a key mechanism of structural plasticity in the hippocampus, as these cells are thought to be for proper memory function in the face of high similarity between items of information to be remembered. Although it is known that birds also generate new GCs throughout life, this process is modulated by experience, and ablating these cells causes memory deficits, our knowledge could be furthered by tracking the activity of newly-born GCs during behavior. As a critical intermediate point towards this goal, here we establish the timecourse by which GCs integrate and become active (i.e., express activity-dependent *Egr1*, a reliable reporter of activity in individual neurons) during spatial behavior. Groups of Japanese quail were injected with 100mg/kg BrdU for a period of 1, 2, 3, 4, 5, or 6 weeks. Following each delay, birds explored a novel environment to engage GCs, and were then sacrificed and the tissue was analyzed using immunohistochemistry for NeuN, BrdU, and Egr1. These data will map the progression of neurogenesis in the avian hippocampus and reveal the optimal timing for examining the activity of these cells in further experiments.

Disclosures: D.F. Marrone: None. **C.C. Damphousse:** None.

Poster

787. Hippocampus, Engrams, and Memory

Location: Hall A

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Program #/Poster #: 787.11/BB16

Topic: H.01. Animal Cognition and Behavior

Support: NSERC

Title: Response in the avian hippocampal formation to incremental changes in context

Authors: *C. C. DAMPHOUSSE, N. Y. MILLER, D. F. MARRONE;
Wilfrid Laurier Univ., Waterloo, ON, Canada

Abstract: Multiple avian species exhibit behaviours consistent with having cognitive maps. Recent data also show that many birds exhibit “place-cell-like” patterns of neuronal activity. In mammals, we know that many different types of information can shift place cell mediated representations but information regarding what kinds of cues most powerfully drive spatial representation in the avian hippocampal formation (HF) is lacking. In the current experiment, quail were placed into an arena in which multiple cues were manipulated over two separate epochs (geometric properties of the arena itself, the objects within the arena, or both). Analysis via catFISH techniques allowed us to determine which condition caused the greatest proportion of remapping within the avian HF. These findings contribute to the potential discovery of an avian hierarchy of spatial information processing in which certain cues within the environment may be more salient and utilized more heavily during encoding of spatial environments.

Disclosures: C.C. Damphousse: None. **D.F. Marrone:** None. **N.Y. Miller:** None.

Poster

787. Hippocampus, Engrams, and Memory

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Simons Foundation

Title: Representation of visual landmark configurations in mouse retrosplenial cortex

Authors: *J. VOIGTS[1], E. H. TOLOZA[2], J. P. NEWMAN[1], I. R. FIETE[1], M. A. WILSON[1], M. T. HARNETT[1];
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Abstract: Navigating an environment using sensory cues requires the context-dependent integration of a multitude of signals over time. For example, visual cues can be used as landmarks for navigation if their position in the environment is known a-priori. Crucially, the

integration of sensory information into an estimate of position occurs while an agent moves through an environment over a period of time. At any given point, an agent might have a hypothesis of its position in space, and this hypothesis is revised based on sensory data. Retrosplenial cortex (RSC) has been proposed to serve a central role in performing such computations by translating between egocentric visual information and allocentric representations of an agent's position. Neurons in RSC are known to integrate multiple navigational variables, including visual information and position relative to landmarks, allocentric location within an environment, and heading. However, the circuit computations in RSC that assign meaning to visual landmarks are not well understood. Here, we examine the role of RSC in forming hypotheses about an agent's position in space by employing a novel miniaturized 3D-tracking system, integrated with the next-generation Open Ephys headstages, in freely behaving mice that perform a landmark-based navigation task. By examining the encoding of visual information and allocentric position while mice localize themselves in an environment, we find that RSC encodes a multitude of egocentric and allocentric navigational variables that are anchored to visual landmarks. Our results indicate that RSC translates between representations of visual information and location in space, based on the animal's prior knowledge of the environment, providing a substrate for memory-guided visual navigation.

Disclosures: **J. Voigts:** None. **E.H. Toloza:** None. **J.P. Newman:** None. **I.R. Fiete:** None. **M.A. Wilson:** None. **M.T. Harnett:** None.

Poster

788. Hippocampus: Learning

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 788.01/BB18

Topic: H.01. Animal Cognition and Behavior

Support: R01NS105472

Title: Spatial learning impairments in mutant mice without a dentate gyrus

Authors: *C. JOU[1,2], S. HU[1], A. RATTNER[3], J. NATHANS[3], A. FENTON[1,4,5];
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Abstract: The dentate gyrus (DG) is crucial for discriminating between similar spatial memories, perhaps because it performs pattern separation computations to distinguish between representations of experiences in similar conditions that are also different in important ways. For example, optogenetic silencing of either mature or immature adult-born dentate granule cells or

ablation of the latter, does not impair learning or memory in an active place avoidance task that requires a mouse on a slowly rotating arena to avoid the location of a stationary shock zone. However, the DG manipulations impair conflict learning in a task variant that requires memory discrimination when the shock zone is relocated in the otherwise unchanged environment. Here we examine spatial learning in a mutant mouse that does not develop a DG. We studied mutant mice (MT, n=14) with Wls deleted in GFAP-expressing cells (mainly astrocytes), the result of crossing GFAP-Cre and floxed-Wls mice. Genotype-blind comparisons were made with littermate control mice (CT, n=15), using both sexes. We observed no differences between the sexes. Nor did we observe alterations in locomotion, motor control, or sensorimotor integration in a battery of neurological tests. In contrast, active place avoidance learning was impaired in the mutant mice according to multiple measures of the conditioned avoidance (number of entrances to the shock zone, latency to first entry, and maximum time avoided). Conflict learning was assessed by relocating the shock zone 180 deg. This learning was also slower in the mutant mice. The genotypes did not differ in extinguishing the avoidance when shock was turned off. Impaired active place avoidance learning in a new environment was again observed in the mutant mice; this also indicated they had not learned to learn during the initial experiences. The learning impairment was then tested using a T-maze left-right discrimination task, requiring mice to successfully remember and choose which one of the two arms was safe and which one was associated with a footshock. The contingencies switched every 10 trials, after a 10-min rest between the 4 sessions. The two groups differed only in the last session, when memory-related interference was maximal. These results are the first behavioral characterization of a mouse model of genetic DG deletion, showing that developmental elimination of DG results in a more general learning deficit than DG lesion in adulthood. This may be due to other consequences of the developmental manipulation.

Disclosures: C. Jou: None. **S. Hu:** None. **A. Rattner:** None. **J. Nathans:** None. **A. Fenton:** None.

Poster

788. Hippocampus: Learning

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Program #/Poster #: 788.02/BB19

Topic: H.01. Animal Cognition and Behavior

Support: National Institute of Mental Health (R01MH115304)
National Institute of Neurological Disorders and Stroke (R01NS105472)

Title: Learning to learn persistently modifies a neocortical-hippocampal inhibitory microcircuit

Authors: *A. CHUNG, A. A. FENTON;
Ctr. for Neural Sci., New York Univ., New York, NY

Abstract: The brain can learn to learn. Although cognitive behavior therapy (CBT) takes advantage of cognitive control training to improve cognitive abilities, the critical neurobiological evidence of 1) CBT-induced 2) long-lasting, and 3) memory-independent changes in synaptic circuit function is lacking. Here, we test predictions of "the neuroplasticity hypothesis" by investigating ifthe entorhinal cortex (EC) to dentate gyrus (DG) perforant path circuit changes after cognitive control training (CCT). Adult mice received either CCT in the active place avoidance task, or place learning (PL) to avoid the same location in a task variant with lower cognitive control demand, or unconditioned spatial exploration (SE) in the same environment with no cognitive demand. Upon subsequent testing to learn a new CCT task in a novel environment, only the CCT-trained mice showed learning to learn. Some mice had been implanted with stimulating electrodes in the perforant path and 32-site recording electrodes spanning the somatodendritic axis of dorsal hippocampus. DG evoked potential responses were measured in response to test stimulation before and 2h after each training session. Initial training in CCT mice but not PL or SE mice, reduced the fEPSP slope localized to the inner molecular layer of the supra-pyramidal blade of DG (supDG); changes were minimal in the population spike and at the infra-pyramidal blade (infDG). This circuit change persisted 60 days without further training. Subsequent learning in a novel environment did not cause further changes. Optogenetic manipulations with evoked potential recording in urethane-anesthetized Gad2-Cre-ChR2-eYFP mice, showed that DG interneuron activation mimics the CCT-induced changes without training, and CCT training occludes the changes, indicating that CCT modifies inhibitory interneuron circuit function. Paired pulse ratio results showed that CCT causes faster activity dependent release from inhibition. Optogenetic manipulations of DG interneurons in *ex vivo* hippocampus slice showed that CCT increases feedforward disinhibition in supDG. Immunofluorescence for PKMzeta, which is necessary and sufficient for maintaining LTP, confirmed that CCT persistently increases PKMzeta expression, specifically in somatostatin expressing GABAergic interneurons in DG hilus. These findings confirm predictions of the neuroplasticity hypothesis, demonstrating that cognitive training causes persistent changes to an entorhinal-hippocampus disinhibitory microcircuit independent of the sparse excitatory-excitatory synaptic changes that are assumed to encode specific memories.

Disclosures: **A. Chung:** None. **A.A. Fenton:** None.

Poster

788. Hippocampus: Learning

Location: Hall A

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Topic: H.01. Animal Cognition and Behavior

Support: R01NS105472
R01MH099128

Title: Cognitive inflexibility in the Fmr1-null mouse model of autism is associated with excessive dentate spikes

Authors: *A. A. FENTON[1], D. DVORAK[2];
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Abstract: Dentate spikes (DS) are large amplitude, short duration field potentials which are localized to the hilar region of dentate gyrus (DG). While the exact role of DS is still unknown, several theories proposed a role in learning, memory consolidation and hippocampal circuit stabilization through anti-excitation.
To understand the role of DS in hippocampal function, we recorded local field potentials (LFP) using 32-channel linear electrode arrays spanning the somato-dendritic axis of dorsal hippocampus in wild-type (WT) and Fmr1-null mice that mimic the genetic cause of Fragile X Syndrome (FXS). Fmr1-null mice express cognitive inflexibility in tasks that require switching between relevant and irrelevant information in memory.
In task-naïve mice, we identified two types of DS based on their current source density profiles. DS type I (DS1) has sinks at the outer molecular layers of DG, corresponding to the lateral entorhinal cortex layer 2 (LECII) terminal, while DS type II (DS2) has middle molecular layer sinks, corresponding to the medial EC terminals (MECII). The DS morphologies, including amplitude and width did not differ between the genotypes. During stillness, DS1 rates were also not different, but DS2 rates were exaggerated in Fmr1-null mice. DS2 often followed DS1 but the opposite was rare.
Effects of DS on oscillatory activity at CA1, were studied using independent component analysis (ICA) to identify input-specific currents. The stratum radiatum IC (srIC) identified slow gamma (25-45 Hz) oscillations associated with the CA3-CA1 pathway. The lacunosum moleculare IC (lmIC) identified mid-frequecy gamma (50-90 Hz) oscillations associated with the MECIII-CA1 pathway. The srIC was strongly increased during DS2 and slightly decreased during DS1. In contrast, lmIC was increased during DS1 and decreased during DS2. DS exhibited strong modulation by CA1 stratum pyramidale theta oscillations. Specifically, DS1 occurred predominantly on the early descending phase of theta, similar to lmIC, while DS2 occurred predominantly around the trough of theta, similar to srIC. Sharp-wave ripples were reduced after DS1 and increased after DS2 with no genotypic differences.
Excessive DS2 rates in Fmr1-null mice suggest a role of DS in the cognitive inflexibility of previously learned hippocampal representations, that manifest as an overexpression of CA3-associated memory recollection events.

Disclosures: **A.A. Fenton:** None. **D. Dvorak:** None.

Poster

788. Hippocampus: Learning

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 788.04/BB21

Topic: H.01. Animal Cognition and Behavior

Support: Psi Chi Undergraduate Research Grant

Title: The effect of high fat diet and sleep deprivation during adolescence on adult behavior and memory

Authors: *K. GLUSHCHAK, J. DAVIS, T. ZEUTHEN, T. J. SCHOENFELD;
Belmont Univ., Nashville, TN

Abstract: The adolescent period is critical for normal brain development. Abnormalities that may occur during the adolescent period can have a profound effect on brain structure and behavior into adulthood. Diet and sleep are two central aspects of life and their compounded impact has not been investigated in rodent models, especially their long-term effects on behavior and brain structure. Therefore, we investigated the effects of high-fat diet (HFD) and sleep alterations (through chronic light deprivation) during adolescence on stress-affected memory in young adult rats. Adolescent Long-Evans rats were given either a HFD, HFD plus light deprivation, or control diet for 4 weeks (4-8 weeks old). After the manipulations, the rats recovered for six weeks, all maintained on control diet and normal light cycles. Adult rats (14 weeks old) were tested using two memory tests: novel object recognition (perirhinal cortex-dependent) and object location (hippocampal-dependent). For both tests, objects were learned and tested 24-hours later by altering either the type of object or location of object in the test phase. Directly after object learning, all rats were physically restrained for 30 minutes to induce stress effects on memory consolidation. Rats given HFD and light deprivation during adolescence were the only group to show significant object recognition learning; all other groups showed no evidence of novel object recognition. However, the object location test revealed that all three groups displayed object location memory equally well. Following the object location test, brains were extracted to measure hippocampal volume and c-fos activation to understand the role of HFD and light deprivation on brain structure and activation changes. This study examined the long-term effects of HFD and light deprivation during adolescence on memory and brain activation in adulthood.

Disclosures: K. Glushchak: None. **T.J. Schoenfeld:** None.

Poster

788. Hippocampus: Learning

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Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 788.05/BB22

Topic: H.01. Animal Cognition and Behavior

Support: Undergraduate Research Grant - Psi Chi

Title: Exercise prevents frustration-induced anxiety-like behavior in rats

Authors: *T. J. SCHOENFELD, J. TAYLOR, B. FICZERE;
Belmont Univ., Nashville, TN

Abstract: Running consistently decreases anxiety-like behavior in experimental rodents, both at baseline and following stressful events. Frustration is an emotional event arising from a decrease in expected reward following motivated behavior and has been associated with stress and anxiety in humans, albeit rarely studied in rodents. Rodent studies do show that anxiety-like behavior is a side effect of inducing frustration in operant conditioning scenarios, although the mechanisms and potential preventative actions for frustration are wholly unknown. Thus, we modeled frustration in both control and running rats and predicted that running would buffer anxiogenic effects of frustration. Long-Evans rats (N = 16) were evenly split into home cage environments with or without access to a running wheel. All rats were trained on a progressive variable ratio (VR) lever pressing schedule up to VR20. After reaching criterion, rats went through a frustration trial, during which no reward was given following lever pressing behavior. After both the first VR20 and frustration trial, corticosterone was measured in tail blood and anxiety-like behavior was analyzed in an open field. Lastly, hippocampal tissue was analyzed for dendritic spine density. Control rats had increased anxiety-like behavior and corticosterone levels following induced-frustration, however running rats were prevented from these increases and had higher spine density throughout the hippocampus. The present findings demonstrate running as a robust stress coper that prevents the maladaptive effects of frustration on physiology and ongoing behavior.

Disclosures: T.J. Schoenfeld: None. **J. Taylor:** None. **B. Ficzere:** None.

Poster

788. Hippocampus: Learning

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 788.06/BB23

Topic: H.01. Animal Cognition and Behavior

Title: Effect of neurogenesis on microglial activation

Authors: *A. SMITH[1], K. M. WILLIAMS[1], T. J. SCHOENFELD[2];
[2]Psychological Sci., [1]Belmont Univ., Nashville, TN

Abstract: The geriatric population of America has grown exponentially in the past century. Health degradations and expensive medical care and attention are characteristic of this population with many of these costs due to age-related cognitive decline. It is essential to completely understand the mechanisms of normal and abnormal aging in the search for treatments for cognitive decline. A reduction of neurogenesis is a common factor in aging, but this reduction is even more drastic in individuals experiencing cognitive decline. It is unclear what effect the reduced neurogenesis has on the extracellular environment, including glial cells. In particular, changes in microglial activation could be related to cognitive decline, and it is possible that reduced neurogenesis could influence microglial activation. To determine the functional effect of prolonged ablation of neurogenesis on microglial activation, a pharmacogenetic rat model (GFAP-TK) was used. Wild type (WT) rats had normal neurogenesis throughout the experiment, while transgenic (TK) rats given valganciclovir (VGCV) had neurogenesis inhibited starting at eight weeks old. Microglial activation and hippocampal volume were measured for three different age groups (VGCV treatment for 4, 9, and 14 weeks) in both WT and TK rats to determine effects of prolonged neurogenesis-ablation on markers related to aging. Despite no rats being old adults in our study, the expected finding is that microglial activation will increase and hippocampal volume will decrease along with aging in TK rats, with little effects in WTs; indicating that reducing neurogenesis speeds up the aging process in the hippocampus of rats.

Disclosures: A. Smith: None. **K.M. Williams:** None. **T.J. Schoenfeld:** None.

Poster

788. Hippocampus: Learning

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Program #/Poster #: 788.07/BB24

Topic: H.01. Animal Cognition and Behavior

Support: NIA grant 5R01AG050598

Title: Hippocampal extracellular potassium levels and spatial memory effects in response to retrodialysis insulin administration

Authors: *S. DOUGLASS, G. M. SHAMES, C. M. LEVINE, E. C. MCNAY;
Behavioral Neurosci., State Univ. of New York at Albany, Albany, NY

Abstract: Insulin is the most common treatment for hyperglycemia, such as that caused by type 1 or type 2 diabetes mellitus. Insulin causes cellular uptake and storage of glucose to restore homeostasis. Importantly, insulin also regulates other systems such that administration of exogenous insulin may cause an imbalance: an important example is regulation of potassium transport. In the periphery, insulin administration has been shown to increase the cellular uptake of potassium via Na^+/K^+ ATPase, leading to hypokalemia. Research in our lab and others has shown that insulin is a key regulator of cognitive function and local metabolism within the hippocampus. To date, however, no studies have examined whether insulin acts to regulate potassium levels within the brain, nor whether such regulation might correlate with cognitive effects caused by administration of exogenous insulin.
The current study sought to extend our previous work on the impact of exogenous insulin delivery to the hippocampus: specifically, we measured the impact of intrahippocampal insulin administration on local extracellular potassium levels, both at baseline and during a cognitive task. Rats were tested using a spontaneous alternation task in a four-arm maze with concurrent microdialysis and retrodialysis of insulin for the period corresponding to the behavioral task. Insulin was added to the perfusate at 6.67 mU/mL in an artificial extracellular fluid vehicle. Samples were collected throughout acclimation, baseline, testing, and recovery periods, then analyzed for potassium and glucose. Hippocampi and prefrontal cortices were collected and analyzed for Na^+/K^+ ATPase protein concentrations. We hypothesized that insulin administration would lower extracellular potassium levels, and Na^+/K^+ ATPase will be upregulated in relation to controls. A key next step will be parsing the cognitive impact of insulin's multiple cellular actions.

Disclosures: S. Douglass: None. **G.M. Shames:** None. **C.M. Levine:** None. **E.C. McNay:** None.

Poster

788. Hippocampus: Learning

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Program #/Poster #: 788.08/BB25

Topic: H.01. Animal Cognition and Behavior

Support: NIA grant 5R01AG050598

Title: A novel substrate-competitive inhibitor of glycogen synthase kinase-3 augments glucose uptake in primary hippocampal cells

Authors: *G. M. OSTRANDER[1], M. ZIAMANDANIS[1], L. P. MALLON[1], E. C. MCNAY[2]; [1]State Univ. of New York At Albany, Albany, NY; [2]Behavioural Neurosci., Univ. At Albany, Albany, NY

Abstract: Inadequate brain and hippocampal utilization of glucose, often linked to dysregulated central insulin signaling, is known to cause cognitive impairment and is a key correlate of Alzheimer's disease (AD). Inhibition of glycogen synthase kinase-3 (GSK3) has recently received attention as a potential treatment for both dysregulated insulin signaling and AD. GSK3 is directly modulated by insulin, and insulin signaling may be simultaneously modulated by GSK3. In the periphery, inhibition of GSK3 facilitates insulin signaling and enhances glucose utilization; however, less is known about these relationships in the brain.
Several studies in this area have used GSK3 modulators that are ATP-competitive. ATP-competitive inhibitors have shown promising results in basic research but failed to achieve success in clinical trials. Many of these inhibitors cause off-target side effects that may be harmful, likely due to evolutionarily-conserved residue sequences of alternative proteins targeted by ATP-competitive small-molecule inhibitors of GSK-3. The current study employed an alternative, substrate-competitive peptide inhibitor of GSK3 (L807-mts), to investigate how an alternative route of GSK3 modulation may facilitate glucose uptake within primary hippocampal neurons. We treated neuronal cultures with several dosages of L807-mts concomitantly with 2NBDG [2-(N-(7-Nitrobenz-2-oxa-1,3-diazol-4-yl)Amino)-2-Deoxyglucose], in order to measure glucose uptake via quantitative immunofluorescent analyses. We found a strong and positive dose-dependent effect of GSK3 inhibition on glucose uptake. Across multiple biological replicates, L807-mts treatment facilitated uptake of glucose in the presence, but not in the absence, of insulin: this is consistent with prior work in the periphery.
Our data suggest a promising, novel alternative for treatment of insulin resistance within the central nervous system. We propose that this pharmacological intervention could potentially mitigate dysregulation of downstream molecular effectors that may contribute to the comorbidity between insulin resistance and AD.

Disclosures: G.M. Ostrander: None. **M. Ziamandanis:** None. **L.P. Mallon:** None. **E.C. McNay:** None.

Poster

788. Hippocampus: Learning

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Topic: H.01. Animal Cognition and Behavior

Support: University of Michigan Rackham Predoctoral Fellowship

Title: Phase coding as a possible mechanism of sleep dependent memory consolidation

Authors: *Q. SKILLING[1], B. C. CLAWSON[1], J. P. ROACH[4], N. OGNJANOVSKI[5], S. J. ATON[2], M. R. ZOCHOWSKI[3];
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Abstract: It has been shown that sleep is critical for consolidation of contextual fear memory and that hippocampus plays central role in that process. However neuronal mechanisms underlying this consolidation are not well understood. In this study, we develop a computational model that closely (a) recapitulates network-level phenomena analyzed from *in vivo* recordings of fear-conditioned mice and (b) provides insights on network-level mechanisms underlying fear-memory consolidation during during sleep. The proposed mechanisms center around cholinergic modulation of network level dynamical behaviors associated with changes in muscarinic membrane currents. Acetylcholine levels are known to be high during wakefulness and rapid eye-movement (REM) sleep but low during non-REM sleep (slow-wave sleep; SWS), resulting in a change in membrane excitability from Type 1 to Type 2, respectively. Previous work has shown that neurons (and networks) exhibiting Type 2 excitability are amenable to sub-threshold resonance and synchronization through simple spike-timing relationships. Here, we expand on this data to show that neuronal networks composed of Type 2 neurons exhibit network-level resonance, whereby fast-spiking neurons recruit slower-spiking neurons to participate in slow oscillatory events in the 4-12 Hz range in a phase-dependent manner, a mechanism we refer to as phase-coding. In contrast, networks composed of Type 1 neurons are amenable to PING-like oscillations, where neuronal firing rates cause network-level bursts of activity, a process referred to as rate-coding. We show that rate-coding and phase-coding result in different functional network properties and conclude that it is phase-coding during non-REM sleep that accounts for fear memory consolidation in mice.

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Poster

788. Hippocampus: Learning

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Support: MEYS CZ.02.1.01/0.0./0.0/15_003/0000419

Title: The effects of enzymatic treatment and genetic modifications of perineuronal nets on memory in a mice model of AMP mediated hibernation like state

Authors: *J. RUZICKA[1], M. DALECKA[2], K. SAFRANKOVA[1], D. PERETTI[3], P. JENDELOVA[1], J. C. KWOK[5], J. W. FAWCETT[4];
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Abstract: Perineuronal nets (PNN) play a crucial role in the maturation and plasticity of neurons and synapses. PNNs have been shown to have effects on memory formation, retention and extinction in a variety of animal models. It has been proposed that the cavities in PNNs containing synapses can act as a memory store, which is stable after events that cause synaptic withdrawal such as anoxia and hibernation. We are examining this idea by monitoring positional memory before and after synaptic withdrawal caused by acute hibernation. This is carried out in normal animals and in animals lacking PNNs due to chondroitinase ABC treatment or knockout of CNS aggrecan.
In our study, we used mice model of induced hypothermia via intraperithoneal injection of 5´adenosine monophosphate (5‘AMP) which leads to a torpid (hibernation-like) state (HLS) with a significant retraction of synapses observed in the CA1 region of the hippocampus (Peretti et al.,2015). In this model we tested the effect of enzymatic digestion of PNN structure ((chondroitinase ABC/ saline control))±HLS, n≥10/group, male) or Cre inducible CNS aggrecan knockout ((Cre $AGG^{-/-}$ / littermate non CRE control)±HLS, n≥10/group, male) on learned behaviour in the Morris water maze task (MWM). The number of synapses retracted by deep cooling and altered by changes in the PNNs, was measured by FIB-SEM electron microscopy. A 3D analysis was performed in the CA1 dendritic area. Western blot analysis (pTau, PSD95, GAD65/67, NMDR1,etc.) and immunohistochemical stainings (WFA, Agg, PVA) confirmed the enzymatic efficacy and impact of the hibernation like state. All treatments i.e. HLS, chondroitinase injection/AGG knockout or their combination, showed a significant effect on the already learned behaviour, affecting both; established memory and learning in MWM task, which was supported by the changes observed in FIB-SEM, IHC and Western blot analyses.

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Poster

789. Intrinsic Hippocampal Circuits: Spatial Navigation

Location: Hall A

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the Human Frontier Science Program RGP0019/2016

Title: Subthreshold coherence of multiple CA1 pyramidal cells during *in vivo* theta oscillations

Authors: *A. NOGUCHI, N. MATSUMOTO, Y. IKEGAYA;
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Abstract: Theta (θ) oscillations (3-10 Hz) in the hippocampal LFPs (θ_{LFP}) are associated with active exploration and attention. Previous reports suggest the role of θ_{LFP} in cognitive function, such as memory encoding and spatial representation; however, how θ_{LFP} originates from collective activity of individual neurons is not fully understood. One of the major contributors of LFP signal is thought to be synaptic transmembrane currents (Buzsáki et al., 2012), which is also the main component of subthreshold membrane potentials (*V*m) of each neuron. We thus focused on how collective dynamics of subthreshold *V*m are reflected in θ_{LFP}. In the present study, we conducted simultaneous recordings of hippocampal CA1 LFPs and subthreshold *V*m of up to four CA1 pyramidal neurons in urethane-anesthetized mice. We found intermittent θ oscillations in subthreshold *V*m (θ_{Vm}), often during θ_{LFP}. In about 50% CA1 pyramidal cells, the time changes in θ_{Vm} powers were positively correlated with those in θ_{LFP} power. In about 70% cell pairs, the time changes in their θ_{Vm} powers were positively correlated between them. The simultaneously occurring θ_{LFP} and θ_{Vm} and the simultaneously occurring θ_{Vm} of CA1 neuron pairs had similar frequencies, although the frequencies of θ_{LFP} and θ_{Vm} per se fluctuated between 3 and 10 Hz over time. We also focused on the relationships between θ_{LFP} and θ_{Vm} of multiple CA1 pyramidal cells. The θ_{LFP} powers became larger when more CA1 pyramidal neurons simultaneously emitted θ_{Vm}. When multiple CA1 pyramidal neurons exhibited θ_{Vm} with more similar frequencies, θ_{LFP} power became greater, and its frequency became more similar to the mean frequencies of the θ_{Vm}s of those neurons. These results suggest that hippocampal CA1 θ_{LFP} is predictable from an ensemble of θ_{Vm} of a few CA1 pyramidal cells.

Disclosures: A. Noguchi: None. **N. Matsumoto:** None. **Y. Ikegaya:** None.

Poster

789. Intrinsic Hippocampal Circuits: Spatial Navigation

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Title: Hippocampal coding of positions of inaccessible objects

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Abstract: The hippocampus is a key structure for processing spatial information including the discrimination of the location of inaccessible objects in space. How this critical ability is represented at the level of hippocampal neuronal ensembles has not yet been clearly described. We combined single-unit electrophysiological recordings in rats with the operant behavior task using virtual reality. This provided us with the possibility to study the discrimination of positions of visual objects located in a part of an environment that is not accessible to the animal. We trained rats to press a lever for food reward when an object displayed on a distant computer screen was at a particular position and not to press it when the object was at other positions. Once a rat reached asymptotic performance, an array of tetrodes was implanted and the activity of hippocampal CA1 neuronal ensembles was recorded during the task. We studied how the activity of neuronal ensembles represents the information about the displayed object's position. We binarized a given experimental session into bins of 2 seconds and obtained spike-counts vector per bin reflecting the number of spikes fired by every cell in the ensemble at that particular moment, and then estimated Kendall's correlation coefficient between all bins and stimuli. Our data suggest that individual positions of an inaccessible object are represented differentially by neural ensembles in the hippocampus.

Disclosures: **D. Levcik:** None. **N. Ahuja:** None. **V. Lobellova:** None. **D. Radostova:** None. **S. Diez Hermano:** None. **A. Sanchez Jimenez:** None. **J.A. Villacorta-Atienza:** None. **V.A. Makarov:** None. **A. Stuchlik:** None.

Poster

789. Intrinsic Hippocampal Circuits: Spatial Navigation

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 789.03/BB30

Topic: H.01. Animal Cognition and Behavior

Support: PAPIIT-DGAPA IN201518
CONACyT Fronteras de la Ciencia No. 846
CONACyT Scholarship 934183 MAC

Title: Neuronal ensembles dynamics during spatial learning in CA1 mouse hippocampus

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Abstract: In recent years, properties of hebbian neural ensembles have been studied in vivo, including overlapping, sparse coding, dynamic persistence and dynamic completion. However, the dynamic construction and reconstruction has been poorly studied due to technical limitations to follow simultaneously groups of neurons along the time. Here, we analyzed the neural activity, in hippocampal CA1 region, during spatial learning in free moving C57BL transgenic mice expressing fluorescent calcium indicator GCaMP6f under Thy1 promoter, using miniaturized microscope to record calcium activity. The animals were trained in a 'Y' maze under two conditions A and B. In condition A, a tone was presented to drive the animals to the maze right side (tone-right). In condition B, a luminic stimulus was presented to drive the animals to the maze left side (light-left). In a second experimental phase, when the animals reached a performance success of 80%, we carry out a re-learning process switching the conditions (tone- left, light- right). In this way, we evaluated behavioral performance and neuronal ensemble composition. Our data show, that during trainning the number of active neurons decreased gradually reaching a stable state, giving rise to two ensembles that represent conditons A and B. Moreover, during re-learning process, we identified modifications in the number of neurons and their activity in both neuronal groups, suggesting a dynamic construction and reconstruction of ensembles. We conclude that is possible to follow the activity of a neuron population over weeks, and thus, analyze the ensemble construction and reconstruction process that underlies a spatial learning.

Disclosures: **M. Altamira:** None. **R. Olivares-Moreno:** None. **M. Lopez-Hidalgo:** None. **G. Rojas-Piloni:** None.

Poster

789. Intrinsic Hippocampal Circuits: Spatial Navigation

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Topic: H.01. Animal Cognition and Behavior

Support: ERC NEURO-PATTERNS
U01 NS090576
U19 NS107464

Title: Encoding of spatial information by calcium dynamics of hippocampal astrocytes

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Abstract: Neural place cells in the hippocampal formation are known to encode navigational information through the modulation of their firing rate as a function of the animal's spatial location, providing a cellular substrate for spatial cognition. Growing evidence suggests that glial cells are involved in the processing of sensory information, but whether navigational information is encoded in glial networks or rather exclusively encoded in neuronal circuits is unknown. Here we tested the hypothesis that astrocytes, the major class of non-neural cells in the brain, encode navigational information in their intracellular calcium dynamics. To this aim, we trained mice to navigate in a virtual environment and we combined astrocyte-specific expression of genetically encoded calcium indicators with two-photon functional imaging to capture subcellular calcium dynamics of hippocampal CA1 astrocytes during spatial navigation in head fixed animals. We found that astrocytic calcium signaling was significantly modulated by the spatial position of the animal in the virtual track. Calcium events accumulated at preferred spatial locations and this phenomenon occurred in topologically restricted regions of the astrocyte, including the cell body and the proximal processes. Importantly, using a support vector machine decoder we found that spatial information in astrocytic calcium dynamics could be reliably decoded and these calcium signals could be used to infer the animal's spatial location. Altogether, these findings indicate for the first time that information-encoding cellular dynamics during high-level cognitive functions such as spatial cognition extend beyond neural circuits to astroglial networks.

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Poster

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Topic: H.01. Animal Cognition and Behavior

Support: GACR grant 17-04047S
AZV grant 17-30833A

Title: Hippocampal neuronal responses in rats during avoidance behaviour relative to a moving robot

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Abstract: Navigation relative to other moving animals (conspecifics, potential prey or predators) or objects is a cognitive ability that is important for animals in many ethologically relevant situations. Our aim is to study neuronal substrates of navigation relative to a salient moving object.
We have developed a behavioural paradigm to study the rat's ability to assess not only distance from, but its position relative to a moving object. Rats were trained to avoid a circular shock zone (39cm in diameter) around a robot moving on a circular arena (130cm in diameter). Shock zone was defined by spatial relationship relative to the robot, it was in front or either side of the robot.
Trained rats made significantly fewer entrances to the shock zone compared to the equidistant safe areas around robot ($p's < 0.05$). Action potential discharges were recorded from neuronal ensembles in the hippocampus of rats interacting with the moving robot without reinforcement. In the CA1 and CA3 hippocampal areas we observed neurons with spatially-tuned responses relative to the room as well as neurons with responses reflecting the relative position of the rat and the robot. We are now in a position to study the dynamics of interacting representations of mutual positions of the rat, robot and the environment.
This work provides new insights into neuronal dynamics underlying the ethologically important ability to navigate with respect to significant moving objects in an environment.

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Poster

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Topic: H.01. Animal Cognition and Behavior

Support: ISF grant 281/15

Title: Representation of head direction and speed in the goldfish brain

Authors: L. COHEN[1], E. VINEPINSKY[1], O. DONCHIN[2], O. BEN-SHAHAR[2], ***R. S. SEGEV**[1];
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Abstract: Navigation is one of the fundamental cognitive skill found in many animals across all of the animal kingdom and it is important for finding food, shelter and mates in order to survive. A critical component of the ability to navigate is a sense of direction and a sense of speed. However, almost nothing is known about the neural representation of direction and speed in the brain of vertebrates outside the mammalian class. The goldfish, which is a bony fish, the largest vertebrate family, have the cognitive ability to navigate using allocentric and egocentric cues. In addition, the lateral pallium in the goldfish brain is a possible homolog of the mammalian hippocampal formation and associated with allocentric navigation. Using a novel wireless recording system, we measured the activity of single cells in the lateral pallium of a freely swimming goldfish and found speed cells and conjunction head-direction and speed cells, i.e. velocity encoding cells. Those cells types are similar to cell which are found in the mammalian hippocampal formation and believed to be the building blocks of path integration. Our study sheds light on how kinematic information is encoded in the fish brain and whether the mechanisms encoding the kinematic variables are shared across evolution.

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Poster

789. Intrinsic Hippocampal Circuits: Spatial Navigation

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 789.07/BB34

Topic: H.01. Animal Cognition and Behavior

Title: A velocity driven oscillatory network model for object vector cells

Authors: J. ELANGOVAN[1], M. PRAKASH[1], ***A. AZIZ**[2], R. NARAYANAMURTHY[2], S. JAYAKUMAR[2], S. V. CHAKRAVARTHY[2];
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Abstract: Objects and landmarks present in an environment are essential for successful navigation through it. Experiments in navigation saw the emergence of various types of spatial cells in the hippocampal-entorhinal complex. However, they were conducted in the absence of any landmark cues (objects) within the enclosure. Recent studies by Hoydal et al. confirmed the presence of cells that exclusively fired in response to the objects placed in an environment namely, the Object cell that fired when the animal was at the location of the object and another type of cell called the Object Vector Cell (OVC) that fired when the animal was at a certain distance and direction from the object (Høydal et al., 2019). The latter was extensively studied by Høydal et al and will thus be the focus of our work as well. We employ a hierarchical oscillatory network model to study the emergence of OVCs in the absence of an explicit visual input. The model constitutes a Head Direction (HD) layer comprising of cells, each coding for a particular direction. The responses of this layer along with the speed information is given to an oscillatory Path Integration (PI) Layer. This is followed by two layers of Lateral Anti- Hebbian Network (LAHN1 and LAHN2) trained by unsupervised learning for optimal feature extraction from the inputs. A virtual agent forages in a circular environment of 2 units radius with a circular object of radius 0.2 units and the representations of neurons in LAHN2 are observed. Neurons that fired at a particular distance and direction from the object are chosen (fig. 1). It is observed that these neurons maintained the distance-direction relationship irrespective of the position of the object within the environment and did not fire in the absence of an object, as observed in the experimental study by Hoydal et al. We also postulate that although visual input might confer stability to OVC firing, the emergence of these cells do not explicitly depend on a visual input and that there is sufficient information in the trajectory dynamics encoded by the path integration to account for this class of spatial cells.

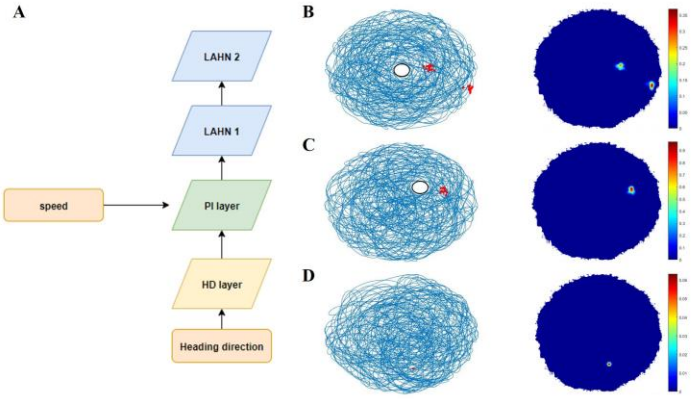

*Figure 1: **A.** Model Architecture. **B,C,D.** Firing field map (left) and Firing Rate maps (right) of the circular environment with an object, shifted object and no object respectively.*

Disclosures: **J. Elangovan:** None. **M. Prakash:** None. **A. Aziz:** None. **R. Narayanamurthy:** None. **S. Jayakumar:** None. **S.V. Chakravarthy:** None.

Poster

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Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant RF1 MH114112
NIH Grant R01 MH094360

Title: Homologous gene expression patterns within the mouse and human subiculum

Authors: *M. S. BIENKOWSKI, N. KHANJANI, H. DONG;
USC Stevens Neuroimaging and Informatics Inst., Keck Sch. of Med. of USC, Los Angeles, CA

Abstract: The hippocampus is widely believed to be structurally and functionally homologous across species. The major output region of the hippocampal formation, the subiculum (SUB), is considered to be organized as distinct columnar subregions along the longitudinal axis (dorsal vs. ventral in rodents; posterior vs. anterior in humans). However, our previous study analyzing gene expression patterns to create the mouse Hippocampus Gene Expression Atlas (HGEA) revealed that the SUB pyramidal layer contained a hidden sublaminar organization that was also highly related to connectivity. Based on the distribution and representation of four SUB gene expression lamina, the mouse HGEA defines five distinct SUB subregions, including a novel caudal ventral extension of the dorsal SUB. Although the HGEA provides a detailed description of the mouse SUB, it is currently unknown if this organization is also present in the human SUB. Using *in situ* hybridization data from the online Allen Human Brain Atlas project, we provide evidence that the same laminar organization of gene expression observed in the mouse is also present within the human SUB. In the posterior human SUB, neurotensin (*Nts)* is strongly expressed within SUB pyramidal neurons closest to the molecular layer, but not in deep pyramidal neurons adjacent to the alveus white matter tract. In contrast, *Chrm2* (muscarinic cholinergic receptor 2) expression reveals the reciprocal distribution pattern. Together, *Nts* and *Chrm2* expression patterns delineate distinct gene expression lamina in the human posterior SUB that is highly similar to the mouse dorsal SUB. Overall, this study provides evidence that the genetic organization of SUB neuronal cell types is conserved across mammals and provides a foundation for creating a translational human HGEA for understanding hippocampal cell types and how they are affected by Alzheimer's disease.

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Poster

789. Intrinsic Hippocampal Circuits: Spatial Navigation

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Program #/Poster #: 789.09/BB36

Topic: H.01. Animal Cognition and Behavior

Support: NSF IIS #1703340

Title: A computational model combining dorsal and ventral hippocampal place field maps: An analysis of multiple-scale contributions

Authors: P. SCLEIDOROVICH[1], J.-M. FELLOUS[2], ***A. WEITZENFELD**[1];
[1]Computer Sci. and Engin., Univ. of South Florida, Tampa, FL; [2]Psychology, Univ. of Arizona, Tucson, AZ

Abstract: We present in this work a model for spatial cognition based on the multi-scale organization of the dorsal-ventral axis of the hippocampus. Existing studies in rodents conducted in simple and small environments show that dorsal place cells are primarily involved in spatial navigation, containing cells with small place fields, while ventral place cells are primarily involved in context and emotional encoding, containing cells with large place fields. Recent findings suggest however that ventral place cells are involved in spatial navigation in complex environments. In this work we examine the effect of combining fields from dorsal and ventral place cells during spatial navigation. For this purpose, we developed a multi-scale computational model where a rat can map an environment by activating partially overlapping place fields from dorsal and ventral place cells. The model shows that combining dorsal and ventral place field maps may improve task learning performance, in terms of either path optimality or learning time, depending on the particular combination of place field sizes. The task consists of a rat learning to find a goal by starting from different locations in both a fully open environment and an environment containing an internal wall that can only be traversed through a corridor. The computational model is based on an actor-critic reinforcement learning architecture with and without eligibility traces. Results were obtained from simulations in a virtual environment. Corresponding statistical results are presented. This computational study suggests that the combination of dorsal and ventral hippocampal information may be advantageous for spatial learning and memory tasks.

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Poster

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Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant 1R15AG045820-01A1

Title: Dynamical analyses of hippocampal local field potential activities across maturation of spatial navigation in the juvenile rat

Authors: *D. G. MCHAIL[1], J. R. CRESSMAN[1], T. BERRY[1], R. OGOE[1], T. C. DUMAS[2]; [2]Psychology, [1]George Mason Univ., Fairfax, VA

Abstract: Hippocampal networks undergo continued refinement during the third postnatal week in rats, around the same time that spatial navigation ability first emerges. This delayed maturation presents an opportunity to identify what characteristics of hippocampal networks are necessary to enable spatial cognition in mature animals. Hippocampal local field potential (LFP) oscillations have been well studied in adult rodents and related to specific aspects of network activity (i.e. coordinating discharge of place cell ensembles) and spatial learning and memory (i.e. route planning and on-line navigation). However, relatively little is known about the development of hippocampal networks in rodents. Prior research has focused on maturation of the theta rhythm in juveniles, and recent investigations have found that gamma rhythms undergo changes during this time period as well. Cross-frequency interactions (such as coupling between theta and gamma wavebands) have not been examined in juveniles. Furthermore, no prior studies have examined changes in local field potential activity relative to performance in spatial tasks in juveniles. Techniques typically applied to analyses of LFP activity and behavior are correlational and cannot identify causation. Tools from nonlinear dynamical analysis may help identify changes in local field potential dynamics that are involved in the maturation of spatial cognition. In particular, diffusion-mapped delay coordinates (DMDC) can help identify and discriminate between attractors in the local field potential during maze performance. In addition, a reservoir computer can be used to model and predict local field potential activity relative to maze behaviors. As such, we recorded from dorsal hippocampal area CA1 as juvenile rats performed spatial tasks (Y-maze, Barnes maze). Using DMDC, we identified changes in hippocampal LFP dynamics specific to age, movement speed, and waveband content. Ongoing analyses will also assess whether LFP dynamics during separate aspects of goal-directed behaviors in the Barnes maze can be discriminated by DMDC. In addition, we will leverage the predictive capability of machine learning (reservoir computing) to determine upcoming LFP states based on prior LFP data.

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Poster

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Program #/Poster #: 789.11/BB38

Topic: H.01. Animal Cognition and Behavior

Support: NIA G1A62660

Title: Selective loss of septohippocampal cholinergic projections is associated with more circuitous homeward progressions

Authors: ***J. R. OSTERLUND**[1], A. A. BLACKWELL[1], M. LIPTON[1], V. CASTILLO[1], G. L. KARTJE[2], S.-Y. TSAI[3], D. G. WALLACE[1];
[1]Northern Illinois Univ., DeKalb, IL; [2]Loyola Univ. Chicago, Chicago, IL; [3]Edward Hines Jr. VA Hosp., Hines, IL

Abstract: Rodents rely on self-movement cues as a source of information to maintain spatial orientation during exploration. The vestibular system provides a source of self-movement cues that are processed by the septohippocampal cholinergic system, and when damaged, disruptions in movement organization are observed. The current study examined the effects of medial septum infusion of 192 IgG-saporin on movement organization during a single exploratory session that limited rats to using only self-movement cues. Rats organize their exploratory behavior into stops and progression. Although stops occur throughout the environment, they tend to cluster within a restricted area indicative of home base establishment. In the current study, movement organization characteristics and home base stability were similar between the lesion and sham groups. However, the lesion group exhibited greater path circuity during progressions returning to the home base. Increases in path circuity have been implicated in spatial disorientation, indicating a role for medial septum cholinergic projections in processing self-movement cues to maintain spatial orientation. These results provide a foundation for future work to investigate the efficacy of interventions that enhance neuroplasticity within the septohippocampal cholinergic system.

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Poster

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Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant 5R21NS098162-02

Title: Restoration of network dynamics and improved cognitive outcome after implantation of inhibitory interneuron progenitor cells in a rodent model of temporal lobe epilepsy

Authors: *W. CURRY[1], A. HERNAN[1], G. RICHARD[1], M. WESTON[1], R. SCOTT[1,2];
[1]Larner Col. of Med., Univ. of Vermont, Burlington, VT; [2]Inst. of Child Hlth., Univ. Col. London, London, United Kingdom

Abstract: The past decade of epilepsy research has revealed both scant evidence for major contributions from seizures to the cognitive deficits associated with epileptic syndromes and urgent need for alternative treatments to combat these cognitive deficits. One possibly fruitful paradigm currently being explored is the implantation of inhibitory interneuron progenitor cells obtained from a developmental structure known as the medial ganglionic eminence (MGE), which is responsible for upwards of 90% of interneurons in the neocortex and hippocampal structures. Previous studies have found that, when implanted into adult mice, progenitors have the ability to mature, migrate, and integrate into neocortical and hippocampal circuits, and do so in several pathological models, including: Parkinson's disease, temporal lobe epilepsy (TLE), and Alzheimer's disease. In an epilepsy framework, integration manifests as increases in inhibitory drive, reductions in the duration and frequency of seizures, and, in at least one study, improvement on a task of spatial working memory. This latter finding, while compelling, has been insufficiently explained. Using *in vivo* electrophysiology, this current work seeks to establish systems-level causality for observed improvements following progenitor implantation. We used the lithium-pilocarpine model of status epilepticus, which reliably induces many human symptoms of TLE. After observing frank seizures, adult epileptic Sprague-Dawley rats were bilaterally implanted with MGE progenitor cells in the dorsal hippocampus. 30 days post-transplantation, sham, SE, and MGE cohorts performed in the Morris Water Maze (MWM), a standard task of spatial working memory. MGE progenitor recipients' performance more closely resembled that of sham animals when compared to SE animals. Single-unit recordings in CA1 of the hippocampus during an open-arena foraging task revealed a partial restoration of excitatory neuron parameters, namely, mean firing rate and spike width, in MGE animals. Postmortem histological analysis confirmed survival and maturation of implanted cells, and their expression of markers of interneuron subtypes such as parvalbumin and somatostatin. Together, these

findings implicate progenitor cells' ability to normalize network parameters as an explanation for the behavioral improvements observed.

Disclosures: W. Curry: None. **A. Hernan:** None. **G. Richard:** None. **M. Weston:** None. **R. Scott:** None.

Poster

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Program #/Poster #: 789.13/BB40

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant 1R03NS109923

Title: Spiking network models of sharp-wave/ripple attractor sequences

Authors: *J. D. MONACO[1], G. M. HWANG[3], K. ZHANG[2];
[1]Biomedial Engin., [2]Dept Biomed Engin., Johns Hopkins Univ., Baltimore, MD; [3]Johns Hopkins Univ. Applied Physics Lab., Laurel, MD

Abstract: The spatial representations of active place cells in a particular environment collectively form a spatial map, the function of which has remained unclear. Sequential place-cell activation organized by theta oscillations during active movement or by sharp wave/ripple complexes (SWRs) during pauses in navigation may serve a critical role in subsequent spatial decision-making and behavior. In particular, SWR sequences have been shown to represent spatial trajectories that follow unexplored paths through space with reward-dependent biases toward goal locations. Pfeifer & Foster (2015) reported compelling evidence that decoded SWR trajectories dwell at discrete locations before discontinuously jumping, potentially reflecting metastable expression of recently experienced attractor states. While that report suggested the attractor expression was phase-locked to slow gamma (ca. 30 Hz) oscillations, a subsequent laminar recording study by Oliva et al. (2018) revealed that relationship as a possible artifact of CA1 ripple-power (150-200 Hz) envelopes. This dispute regarding the existence of neuronal gamma-locking during SWRs raises critical questions about the dynamical basis of SWR trajectories. Here, we propose a theoretical framework for flexible, internal sequence generation for online route planning during spatial navigation. We embedded realistically Poisson-distributed place-field maps into the synaptic weights of a CA3 network model to quantify sharp waves as a stochastic sampling process of spatial attractors. We projected CA3 output to a CA1 network model with recurrent inhibition producing transient ripple currents. The excitatory (pyramidal cell) and inhibitory (interneuron) connectivity of our CA3/CA1 models were subsequently tuned to generate theta oscillations driven by high levels of cortical/subcortical input and to stochastically produce SWRs during an irregular state driven by reduced input

levels. Modulating gamma power via inhibitory coupling revealed minimal gamma-dependence of CA1 ripple-filtered outputs. Alternatively, factors including noise, synaptic depression, sporadic ascending inputs, and reduced subcortical inhibition supported online dynamics that explain physiological and computational features of SWR trajectories. Thus, SWR trajectory sequences may rapidly collapse the slowly varying cognitive map into transitory metastable states that probabilistically sample possible routes through an animal's immediate surroundings.

B. E. Pfeiffer and D. J. Foster. *Science*, 349:180-3, 2015; A. Oliva, A. Fernández-Ruiz, E. Fermino de Oliveira, and G. Buzsáki. *Cell Rep*, 25:1693-1700, 2018.

Disclosures: **J.D. Monaco:** None. **K. Zhang:** None. **G.M. Hwang:** None.

Poster

789. Intrinsic Hippocampal Circuits: Spatial Navigation

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Program #/Poster #: 789.14/BB41

Topic: H.01. Animal Cognition and Behavior

Support: Office of Naval Research MURI Grant N000141310672
NSF Grant IIS 1703340
Undergraduate Biology Research Program

Title: The role of objects during complex spatial navigation in the rat

Authors: *M. P. SOUDER[1], M. ROGERS[1], Y. QIN[2], P. SCLEIDOROVICH[3], A. WEITZENFELD[3], J.-M. FELLOUS[1];
[1]Dept. of Psychology, [2]Undergraduate Biol. Res. Program, Univ. of Arizona, Tucson, AZ; [3]Dept. of Computer Sci. and Engin., Univ. of South Florida, Tampa, FL

Abstract: The neural substrate of rodent spatial navigation involves a large variety of cells selective to place, reward, head direction, object location and borders. This complex system is usually studied in small and simple mazes. However, both humans and rats need to navigate in complex environments, and accordingly need to use dedicated neural systems for complex spatial navigation. Spatial navigation utilizes both path integration and landmark navigation, and it has been shown that the hippocampus and its place cells are involved in both. Previous studies (The Traveling Salesrat: Insights into the Dynamics of Efficient Spatial Navigation in the Rodent. Watkins L., Gereke B. G. M. Martin, JM Fellous. J Neural Engineering, 8(6), 2011) have used the Traveling Salesperson Problem (TSP) as a model to study spatial navigation optimization in rats. This model is a spatial problem in which the shortest path between a number of rewarded ‘cities’ must be found over multiple trials. Previous versions of this task utilized small environments with cities represented by identical copies of rewarded cups. In the current

study, we used a much larger environment and different objects, each paired with a reward. The objects were used in a configuration designed to study optimization and the effect of object manipulation on navigation. After the rats optimized their navigation through 6 rewarded locations, we switched two of the objects with each other and hypothesized that if the rats were using the objects as landmarks for finding the optimal path, the object switch would affect their navigation. These configurations were compared with the identical reward cups configurations for both male and female rats. Single cell and network activity were recorded from the dorsal CA1 area of hippocampus while rats performed the task. Preliminary results show differences in sharp wave activity between cup and object configurations. The results also show that the presence of objects decreases the number of trials to task completion. Current work focuses on the analysis of place cells during the task.

Disclosures: M.P. Souder: None. **M. Rogers:** None. **Y. Qin:** None. **P. Scleidorovich:** None. **A. Weitzenfeld:** None. **J. Fellous:** None.

Poster

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Program #/Poster #: 789.15/BB42

Topic: H.01. Animal Cognition and Behavior

Support: VIEP-BUAP

Title: Temporal analysis of spatial learning and memory in metabolic syndrome model plus hippocampal injection of amyloid-β $_{25\text{-}35}$ peptide

Authors: *O. REYES-CASTRO[1], G. MORALES-FLORES[1], A. PATRICIO-MARTÍNEZ[1,2], I. D. LIMÓN PÉREZ DE LEÓN[1];
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Abstract: The effect of Metabolic Syndrome (MetS) on spatial learning and memory and the temporal effect of the induction of this experimental model has not been thoroughly reported. In our laboratory, use the injection of amyloid-$\beta_{25\text{-}35}$ peptide ($A\beta_{25\text{-}35}$) to investigate some neurotoxic mechanisms and memory impairment in rats, in association with Alzheimer's disease. The aim of this work was evaluate if MetS at 2 and 6 months of induction produce a differential effect on spatial learning and memory in hippocampal lesioned rats with the $A\beta_{25\text{-}35}$. We used *Wistar* male rats (250-280 g) randomly assigned in MetS and Control (C) group. MetS model was obtained by consumption of 20% sucrose solution meanwhile C received drinking water, *ad libitum* for two (2mo) and six (6mo) months in separate cohort of rats. At the end of each period, the MetS model was evaluated. After, all rats were yield to stereotaxic surgery to the injection of

vehicle or $A\beta_{25-35}$ [100µM] into CA1 subfield of Hippocampus, (coordinates; AP: -4.0, L: ±2.3, P: -2.6). The experimental groups were C+Vehicle, MetS+ Vehicle, C+$A\beta_{25-35}$ and MetS+$A\beta_{25-35}$ 2mo and 6mo for each cohort of rats. At 15th day post-surgery, experimental groups were tested for spatial learning in Morris Water Maze (MWM) and 5 days later, were memory tested. Our finding indicates that MetS+Vehicle 2mo does not impair learning and memory in MWM. Regarding to MetS+$A\beta_{25-35}$ 6mo, showed an increase in the scape latency on 15, 16 and 17 days post surgery compared to MetS+$A\beta_{25-35}$ 2mo. The MetS+Vehicle 6mo exhibited memory impairment with an increase in latency to the first crossing at platform zone (40%) and decrease de crossing number (41%) at this site. We conclude that the induction time on MetS is determining to cause damage in spatial learning and exacerbate the memory impairment evaluated in MWM probably by a disturbance of neuronal function associated with oxidative stress, neuroinflammation and loss of neurochemical communication, therefore it is necessary to evaluated proteins involved in modulation of spatial learning and memory.

Disclosures: O. Reyes-Castro: None. **G. Morales-Flores:** None. **A. Patricio-Martínez:** None. **I.D. Limón Pérez de León:** None.

Poster

789. Intrinsic Hippocampal Circuits: Spatial Navigation

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 789.16/BB43

Topic: H.01. Animal Cognition and Behavior

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Department of Biotechnology, IISc-DBT partnership program
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Ministry of Human Resource Development, India

Title: Robust emergence of sharply tuned place cell responses in hippocampal neurons with structural and biophysical heterogeneities

Authors: *R. BASAK, R. NARAYANAN;
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Abstract: Place cells in the hippocampal CA1 region are endowed with complex dendritic arborization, exhibiting heterogeneity in structural features such as length, diameter and branching patterns. These neurons are electrotonically non-compact structures effectuating immense bidirectional attenuation to signal propagation, and are capable of sustaining the generation and active propagation of dendritic spikes. We recently showed that synapses that are randomly dispersed across the dendritic arbor of such neurons endowed with disparate ion channel distributions yield sharply tuned place cell responses through dendritic spike initiation

[1]. Although our analyses had demonstrated that sharp place-cell tuning could emerge in the presence of expansive heterogeneities in synaptic and channel profiles, the impact of morphological heterogeneities on place-cell tuning has remained unexplored. In this study, we asked if sharply tuned place-cell responses mediated by dendritic spikes would emerge in different CA1 pyramidal neuron morphologies, each expressing heterogeneities in channel expression and synaptic localization as well. To do this, we performed independent stochastic searches of a 21-parameter space (covering passive and active properties involving 6 somato-dendritic channels) in 5 distinct morphologies, each endowed with randomly dispersed synapses (100 synapses carrying place-field information), and found models that manifested sharp place-field tuning. Next, we validated this subset of sharply-tuned models against 12 electrophysiological measurements (input resistance, resonance frequency, total inductive phase and backpropagating action potential amplitude at 3 locations each) from CA1 pyramidal neurons. This two-step validation process from stochastic searches spanning thousands of parametric combinations yielded several models that were both sharply tuned and intrinsically valid, independently for each of the five morphologies, with disparate profiles of synaptic localization and parametric combinations. Mechanistically, employing virtual knockouts of NMDA receptors or dendritic sodium channels, we found the initiation of dendritic spikes to be a critical contributor to sharpness of place-cell responses in all morphologies. From the functional standpoint of achieving sharply-tuned feature encoding and concomitantly maintaining homeostasis of intrinsic excitability, our results point to ion channel degeneracy and suggest neuronal morphology to be a “sloppy” parameter even in electrotonically non-compact structures.

1. Basak R. and Narayanan R., J. Physiol., 2018 (http://dx.doi.org/10.1113/JP275310)

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

Poster

789. Intrinsic Hippocampal Circuits: Spatial Navigation

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 789.17/BB44

Topic: H.01. Animal Cognition and Behavior

Support: Canadian Institutes of Health Research

Title: Representation of 3D space in the hippocampus of freely moving marmosets

Authors: *D. BUITRAGO-PIZA[1], B. W. CORRIGAN[4], B. MAHMOUDIAN[2], R. A. GULLI[3], W. J. ASSIS[1], L. E. MULLER[5], J. C. MARTINEZ-TRUJILLO[6];
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Jolla, CA; [6]Dept. of Physiol. and Pharmacol. and Psychiatry, Brain and Mind Institute, Univ. of Western ON, London, ON, Canada

Abstract: The role of the hippocampus in representing space is widely supported. Neurons that increase their firing rate when an animal occupies a certain region, 'Place Cells', have been thoroughly identified and studied in multiple species. This unique population of neurons has been thought to support a cognitive-map like representation of space in the brain; however, little is known about how these representations are formed in the common marmoset during free navigation in a 3D environment. Moreover, whether these representations are modulated by the position of conspecifics or the presence of reward has yet to be determined. In this work, we sought to identify the firing properties of neurons in the CA fields of the hippocampus while we register spatial and view information of freely navigating marmosets as they engage in a variety of foraging and social behaviours in 3D space. For this purpose, we habituated the experimental subjects in pairs, to freely move inside a plexiglass recording chamber with four vertical levels while wearing affixed infrared reflective markers on top of skull implants that allowed for 6 degrees of freedom position and head direction camera tracking (Optitrack, Natural Point Inc, USA). Using MRI guided neuro-navigation techniques we chronically implanted a 34-microwires array in the left hippocampus region CA1 (Microprobes Inc., USA) of common marmosets. We recorded the responses of neurons using a wireless recording system during the aforementioned behaviors. Data from 2 animals was analyzed, subjects were able to successfully forage in 4 different locations in 2 different levels of the chamber, animals also explored most of the space within the chamber and they engaged in socially relevant behavior (mutual gaze contact and grooming). Single units were found to respond significantly as a function of spatial position, reward location and head orientation.

Disclosures: D. Buitrago-Piza: None. **B.W. Corrigan:** None. **B. Mahmoudian:** None. **R.A. Gulli:** None. **W.J. Assis:** None. **L.E. Muller:** None. **J.C. Martinez-Trujillo:** None.

Poster

789. Intrinsic Hippocampal Circuits: Spatial Navigation

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 789.18/BB45

Topic: H.01. Animal Cognition and Behavior

Support: NIH DK104897

Title: A ventral hippocampus CA1-lateral septum pathway regulates spatial memory for food location

Authors: *E. A. DAVIS[1], C. M. LIU[2], A. N. SUAREZ[1], E. E. NOBLE[1], S. E. KANOSKI[1,2]; [1]Human and Evolutionary Biol., [2]Neurosci. Grad. Program, USC, Los Angeles, CA

Abstract: Research on rodent hippocampal involvement in visuospatial memory has predominantly focused on the "dorsal" (septal) hippocampus, and has utilized memory tasks that involve escaping aversive conditions (e.g., swimming, bright lights). Comparatively much less is known about the functional role of the "ventral" (temporal) hippocampus (vHPC) in spatial memory, and more specifically, the role of the vHPC in spatial memory related to food location. Given recent findings revealing that the vHPC is critical in regulating food intake and conditioned aspects of feeding behavior, we hypothesized that vHPC neurons play a role in memory for the spatial location of food. Our results reveal that vHPC excitotoxic lesions in rats impair memory retention for food location using a novel spatial food seeking procedure developed in our lab. To further elucidate the precise neural pathways that mediate these effects, we next investigated whether the lateral septum (LS) is a downstream target mediating vHPC-dependent food-related spatial memory. To examine this hypothesis, we used conditional dual viral approaches to either reversibly (via cre-dependent pathway-specific inhibitory chemogenetics) or permanently (via cre-dependent pathway-specific caspase-induced lesions) disconnect the ventral CA1 (vCA1) to LS monosynaptic pathway. Results show that both acute and chronic disruption of vCA1 to LS signaling impairs memory retention in the spatial food seeking task. Collectively, these data indicate that vHPC communication to the LS plays an important role in memory retention for food-related environmental spatial cues, thereby identifying a novel neural pathway of relevance to foraging behavior.

Disclosures: E.A. Davis: None. **C.M. Liu:** None. **A.N. Suarez:** None. **E.E. Noble:** None. **S.E. Kanoski:** None.

Poster

789. Intrinsic Hippocampal Circuits: Spatial Navigation

Location: Hall A

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Program #/Poster #: 789.19/BB46

Topic: H.01. Animal Cognition and Behavior

Support: NSF integrative Strategies #1533598
Vallee Foundation

Title: Correction for single-event path integration errors in the hippocampal place code using visual cues

Authors: *E. R. REDINGTON[1], S. SOLTANIAN-ZADEH[1], A. SILBERSTEIN[1], E. QIAN[1], R. ZHANG[1], S. FARSIU[1], Y. GONG[2];
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Abstract: Hippocampal place cells become active when an animal visits specific spatial locations. The spatially tuned activity of place cells arises from a combination of internal,

movement-related cues and external, sensory-related cues. Multiple models of hippocampal activity suggest that the internal cues generate a continuous representation of self-location via path integration while the external cues correct the errors that accumulate in path integration. We wish to determine how information from external visual cues corrects sudden errors in the place code's representation of self-location. We hypothesize that the place code combines visual sensory information with path-integration information on different timescales. We tested this hypothesis by using virtual reality (VR) to decouple movement from sensation; we rapidly shifted the position of mice along a VR track while optically recording the activity of hippocampal pyramidal neurons. We found that unexpected changes in visual scenery created a mismatch between the place code's representation of position and the animal's VR position but did not completely change the representation of the environment. From this evidence, we reached two conclusions: (1) visual information is sufficient to overwhelm movement-related input and drive large shifts in the place code following an error in the place code's representation of self-location; and (2) the correction in place code lags behind visual sensory inputs.

Disclosures: E.R. Redington: None. **S. Soltanian-Zadeh:** None. **A. Silberstein:** None. **E. Qian:** None. **R. Zhang:** None. **S. Farsiu:** None. **Y. Gong:** None.

Poster

789. Intrinsic Hippocampal Circuits: Spatial Navigation

Location: Hall A

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Program #/Poster #: 789.20/BB47

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant U19
Fundació CELLEX

Title: Correlated fluctuations in hippocampal neural ensemble activity patterns limit the accuracy of spatial representations

Authors: *O. HAZON[1], D. P. TOMÀS[2], V. H. MINCES[3], S. GANGULI[1], M. J. SCHNITZER[1], P. E. JERCOG[4];
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Abstract: A substantial body of theoretical and experimental research has shown that correlated noise fluctuations in the dynamics of multiple neurons can affect the ability of a neural ensemble to encode and transmit high-fidelity information. In essence, correlated fluctuations can limit the extent to which downstream brain areas are able to improve signals by pooling the outputs of multiple cells. Theoretical work suggests that this phenomenon is likely to be especially important when considering large neural ensembles. However, experimental studies of correlated

fluctuations have usually examined cell pairs, and the published literature is inconclusive as to whether correlated noise fluctuations truly limit information-encoding by neural populations. To study activity correlations at the level of neural ensembles, we used a miniature, head-mounted fluorescence microscope to image the somatic calcium dynamics of hundreds of CA1 hippocampal pyramidal neurons in freely behaving mice trained to run back and forth on a linear track. We monitored hundreds of neurons in each mouse across hundreds of running laps, allowing accurate characterizations of both the average neural ensemble activity patterns as well as fluctuations about the mean values. We constructed computational decoders that estimated the mouse's running trajectory based on the set of neural activity traces. Correlated fluctuations in the neural ensemble activity patterns limited the accuracy with which these decoders could estimate the mouse's position. Notably, decoders that accounted for the statistical structure of these correlated fluctuations achieved higher accuracy than decoders that were insensitive to such fluctuations. Overall, these findings reveal information-limiting noise correlations in hippocampal neural ensembles and demonstrate the importance of accounting for these correlations to achieve optimal decoding of animal behavior.

Disclosures: O. Hazon: None. **D.P. Tomàs:** None. **V.H. minces:** None. **S. Ganguli:** None. **M.J. Schnitzer:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Inscopix Inc.. **P.E. Jercog:** None.

Poster

789. Intrinsic Hippocampal Circuits: Spatial Navigation

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 789.21/BB48

Topic: H.01. Animal Cognition and Behavior

Support: CIHR
NSERC

Title: Naturalistic encoding of spatial working memory in the primate lateral prefrontal cortex in a virtual environment

Authors: *M. KHAKI[1], M. ROUSSY[1], N. MORTAZAVI[1], R. LUNA[1], A. J. SACHS[2], J. C. MARTINEZ-TRUJILLO[3,1];
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Abstract: Since Fuster and Alexander (1971) provided the first electrophysiological evidence of persistent neural activity during the delay in the prefrontal cortex, spatial working memory

(WM) has been studied using highly controlled tasks that utilize simple visual stimuli and constrain eye movement. Using these tasks, a myriad of studies has shown that neurons in the primate lateral prefrontal cortex (LPFC) encode WM representations in the absence of external stimuli. One caveat of this highly controlled approach is that it departs from natural behaviour. One issue that remains unclear is whether neurons in the LPFC encode spatial WM during natural behaviour, that is, in the presence of distracting information and eye movements.
To address this issue, we created a naturalistic spatial WM task that takes place in a virtual environment that incorporates complex 3D visual stimuli and does not constrain eye movement. During a trial, a cue is presented to the subject in a virtual arena in one of nine possible locations. This cue disappears during a delay period and must be remembered in order for the subject to navigate towards the target's location using a joystick in the response period. Position in the virtual environment and eye position were recorded during all trials. Neural recordings were conducted in two male rhesus macaques during this task using two 10×10 microelectrode arrays located in the LPFC (areas 8Ad/v).
Both animals successfully performed this task and demonstrated neural tuning during cue and delay periods at the level of individual neurons and neuronal population. A classifier was able to decode target location on a single trial basis during cue and delay periods with accuracies >80% (chance = xx). These findings were not explained by neural activity influenced by target location-specific patterns of eye movement. Moreover, we found that only a small subpopulation of neurons was required (>20) to decode correct target location robustly. We were also able to distinguish between correct and incorrect trials using this method. These findings show that primate LPFC neurons encode both perceptual and WM representations of space in conditions resembling natural environments

Disclosures: **M. Khaki:** None. **M. Roussy:** None. **N. Mortazavi:** None. **R. Luna:** None. **A.J. Sachs:** None. **J.C. Martinez-Trujillo:** None.

Poster

789. Intrinsic Hippocampal Circuits: Spatial Navigation

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 789.22/BB49

Topic: H.01. Animal Cognition and Behavior

Support: NIH R01 NS104193
NIH R21 NS106218

Title: Vestibular updating of the head direction cell signal during movement between vertical planes: Inside corners

Authors: *P. OZEL, P. A. LACHANCE, J. L. MARCROFT, J. S. TAUBE;
Dartmouth Col., Hanover, NH

Abstract: Head direction (HD) cells encode an animal's directional heading in the azimuth plane of an environment. How do the compass-like properties of HD cells apply to navigation in three-dimensional (3D) space? Two models, the rotational plane hypothesis and the dual-axis model, offer different accounts for how HD cells shift their preferred firing directions (PFD) during 3D movement across horizontal and vertical 2D planes. The rotational plane hypothesis (Taube et al., 2013) postulates that the cell's PFD shifts to align with any plane that the animal is moving in—except if the animal is inverted—and treats the new plane as an extension of the horizontal plane. The dual-axis model (Page et al., 2018) predicts a 90º PFD shift when crossing vertical boundaries—clockwise for rightward travel and counterclockwise for leftward travel across 'outside' vertical corners. In contrast, the model postulates that the PFD should shift in the opposite direction when crossing 'inside' vertical corners. Previous work has only tested this hypothesis in animals that travel around outside vertical corners. Here, we tested these hypotheses by recording anterodorsal thalamic HD cells from 4 rats as they traversed an inside vertical corner. Cells were monitored as the rat moved from the floor onto an elevated horizontal surface after traversing a route that comprised both outside and inside vertical corners. Results revealed PFD shifts consistent with the dual-axis model for both outside and inside corners. The mean shift when going around an outside corner towards the left was 88.9 ± 7.2º (range: 48 to 144°; n = 22). For traversing a leftward inside vertical corner, the PFD shifted -87.8 ± 7.2º (range: -156 to -24°; n = 22). Similar firing patterns occurred when animals completed the task in the dark in the absence of visual information; left outside corner: 75.4 ± 7.3°; left inside corner: 70.3 ± 8.5° (n = 15 sessions). The peak firing rate (PFR) remained stable across all planes, with a small rate decrease on the top horizontal plane. Across all cells the mean PFR decreased -24.1 ± 0.04% (n = 24) from the initial floor session to the top horizontal plane under light conditions and -24.4 ± 0.1% for dark sessions (n = 6). Compared to the floor session, the mean PFR change was +5.3 ± 0.1% for the first wall (-9.4 ± 0.1% dark), +0.6 ± 0.1% for the wall following an inside corner (-9.4 ± 0.1% dark), and -2.7 ± 0.1% for the wall after an outside corner (-22.2 ± 0.1% dark). Our results suggest that the vestibular system, both the semicircular canals and the otoliths, plays a key role in updating the HD cell's PFD when the animal moves between horizontal and vertical planes, even in the absence of visual information.

Disclosures: P. Ozel: None. **P.A. LaChance:** None. **J.L. Marcroft:** None. **J.S. Taube:** None.

Poster

789. Intrinsic Hippocampal Circuits: Spatial Navigation

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 789.23/BB50

Topic: H.01. Animal Cognition and Behavior

Support: NIH R01 NS104193
NIH R21 NS106218

Title: Criteria for three dimensional tuning in head direction cells

Authors: *J. S. TAUBE;
Psychological & Brain Sci., Dartmouth Col., Hanover, NH

Abstract: Head direction (HD) cells fire as a function of the rat's head direction in the horizontal plane, independent of the animal's location and on-going behavior. They have been identified in a number of species and different brain areas. HD cells are now considered to be classified into two broad categories of 'classic' cells and HD-modulated cells - the latter having low peak firing rates and modulated by secondary spatial parameters. Many so-called HD cells in bats and monkeys appear to be tuned to orientations outside the horizontal plane in allocentric (world-centered) coordinates. However, it is has been questionable whether HD cells in rodents can also be optimally tuned to orientations outside the horizontal plane. Here we describe the criteria that should be satisfied in order to establish that a HD cell is tuned in 3D space. By definition, for a cell to be considered tuned to an orientation outside the horizontal plane, cell firing should be related to the allocentric reference frame and have a 1) substantial, 2) consistent, and 3) meaningful firing rate that is elevated over that observed when the animal is in the horizontal plane. Previous studies have shown that HD cell peak firing rates are similar when an animal locomotes on the floor and along a vertical wall (Stackman et al., 2000; Calton and Taube, 2005; Taube et al., 2013). This finding makes it problematic for arguing that HD cells are tuned to 3D volumetric space in allocentric coordinates because there is more than one direction in allocentric space in which the cell is tuned. Alternatively, the cell's reference frame could be defined in both egocentric and allocentric coordinates, whereby the cell's reference frame shifts with the animal's plane of locomotion as it moves between different planar surfaces, which is consistent with the dual-axis model. Another criteria is that the cell's firing rate should be greater than that in the horizontal plane - keeping in mind that a cell's peak firing rate varies between different sessions. For example, when rats were passively rotated in different tilt and roll planes, HD cell peak firing rates varied across sessions even when the rat was in the same upright orientation. The mean percent increase or decrease between sessions was 32.1 ± 5.8% (range: 0.70 - 100.4%, n=23) or -20.3 ± 3.3% (range: -0.80 to -60.7%, n=21), respectively. Due to this variability, a cell should change its peak firing rate consistently by more than these amounts when the animal is in a different tilt or roll plane, in order to consider a cell 3D-tuned. Finally, cells should show a 'meaningful' change in their firing rate, such that it would have a significant impact on downstream networks.

Disclosures: J.S. Taube: None.

Poster

789. Intrinsic Hippocampal Circuits: Spatial Navigation

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 789.24/BB51

Topic: H.01. Animal Cognition and Behavior

Title: Reasons why Alzheimer's disease is “diabetes of the brain”

Authors: *A. S. SHINGO[1], S. KITO[2];
[1]Section of Neurosci., Okinaka Mem. Inst. For Med. Res., Tokyo, Japan; [2]Shonan Hosp., Kanagawa, Japan

Abstract: The object of this study is showing evidence that the intraventricularly streptozotocin injected rat (brain diabetes rat) is a definite Alzheimer disease model. Behavioural, immunohistochemical studies were performed together with dendritic spine analysis of the hippocampal granular cells. As methods, 1) Spatial cognitive function tests were performed on intraventricularly streptozotocin injected “brain diabetes” rats by the Morris water maze (n=7). Controls were injected with PBS (n=10). 2) Quantitative immunohistochemicalexaminations of amyloid β protein, insulin-degrading enzyme, somatostatin, AKT, p-CREB were performed using the rat hippocampal tissue (brain diabetes: n=7, control: n=10). 3) Dendrites of granular cells of the hippocampal dentate gyrus were quantitatively evaluated. 4) A single injection of detemir, a long-acting insulin analogue, into the third ventricle of the rat was done (brain diabetes: N=3, n=1, control: N=3, n=15). The results were summarised as follows. The spatial cognitive function of rats with “brain diabetes” has been impaired. Immunohistochemistry of the hippocampus revealed an increase in amyloid β protein and decreases in all other tested values. Spine densities of the granular cells were significantly decreased. By intraventricular single injection of the insulin analogue, all the tested values approached to those of control rats. From the results above, we concludedthat the “brain diabetes” rat is a definite model of Alzheimer disease.

Disclosures: A.S. Shingo: None. **S. Kito:** None.

Poster

789. Intrinsic Hippocampal Circuits: Spatial Navigation

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Program #/Poster #: 789.25/BB52

Topic: H.01. Animal Cognition and Behavior

Support: ERC - AdG 787450

Title: Contextual remapping of medial entorhinal cortex inputs to CA1 in head-fixed mice exposed to a virtual environment

Authors: *T. CHOLVIN, T. HAINMUELLER, M. BARTOS;
Univ. of Freiburg - Inst. For Physiol. I, Freiburg Im Breisgau, Germany

Abstract: The medial entorhinal cortex (MEC) harbors numerous different spatially tuned cells including grid cells, border cells, head-direction cells, and cells with conjunctive responses, i.e. combining several of those spatial patterns of activity. Overrepresented within the superficial layers of the MEC, those excitatory neurons are either pyramidal cells or stellate cells. Fibers originating from those cells distribute extensively over the hippocampal area: pyramidal cells of the MEC project to CA1, while stellate cells are innervating the dentate gyrus (DG) and CA3. MEC inputs provide the major spatial contextual information to the hippocampus. A fraction of hippocampal place cells typically display environment-specific spatial activity patterns called place fields. While hippocampal place cells encode particular locations in a given environment, MEC spatially modulated cells are known to mainly retain their basic firing characteristics between environments, providing a metric to the neuronal representation of space. How spatial information from the MEC is translated to hippocampal place cells remains so far unclear. Previous investigations suggested that grid cells are the primary determinant of hippocampal place cell firing. However, while hippocampal neurons can retain context-specific spatial firing in the absence of MEC inputs, the inhibition of those inputs reduces the stability of CA1 place cells, indicating their importance for place cell activity and stability. Thus, knowing the relationship between MEC inputs and CA1 place cell activity would shed new light on this central problem. It has recently became possible to use Two-Photon (2P) Ca^{2+} imaging to record axons *in vivo* during behavioral tasks in head-fixed mice. Here we established and used 2P functional imaging to assess in CA1 the activity of GCAMP6s-loaded axon terminals originating in the MEC while animals are running through virtual environments. Our preliminary data indicate that MEC inputs are spatially tuned and undergo remapping once mice are exposed to different virtual environments.

Disclosures: T. Cholvin: None. **T. Hainmueller:** None. **M. Bartos:** None.

Poster

790. Human Perception and Imagery III

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 790.01/BB53

Topic: H.02. Human Cognition and Behavior

Support: Lenfest Junior Faculty Development Award

Title: Manipulating temporal event structure via top-down script activation

Authors: *A. REBLANDO[1], T. KELISHADI[1], C. BALDASSANO[2];
[1]Columbia Univ., New York City, NY; [2]Psychology, Columbia Univ., New York, NY

Abstract: The brain “chunks” the continual stream of sensory information into discrete events of increasing timescales along the cortical hierarchy. Event segmentation is not driven solely by the

external features of the current stimuli, but is also influenced in a top-down manner by activated internal representations of the current situation. These internal "event scripts," constructed by abstracting consistent schematic structure from prior experiences, can mold online perception and memory for the current stimulus. An unexplored question is the extent to which an activated script affects the segmentation of a naturalistic narrative into events. We designed an experiment with a novel set of stories, in which each story features a combination of two different scripts. For example, a story about two people conducting a business deal while eating at a restaurant contains two overlapping stereotyped sequences of events: eating at a restaurant (entering, being seated, ordering, and getting food), and conducting a business deal (greeting, making the initial offer, making a rebuttal, concluding the deal). This is consistent with realistic experiences in which multiple sequences of events often occur simultaneously, requiring top-down attentional guidance to choose an appropriate temporal representational structure. In this experiment, the most relevant event segmentation of the story is manipulated across subjects, e.g. by placing subjects into the role of a restaurant critic or a business reporter. Our hypothesis is that changing the script that subjects are deploying will lead to changes in both the timing of neural pattern shifts and the information content of these patterns themselves. In preliminary behavioral experiments, subjects were asked to provide a subjective segmentation of the stories into discrete, coherent events. Participants primed with the same script had significantly more correlated judgements of when new events in the story began, compared with participants primed with the alternative script ($p = .045$), supporting our hypothesis that activation of a top-down event script influences perceived the temporal structure of a narrative.

Disclosures: **A. Reblando:** None. **T. Kelishadi:** None. **C. Baldassano:** None.

Poster

790. Human Perception and Imagery III

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Program #/Poster #: 790.02/BB54

Topic: H.02. Human Cognition and Behavior

Support: Gift from Ford
NSF DGE 1752814
NSF DGE 1106400

Title: A naturalistic navigation task reveals rich distributed representations of information across the human cerebral cortex

Authors: *T. ZHANG[1], J. L. GALLANT[1,2];
[1]Joint Grad. Group in Bioengineering, [2]Dept. of Psychology and Helen Wills Neurosci. Inst., Univ. of California, Berkeley, Berkeley, CA

Abstract: Navigation in the natural world is a challenging problem that requires the interaction of multiple cognitive systems, including those for evaluating and integrating cognitive maps, attention, motor control, and planning (Spiers & Maguire 2006). However, most fMRI navigation studies use highly simplified environments and tasks that are unlikely to engage a broad range of cognitive processes. Thus, they do not provide information sufficient to create detailed functional cortical maps of the many different types of information that are likely relevant for natural navigation.
To recover detailed functional cortical maps of navigation-related information, we used fMRI to record brain activity while subjects performed a taxi driver task in virtual reality. The pilot environment used a 1×1 km town without other agents. The main environment used a 1×2 mile map that includes traffic, traffic rules, pedestrians, and various neighborhoods and off-road areas. Subjects drove using an MR-compatible steering wheel and pedal set constructed in our lab. Whole-brain activity was recorded from two subjects using a 3 T Siemens Tim Trio scanner. One subject participated in the pilot for 130 minutes and the main environment for 260 minutes. A second subject participated in the pilot for 90 minutes.
We applied the voxelwise modeling framework developed in our lab (Kay et al. 2008, Naselaris et al. 2009, Nishimoto et al, 2013) to the data. We extracted stimulus and task features from the experiment, and used regularized banded ridge regression to find an optimal set of weights for each feature for every voxel in each subject. We evaluated 6 feature spaces: route progression, semantic segmentation, navigational affordances, planned path, spatial position, and visual motion-energy. We then used a separate data set to test statistical significance, prediction accuracy, and generalization of each model in each subject.
The recovered functional cortical maps from each of the two subjects show the parahippocampal place area (PPA), retrosplenial cortex (RSC), and occipital place area (OPA) represent information about roads, buildings, and boundaries. RSC and OPA also represent navigational affordances. RSC and precuneus tracks route progression. Visual motion-energy is represented across much of visual cortex, including the posterior parts of RSC, OPA, and PPA. The fusiform face area and extrastriate body area represent information about pedestrians and other vehicles. Our data replicate many results reported previously in the human and rodent literature, and they reveal how navigation networks interact with other cognitive systems during naturalistic navigation.

Disclosures: **T. Zhang:** None. **J.L. Gallant:** None.

Poster

790. Human Perception and Imagery III

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 790.03/BB55

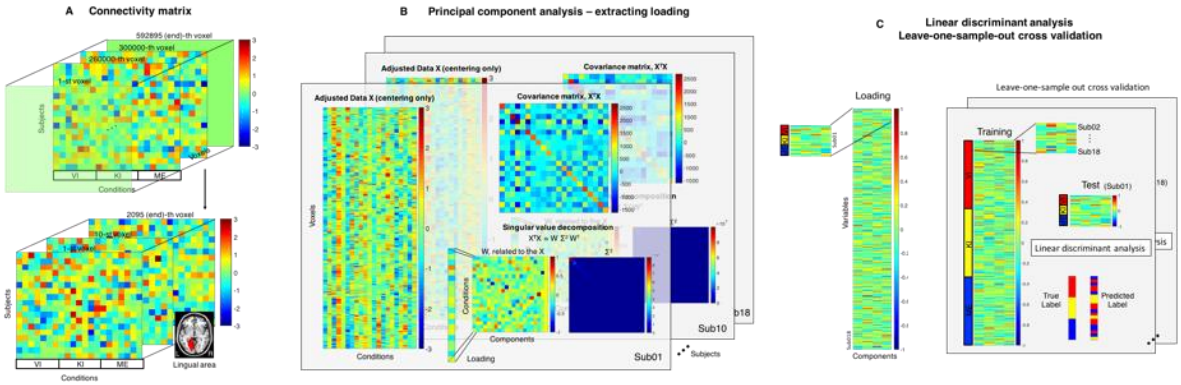
Topic: H.02. Human Cognition and Behavior

Support: NRF 2018R1C1B6002554
NRF 2016M3C7A1904984

Title: Discriminating functional connectivity patterns during visual and kinesthetic motor imagery, and motor execution

Authors: *E. KIM[1], W. LEE[2], H. SEO[1], B.-M. OH[1], M. BANG[1];
[1]Seoul Natl. Univ. Hosp., SEOUL, Korea, Republic of; [2]Seoul Natl. Univ. Col. of Med., Seoul, Korea, Republic of

Abstract: How motor-related functional connectivity patterns are distributed during visual motor imagery (VI), kinesthetic motor imagery (KI), and motor execution (ME) is interest of this study, which may determine effectiveness of motor imagery training for rehabilitation. Block-designed 3T fMRI experimental paradigm was given to 18 participants (30.3+-4.3 years). During 5 experimental sessions, each condition was presented 7 times as a block, consisting of 5 trials of grasping/releasing of right hand (or motor imagery) in every 4 seconds. The data was preprocessed (slice-timing correction, realignment, coregistration, normalize, and smoothing). To find out the most fundamental motor-related functional connectivity patterns, region of interest (i.e., the left primary motor area; M1) was determined by examining contrast of ME and perceptual control condition in a group level analysis. Temporal correlations between the seed region and other whole brain voxels were computed in each block, and converted to z scores. Maximally 21 seed-based functional connectivity were constructed in each individual. We generated data matrix consisting *individuals*-by-*conditions*-by-*voxels*, and segmented it based on the Automated Anatomical Labeling template. Multi-voxel pattern analysis was applied to the data to find brain regions where functional connectivity patterns during the conditions were significantly different (Fig1). As a result, functional connectivity patterns during VI, KI and ME were all classified above chance level within 6 ROIs. Among them, the seed-based functional connectivity patterns within the right cerebellum VI, vermis VIII, and left lingual areas were classified significantly above chance level ($P<0.05$), The null hypothesis was that sum of the correctly predicted label across all three conditions is obtained by random chance. Taken together, this study provided evidence that patterns of functional connectivity with the left primary motor cortex within the cerebellum and visual area is important to discriminate the two types of motor imagery and motor execution.



Disclosures: **E. Kim:** None. **W. Lee:** None. **H. Seo:** None. **B. Oh:** None. **M. Bang:** None.

Poster

790. Human Perception and Imagery III

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 790.04/BB56

Topic: H.02. Human Cognition and Behavior

Support: Intramural Research Program of NIMH (ZIAMH 002909)

Title: Temporal dynamics of memory recall for familiar people and places

Authors: A. KIDDER[1], ***A. L. CORRIVEAU**[1], S. G. WARDLE[1], E. H. SILSON[2], C. I. BAKER[1];
[1]Natl. Inst. of Mental Hlth., [2]NIH, Bethesda, MD

Abstract: Recall of familiar people or places elicits activation in distinct sets of cortical regions, including ventral temporal cortex, medial parietal cortex, and posterior parietal cortex. To investigate the temporal dynamics of recall, we collected magnetoencephalography (MEG) data while participants visualized highly familiar people or places. Prior work looking at the temporal dynamics of memory and imagery have often focused on the visualization of recently seen novel images. In contrast, participants in our study were asked to recall highly familiar people or places in the absence of any prior visual presentation, relying on retrieval of long term internal representations. Conditions were personalized to each participant and they each provided the names of six personally familiar people (e.g. Aunt Shirley, Dr. Silson) and places (e.g. office desk, Metro Center). In a retrocue paradigm, two names were presented sequentially on the screen (800 ms each with a 200 ms gap) followed by a blank screen (400 ms) and then the presentation of a retrocue (500 ms). This retrocue was either the number 1 or 2, indicating that the participant should recall and visualize either the first or the second item named. Participants then visualized the cued item as vividly as possible for 4000 ms. Each condition was presented 32 times and cued 16 times over the course of 192 trials. Trials were broken into 8 runs in which each name was seen 4 times and cued for recall twice. Data was sampled across 272 channels at 600 Hz with whole-brain coverage, then downsampled to 200 Hz. Principal component analysis was implemented to retain the components explaining 99% of the variance. We applied multivariate pattern analysis to the responses measured across sensors using a pair-wise linear discriminant analysis classifier. We primarily focused on the ability to decode whether the participant was recalling a person or a place. Decoding showed a transient peak immediately after the presentation of the retrocue (~ 300 ms after onset), before declining and then strengthening again into the recall period, persisting until the end of the trial. These results reveal the evolution of the temporal representation of memory recall over time.

Disclosures: **A. Kidder:** None. **A.L. Corriveau:** None. **S.G. Wardle:** None. **E.H. Silson:** None. **C.I. Baker:** None.

Poster

790. Human Perception and Imagery III

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 790.05/BB57

Topic: H.02. Human Cognition and Behavior

Support: Dream Science Foundation
Mind Science Foundation
Northwestern University Psychology

Title: Performing actions in lucid and nonlucid dreams

Authors: *K. KONKOLY[1], R. MALLETT[2], M. CARR[3], C. MAZUREK[1], K. A. PALLER[1]; [1]Dept. of Psychology, Northwestern Univ., Evanston, IL; [2]Psychology, The Univ. of Texas at Austin, Austin, TX; [3]Swansea Univ., Swansea, United Kingdom

Abstract: The scope of behavioral output that is possible during human sleep may not be as limited as commonly assumed. Here we evaluated this speculation in the context of lucid dreaming--being aware that one is dreaming while asleep. Furthermore, we combined lucid dreaming with a methodology for altering dream content, which can open up new opportunities for insights into downstream effects of dreaming and into the contrast between dream versus wake experiences. We recently developed a method of "hypertraining," whereby existing methods of cognitive training for inducing lucid dreams are accelerated in a 20-minute pre-sleep session linked with visual and auditory cues. The same cues are then presented during Rapid Eye Movement sleep (REM). This method can be considered a variant of targeted memory reactivation (TMR), by which memories are reactivated during sleep via stimuli previously associated with learning. In our prior study, this method induced lucid dreams in 50% of laboratory participants in a morning nap. However, it is unknown whether lucid dreams induced by this method would enable enough volitional control to complete complex tasks. Here, we expand hypertraining by investigating whether participants can perform a predetermined sequence of eye-movement and fist-clench actions in their dreams. One group received hypertraining in which cues were associated with lucidity, and participants were asked to, once lucid, complete the sequence of actions (lucid group). A second group of participants completed modified hypertraining in which cues were associated with mental rehearsal of the sequence of actions, but not lucidity (task group). Thus far, 9 participants in the lucid group were cued during REM; 5 completed varying steps of the task, evidenced by EOG and EMG activity (electro-oculography and electromyography) and accompanying dream reports. Four participants in the task group were cued during REM; all 4 completed parts of the task. Results showed that lucidity

can be induced via hypertraining, and that lucid participants had varying levels of success in completing tasks within the dream environment. We conclude that electrophysiologically verified actions within a dream can be elicited following the hypertraining procedures, and that we can systematically manipulate dream content to engender eye-movement and fist-clench actions during both lucid and nonlucid dreams.

Disclosures: K. Konkoly: None. **R. Mallett:** None. **M. Carr:** None. **C. Mazurek:** None. **K.A. Paller:** None.

Poster

790. Human Perception and Imagery III

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 790.06/BB58

Topic: H.02. Human Cognition and Behavior

Support: Grant n. 0193.001486/2017 from FAP-DF

Title: Behavioral and electrophysiological effects of transcranial direct current stimulation (tDCS) in the Müller-Lyer illusion

Authors: *F. V. CAIXETA, W. MEDEIROS, G. S. P. DAL PONT, E. M. BORIGATO, Í. B. RIOS, J. BRASIL-NETO, C. H. TAVARES, R. S. MAIOR;
Univ. of Brasilia, Brasilia, Brazil

Abstract: Recent evidence suggests that the neural substrate responsible for the Müller-Lyer illusion is located in the extrastriate visual cortex, most likely in the lateral occipital cortex, where the ventral visual processing pathway starts. The use of tDCS, a non-invasive method capable of altering cortical excitability may yield insights into the local contribution of cortical areas to cognitive processes. In this study, we recorded the pattern of neural activation of healthy subjects under the Müller-Lyer illusion and tested the effect of tDCS on the perception of this illusion. Healthy participants were divided into three groups, all of which were exposed to the Müller-Lyer illusion: electroencephalography (EEG) only, tDCS only, and tDCS with simultaneous EEG recording. The stimuli were presented on a computer screen. We assessed whether tDCS over various regions involved with visual processing altered either the participant's point of subjective equality or the temporal latency of the responses but found no statistically significant differences between the control group and the stimulated group. We also characterized EEG activity and the evoked potential in occipital and temporal electrodes. In the group with simultaneous EEG and tDCS the behavioral data generated again showed no significant difference in the perception of the Müller-Lyer illusion, but there was a marginal difference in the electrical activity between P280 and P450 on the O2 and T6 electrodes. In the present study, the perception of the Müller-Lyer illusion was not modified by tDCS stimulation

of the lateral occipital cortex. More studies will be conducted to test whether tDCS stimulation in different sites can alter perception and neural activity during the Müller-Lyer illusion.

Disclosures: F.V. Caixeta: None. **W. Medeiros:** None. **G.S.P. Dal Pont:** None. **E.M. Borigato:** None. **Í.B. Rios:** None. **J. Brasil-Neto:** None. **C.H. Tavares:** None. **R.S. Maior:** None.

Poster

790. Human Perception and Imagery III

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 790.07/BB59

Topic: H.02. Human Cognition and Behavior

Title: Knowledge about the action goal modulates posterior parietal activity during action observation

Authors: *L. GROSSE, A. ZABICKI, J. MUNZERT, B. KRUEGER;
Justus Liebig Univ., Giessen, Germany

Abstract: It has been proposed that the frontoparietal action observation network (AON) plays a central role in understanding observed actions. Within this network, the posterior parietal cortex (PPC) has been discussed as a key node for detecting the intentions of the observed act, being linked to action prediction and simulation. However, there has been an ongoing debate regarding the contribution of higher-order knowledge about the actor's intention prior to the action observed. While some theories favor a bottom-up explanation of intention decoding, others suggest a top-down modulation of the AON. Using fMRI and Representational Similarity Analysis, we sought to compare the activation patterns elicited in PPC and visual area 5 (V5) during observation of actions both with and without prior knowledge about the intention. 16 right-handed adults (eight females) observed videos of an arm performing reaching movements along four straight paths sharing a common origin. In each video, the movement was performed either from the origin to an end point (forward) or vice versa (back). Participants either knew (for the back conditions) or did not know (for the forward conditions) what the intended movement path and goal were going to be, before observing the movement. Participants completed twelve fMRI runs, each containing two trials of every video. Region of interest maps (ROIs) for PPC (i.e. SPL, IPL, IPS) and visual area 5 (V5) were computed for each subject. Noise-normalized beta maps corresponding to the activation during the observation of the movement were compared to each other. The resulting representational dissimilarity matrices were then compared to three different models. Model 1 predicted structured activation (low dissimilarity) within both the back and forward conditions, model 2 only during the forward conditions (no knowledge about intention) and model 3 only during the back conditions (knowledge about intention). While in V5, model 1 performed significantly better than the other models, this was

not the case for SPL. Here, model 2 showed significantly higher correlations to subject's RDMs. These results indicate that during action observation, PPC activity is indeed modulated top-down by prior knowledge about the intended movement goal, especially within the SPL.

Disclosures: L. Grosse: None. **A. Zabicki:** None. **J. Munzert:** None. **B. Krueger:** None.

Poster

790. Human Perception and Imagery III

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 790.08/BB60

Topic: H.02. Human Cognition and Behavior

Support: Azrieli Program in Brain, Mind & Consciousness, Canadian Institute for Advanced Research

Title: Content-specific neural patterns in sensory cortices during auditory imagery

Authors: *M. REGEV[1], A. R. HALPERN[2], A. M. OWEN[3], A. D. PATEL[4], R. J. ZATORRE[1]; [1]Montreal Neurolog. Inst., Montreal, QC, Canada; [2]Psychology, Bucknell Univ., Lewisburg, PA; [3]Western Univ., Brain and Mind Inst., London, ON, Canada; [4]Psychology, Tufts Univ., Medford, MA

Abstract: As part of their mental world, humans are able to internally represent ongoing auditory information without a direct external stimulus. Auditory imagery, the internal representation of sounds, has been mostly studied by looking for spatially overlapping neural responses while listening versus internally recalling sounds. However, that approach does not allow a distinction between general mechanisms of imagery as opposed to representation of specific imagined content. In the present work, we venture beyond basic spatial localization of averaged signals by comparing the unique temporal response profile of heard and imagined complex and continuous sounds. Twenty-five subjects memorized six distinct minute-long melodies to a high standard of accuracy in musical content and timing. Next, using whole-brain 3T fMRI, we recorded neural responses in three conditions: 1) silently imagining each melody to the rhythm of a visual metronome ("imagery"), while either tapping a finger to the beat of the melody or keeping motionless; 2) passively listening to the original melodies ("listening"); and 3) watching the visual metronome without imagining the melody ("control"). We directly compared the response time-courses in the imagery and control conditions to the listening condition within different brain regions, using inter- and intra-subject correlation. During imagery, melody-specific response patterns were reinstated in the superior and medial temporal gyri (lateralized to the right), the visual cortex, and the supplementary motor area. In addition, the melody-specific patterns in the temporal cortex were more strongly reinstated when imagery was accompanied by rhythmic tapping, compared to motionless imagery. These results indicate

that areas in sensory cortices are not only involved in recreating a complex internal experience of music, but that they can also encode melody-specific information similarly, both when it is externally perceived or internally recalled. Furthermore, rhythmic motion can enhance the reinstatement of neural patterns associated with the experience of complex musical content, in keeping with models of motor to sensory influences in auditory temporal processing.

Disclosures: M. Regev: None. **A.R. Halpern:** None. **A.M. Owen:** None. **A.D. Patel:** None. **R.J. Zatorre:** None.

Poster

790. Human Perception and Imagery III

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 790.09/BB61

Topic: H.02. Human Cognition and Behavior

Support: Natural Sciences and Engineering Research Council of Canada

Title: The relationship between motor system activation during movement imagery and motor system adaptation following movement imagery training

Authors: *E. YOXON, T. N. WELSH;
Fac. of Kinesiology and Physical Educ., Univ. of Toronto, Toronto, ON, Canada

Abstract: Movement imagery (MI) is a cognitive-motor process that shares neural networks with movement execution and observation. As such, MI may play an important role in motor learning and rehabilitation. Previous research has demonstrated that both physical and action observation training can elicit rapid neuro-plastic changes in the cortical representation of movement (e.g. Stefan et al., 2005). In these studies, a series of TMS pulses was used to generate thumb movements and the dominant direction of these thumb movement as used as the index of the neural representation of thumb movements. This dominant direction of TMS-evoked movements changed after training by physically executing or observing thumb movements in the opposite direction. We have recently demonstrated this same effect with MI training (Yoxon & Welsh, submitted). In action observation, the magnitude of these training effects is related to the magnitude of corticospinal system activation during individual instances of action observation (i.e. the change in amplitude of TMS induced motor evoked potentials [MEPs]; Ray et al. 2013). To further understand the mechanisms of MI training, the relationship between neuro-plastic MI training effects and the amplitude of MEPs during MI was examined. In Experiment 1, the dominant direction (i.e. flexion or extension) of TMS-evoked thumb movements was assessed before and after MI training. During training, participants imagined moving their thumbs in the direction opposite to the pre-determined dominant direction. Prior to training, TMS was also used to determine the change in corticospinal excitability during MI (amplitude of MEPs during

MI of thumb movements in both the flexion and extension directions). There was no significant relationship between MEP amplitude during MI and the pre-post changes in the direction of TMS-evoked thumb movements in Experiment 1. However, pre-post changes in the direction of these thumb movements were modest. The MI intervention in Experiment 2 was modified to enhance the potential of training effects. The preliminary results of Experiment 2 suggest that there may be a relationship between corticospinal activation during MI and neuro-plastic changes in the representation of movement following MI training.

Disclosures: E. Yoxon: None. **T.N. Welsh:** None.

Poster

790. Human Perception and Imagery III

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 790.10/BB62

Topic: H.02. Human Cognition and Behavior

Support: Swedish fundation for humanities and social sciences

Title: Changes in the global state of consciousness affect brain activity related to conscious and non-conscious visual perception differently

Authors: *A. FONTAN[1], L. LINDGREN[2], T. PEDALE[1], F. BERGSTRÖM[3], C. BRORSSON[4], J. ERIKSSON[1];
[1]Dept. of Integrative Med. Biol., Umeå Ctr. For Functional Brain Imaging, Umeå, Sweden; [2]Dept. of Nursing, Umea Univ., Umea, Sweden; [3]Coimbra Univ., Fac. of Psychology and Educ. Sci., Coimbra, Portugal; [4]Dept. of Anaesthesia and Intensive Care, Inst. of Surgery and Perioperative Sci., Umeå, Sweden

Abstract: Until now, investigations of consciousness have used two basic experimental paradigms: one evaluating differences related to the content of consciousness (*i.e.* what is it like to experience something) and the other evaluating differences related to the global state of consciousness (*e.g.* sedated *vs.* non-sedated). There is currently a debate regarding how to conceptualize the relation between these two aspects of consciousness. Therefore, in this fMRI study, both aspects of consciousness were manipulated for the first time within a single experimental setting, which enabled us to formally investigate the relation between these two fundamental aspects of consciousness. We used continuous flash suppression to present visual stimuli consciously or non-consciously while participants performed a simple perceptual detection task during fMRI scanning and simultaneously, the state of consciousness was manipulated by injecting a sedative (Propofol). Participants could perform the task at all times under two different levels of sedation (*i.e.* low and moderate). Reaction time increased with the level of sedation, confirming the experimental manipulation of the state of consciousness.

Irrespective of sedation level, task accuracy was near perfect for conscious trials, but at chance level for non-conscious trials. Crucially, multivariate pattern analyses of BOLD signal in the occipital cortex revealed that sedation levels affected both conscious and non-conscious perceptual processes (significant classification of low *vs.* moderate sedation levels). In addition, low *vs.* moderate levels of sedation was significantly better classified for non-conscious processes than for conscious processes, showing that non-conscious processes were affected more than conscious processes by the sedation. Thus, contrary to intuition, a reduction of the global state of consciousness does not primarily affect neural activity related to conscious experiences.

Disclosures: A. Fontan: None. **L. Lindgren:** None. **T. Pedale:** None. **F. Bergström:** None. **C. Brorsson:** None. **J. Eriksson:** None.

Poster

790. Human Perception and Imagery III

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 790.11/BB63

Topic: H.02. Human Cognition and Behavior

Support: Albright Creative Research Experience

Title: Effects of the hollow mask illusion on children

Authors: *A. KATES;
Albright Col., Reading, PA

Abstract: The Hollow Mask Illusion depicts a concave mask (pointing away from the viewer) that is painted in a manner that creates an illusion of convexity (pointing towards the viewer. The illusion itself has been used before in various areas of research, including infant perceptual development and areas regarding perception in individuals with schizophrenia. The current study aimed to examine potential differences in children's (4-6-years old) perception of this illusion in comparison to adults. We hypothesized that the illusion would be stronger in adults than in children. Additionally, a new mask was created from a popular character (Elmo), to investigate if there are other faces that may be more palatable to children for use in this experiment, as the human mask has the potential to appear less friendly to children. Data analyses found that children see a stronger illusion than adults ($F(1,27) = 4.402$, $p < .05$) suggesting the contribution of top-down processes in perceiving faces is stronger in children, who may be primed to see faces as convex even when context is deceitful.

Disclosures: A. Kates: None.

Poster

790. Human Perception and Imagery III

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 790.12/BB64

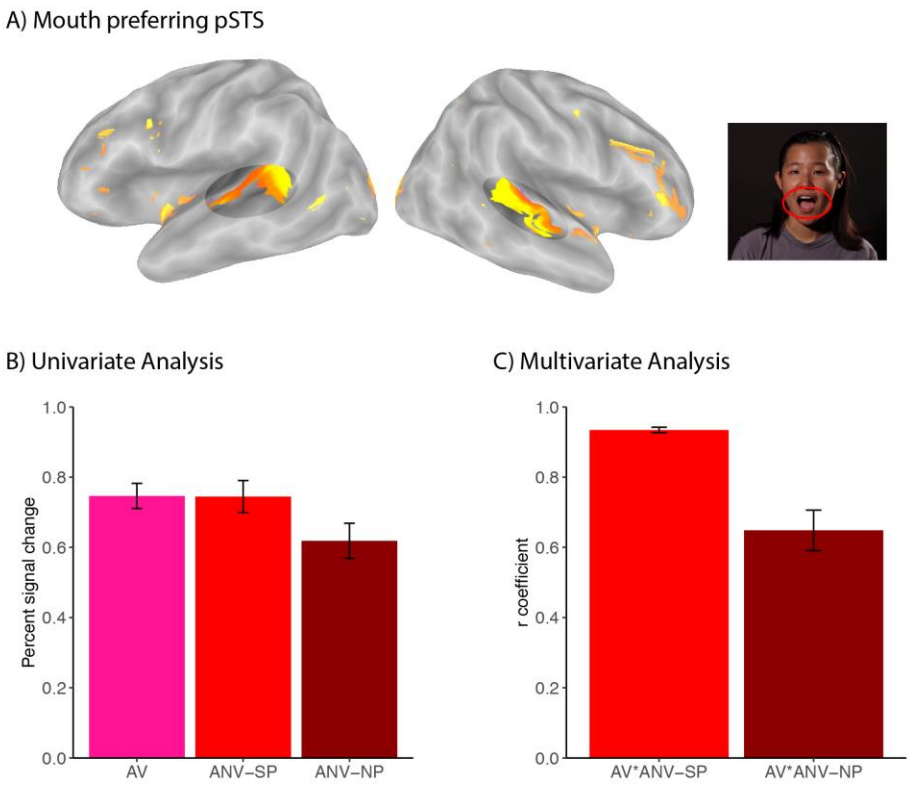
Topic: H.02. Human Cognition and Behavior

Support: NIH Grant R01NS065395
DFG Grant RE 3693/1-1

Title: Bold activity in the posterior superior temporal gyrus and sulcus predicts comprehension of noisy audiovisual speech

Authors: *J. RENNIG, M. S. BEAUCHAMP;
Neurosurg., Baylor Col. of Med., Houston, TX

Abstract: Regions of the human posterior superior temporal gyrus and sulcus (pSTS) respond both to the visual mouth movements that comprise visual speech and the auditory vocalizations that comprise auditory speech (Zhu & Beauchamp, 2017; Rennig & Beauchamp, 2018). We hypothesized that these multisensory responses in pSTS underlie the observation that comprehension of noisy auditory speech is improved when it is accompanied by visual speech (*e.g.* Sumby & Pollack 1954). To test this idea, we presented audiovisual sentences that contained either a clear auditory component or a noisy auditory component while measuring brain activity using BOLD fMRI. Participants (N = 22) reported the intelligibility of the speech on each trial with a button press. *Post hoc* trial sorting was used to examine brain activations during sentences that were more or less intelligible. Our analysis focused on regions of the pSTS identified with a visual speech localizer, consisting of the contrast between viewing faces making silent mouth movements and faces making silent eye movements (Fig. 1A). For noisy audiovisual sentences (AnV) that were rated as intelligible (AnVintel), the amplitude of the BOLD signal in the pSTS did not differ from the response to clear audiovisual (AV) sentences (0.75% *vs.* 0.74%, $p = 0.959$; Fig. 1B). In contrast, for noisy sentences that were rated as unintelligible (AnVunintel) the pSTS response was significantly less than the response to clear sentences (0.75% *vs.* 0.62%, $p = 0.011$) and the response to intelligible noisy sentences (0.74% *vs.* 0.62%, $p = 0.019$). To better understand the fine-grained structure of these differences, we conducted a multivariate representational similarity analysis. The neuronal representation of intelligible noisy speech was more similar to clear audiovisual speech than the representation of unintelligible noisy speech was (average $r = 0.93$ for AV*AnVintel *vs.* average $r = 0.65$ for AV*AnVunintel, $p = 0.008$, Fig. 1C). These results suggest that visual speech regions of pSTS are related to the perceptual benefit of visual speech during perception of noisy auditory speech.



Disclosures: **J. Rennig:** None. **M.S. Beauchamp:** None.

Poster

790. Human Perception and Imagery III

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 790.13/BB65

Topic: H.02. Human Cognition and Behavior

Support: BCS-1534823

Title: Insight into objects' function biases perception

Authors: *D. DUBBELDE[1], S. S. SHOMSTEIN[2];
[2]Psychology and Inst. for Neurosci., [1]George Washington Univ., Washington, DC

Abstract: Perception is largely a result of visual processing in two streams: ventral, underlying object identity recognition, and dorsal, underlying physical interaction with objects (Kravitz et al., 2013). Segregation of processing into two streams is supported by differing proportions of parvocellular (p) and magnocellular (m) input (Livingstone & Hubel, 1988). The p-pathway has

higher spatial resolution and projects primarily to the ventral stream, while the m-pathway has higher temporal resolution and projects primarily to the dorsal stream. Furthermore, recognition of objects associated to action (tools) evokes more dorsal stream processing than objects without such associations (non-tools) (Smith & Goodale, 2015). We hypothesize that differing processing of tools and non-tools across the two streams should lead to perceptual differences concurrent with the resolution of each stream - non-tool recognition should yield higher sensitivity to spatial detail and tool recognition should yield higher sensitivity in temporal changes. To test the hypothesis predicting behavioral differences between perception of tools and non-tools, participants were presented with either tool or non-tool objects (10 tools and 10 non-tools) with one of two target types each exploiting the streams' resolution: detecting object flicker for the temporal resolution of the dorsal stream and detecting a small gap in object outline, for the spatial resolution of the ventral stream. Non-tools induced higher sensitivity for detecting spatial gaps as compared to tools, suggesting that the differences in dorsal stream recruitment between tools and non-tools directly predicts behavioral benefits. A follow-up experiment controlled for possible low-level differences between tool and non-tool objects by inverting objects (preserving low-level characteristics while reducing object-recognition). Inversion abolished differences between tools and non-tools, suggesting that the perceptual difference between the object groups is driven by semantic content. The final experiment tested the influence of the m-pathway by manipulating background color as red or green. The m-pathway is suppressed by red light due to the inhibitive, red-selective receptive field surrounds of many m-cells (Wiesel & Hubel, 1966), which predicts reduction in difference between object groups with red light. As predicted, the perceptual advantage for non-tools in the spatial task was observed only under green light. Together, these experiments show there are perceptual differences between tool and non-tool recognition which arise from differential recruitment of the two visual processing streams.

Disclosures: D. Dubbelde: None. **S.S. Shomstein:** None.

Poster

790. Human Perception and Imagery III

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 790.14/BB66

Topic: H.02. Human Cognition and Behavior

Title: Mental rotation task and brain structural changes in early onset Parkinson's disease

Authors: *C. DOUGHERTY[1], B. MULLEN[1], M. P. SUBRAMANIAN[1], S. RAVI[1], K. VENKITESWARAN[1], D. WAGNER[1], P. ESLINGER[1], J. WANG[2], T. SUBRAMANIAN[1]; [1]Neurol., [2]Radiology, Penn State Col. of Med., Hershey, PA

Abstract: Early onset Parkinson's disease (EOPD) is characterized by onset of symptoms between the ages of >40 <60 without any known genetic cause. Previous research indicates that decreased performance on mental rotation task (MRT) (Mullen 2018 SfN) in individuals with EOPD. To date, no studies have compared brain structure between left and right sided onset PD. In this study we examined brain structure in cognitively intact EOPD patients and its relationship to MRT performance. Structural MRIs and MRT data from 32 EOPD subjects were analyzed. All subjects were right handed and had to be in H&Y stage I PD to enroll. The sample consisted of 20 males of which 9 were left sided onset (L) and 11 right sided onset (R) PD and 12 females of which 5 were L onset and 7 R onset PD. Of the above, 10 males (6L and 4R) and 11 females (4L and 7R) had MRT data. Data from visit 1 of this long-term natural history study is presented here. Freesurfer V6.0 was utilized to obtain volumetric data for five parietal lobe regions. Two sample T-test was performed between L and R onset PD brain volumes for males and females. Significantly different regions were then correlated with MRT data using Pearson's R. We found that left ($p < .012$) and right ($p < .0017$) Inferior parietal lobe volume was significantly different between L and R onset male PD patients and left ($p < .049$) inferior parietal lobe was significantly different between L and R onset females. MRT performance was significantly positively correlated with left inferior parietal volume in left onset males ($r = .87$, $p < .02$) and left and right inferior parietal volume in left onset females ($r = .96$, $p< .04$ and $r = .96$, $p < .04$). Right onset male or female groups' MRT scores did not correlate significantly with inferior parietal volumes. Our findings show that inferior parietal lobe may be related to MRT performance in EOPD. The inferior parietal lobe closely corresponds with the angular gyrus which has been shown to be involved in manipulation of internal mental representations. This study is the first to report structural differences between left and right sided onset EOPD patients and their relationship to MRT performance. Our findings further define the neural substrates which mediate MRT performance in EOPD and may represent a new biomarker for disease progression.

Disclosures: C. Dougherty: None. **B. Mullen:** None. **M.P. Subramanian:** None. **S. Ravi:** None. **K. Venkiteswaran:** None. **D. Wagner:** None. **P. Eslinger:** None. **J. Wang:** None. **T. Subramanian:** None.

Poster

790. Human Perception and Imagery III

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 790.15/BB67

Topic: H.02. Human Cognition and Behavior

Title: The neural basis of mental calendars

Authors: *V. RAMACHANDRAN, Z. MARCUS;
UCSD, San Diego, CA

Abstract: We explored the manner in which we construct an internal mental calendar, involving mapping time-sequence onto spatial maps.
When asked to visualize an annual calendar, the majority of people (over 98%) report seeing a vague, indistinct, rectangular shape hovering in front of a face. But about 2 % of the population almost literally "see "the calendar as a hoola-hoop, U, L or V shape with actual letters and words (e.g., January 22) being clearly visible. We now use a novel reverse reading task to establish that these calendars act more like real objects activating sensory pathways rather than purely abstract symbolic descriptions that need bear no geometric resemblance to an actual calendar. For example, when projected on real tilted lines or curves the calendar gets tilted or deformed as in geometric illusions. If the background of straight or curved lines are alternated at 3hz, the calendar deforms in opposite directions in the two frames - generating vivid apparent motion (a case of illusory motion produced from internally generated - non-existent - lines). Furthermore, if the subject looked to the right, the memories from months on the left became blurred and hard to retrieve. And when questioned about events pertaining to specific months her eyes spontaneously moved toward appropriate spatial location. In Subject RN the calendar was a U-shaped, coronal ribbon - the top of the right limb twisted (as in a mobius strip). Remarkably, when switching to an allocentric point of view, the words that were mirror reversed-on the subject's right became legible, and those on what was originally the left became reversed and less legible.
We propose the calendar is enshrined in a circuitry involving the hippocampal place cells and entorhinal grid cells. These are connected to the dominant angular gyrus via the inferior longitudinal fasciculus. Our research has shown that this gyrus embodies a sequence module; we have found that patients with angular gyrus lesions have pronounced difficulty with cognitive tasks involving sequence. This may explain their deficits with reading, writing, left-right confusion, arithmetic (and - we suspect - calendars). Similar lesions in children produces similar deficits, as well as a new one that we dubbed 'calendar agnosia'(difficulty with temporal sequencing of memories whose content is, nonetheless, preserved). Sequence agnosia may - in turn - explain our observation that the rules of transitivity (e.g., A>B, B>C, therefore A>C) are compromised in dyslexics. It is a sobering thought - that the dominant angular gyrus - originally evolved for grasping branches, enables us to reach for the stars.

Disclosures: V. Ramachandran: None. **Z. Marcus:** None.

Poster

790. Human Perception and Imagery III

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 790.16/BB68

Topic: H.02. Human Cognition and Behavior

Title: Breathing load effect on perception and emotion during exercise

Authors: C. MABE, ***S. ADAMS**;
Pfeiffer Univ., Misenheimer, NC

Abstract: Anxiety amplifies afferent sensory components of breathing which can alter the perception of need for air and breathing load. It is unknown if baseline anxiety will alter a collegiate athletes interoception to a respiratory load during a submaximal treadmill test. PURPOSE: Determine if a breathing load (restricted snorkel) affects a collegiate athletes' perception of need for air, perception of exertion, urge to stop, and emotion. METHODS: Collegiate athletes were separated into low anxiety (n=8) and moderate anxiety (n=5) based on State Trait Anxiety Index (STAI) pre-testing. Baseline testing included a VO_{2max} test, one week later a 40-60% $VO_{2submax}$ restricted breathing (10%) for 1.6 miles. During the restricted breathing protocol, Urge-To-Stop (UTS), Rating of Perceived Exertion (RPE), Perceived Breathing Effort (RBE), Need for More Air (NFA), and post-test Self Assessment Manikin (SAM) outcomes were measured. RESULTS: RPE was 18% higher with moderate anxiety (11.96±1.6 SD, p=0.03) compared to low anxiety (9.8±1.67 SD). RBE was 22% higher in moderate anxiety (11.72±1.39 SD, p=0.01) compared to low anxiety (9.1±1.72 SD). NFA was 33% higher in moderate anxiety (1.5±0.0 SD, p=0.02) compared to low anxiety (1.0±0.5). Sense of Happiness (SOH) was 17% lower in moderate anxiety (3.8±0.75 SD, p=0.05) compared to low anxiety (4.6±0.07 SD). Sense of Control (SOC) was 17% lower in moderate anxiety (3.8±0.75 SD, p=0.03) compared to low anxiety (4.8±0.43 SD). CONCLUSION: A restricted breathing load appears to elicit a heightened afferent sensation evidenced by higher body-state scores in collegiate athletes with moderate levels of anxiety.

Disclosures: C. Mabe: None. **S. Adams:** None.

Poster

790. Human Perception and Imagery III

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 790.17/BB69

Topic: H.02. Human Cognition and Behavior

Support: Tempus Public Foundation grant 16/1/KA201/022988

Title: The comparison of the ability of stereoscopical spatial vision of children with special needs, their age-matched mainstream peers, and the members of the year 2018 U16 European Champion Hungarian women's adolescent national handball team based on a new functional stereo test

Authors: *J. PALI[1], I. STUBER[2], S. MOLNAR[4], Z. ELEK[4], P. WALSH[5], E.-M. BAKO[6], C. KOROM[7], S. TAYLOR[5], L. EICKE VON H[5], J. DODLA-BHEMAH[5], G. FARKAS[3], S. KISS[8], A. PETERVARY[2], I. TAMAS[9];
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Abstract: On behalf of the Hungarian governmental organization North-Budapest School District Office, we have been developing a special educational methodology utilizing a 3D television screen with polarization glasses and synchronized camera pairs of different viewpoints for children with special needs in three independent locations (Woking (UK), Sepsiszentgyörgy (Romania), and Budapest (Hungary)).
Before having started the proper somatopedagogic programs, children aged 7-17 (n=191; 65 girls, 126 boys; autism: 43, Down's syndrome: 7, ADD and ADHD: 29, severe mental handicap: 17, SLCN and/or learning difficulties: 95) were examined using a sequence of figures comprising 15 stereo picture pairs with special spatial vision-related clues. Each of the 15 pieces of 3D images showed a number of balls (1-5), the friendliest object, of different colours (white, blue, yellow, red). No child rejected to perform the test. Even non-speaking autists (they have not been involved in the current study) could pick and show them from a set of balls in front of them.
The first 5 pictures of the vision test served to examine blindness and eye domination problems (7 children were found). Nevertheless, the repeating of the vision test once or twice as a training (3-5 min) could switch on the weaker eye.
The second five images tested the basic stereoscopical vision abilities. 6 boys from the control group (n=226; 104 girls, 122 boys) and 5 from the mentally impaired group could not execute all of the images properly.
In the last 5 pictures, balls were arranged in a very tricky manner. Children with special needs could successfully accomplish pictures #11-15 in 95.45%, 91.19%, 75.28%, 47.73%, and 45.53% whereas their healthy peers in 99.54%, 100%, 85.05%, 57.42%, and 53.08%, respectively. No significant difference was found comparing the scores of the healthy boys and girls regarding the last 5 pictures (3.85 ± 1.03 vs. 4.06 ± 1.04, respectively; $p>0.05$ (Student t test)). Having compared the groups of mentally impaired boys and girls, there was also no significant difference between their test results (3.49 ± 1.3 vs. 3.66 ± 1.21; $p>0.05$). By contrast, in cases of both girls and boys, children with special needs could obtain slightly but significantly less scores while performing the stereo test than their healthy mates ($p<0.05$). The European Champion Hungarian women's adolescent national handball team members (n=17) performed 3.65 ± 1.22 in average on the test whereas their age-matched (15-16 years old) control peers (n=25) scored 3.71 ± 1.04 ($p>0.05$).

Finally, 0.79% of all tested children in Hungary, 6.35% in the UK, and 10.17% in Romania perceived the yellow balls in test images to be green (9 girls, 9 boys).

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Poster

790. Human Perception and Imagery III

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 790.18/BB70

Topic: H.02. Human Cognition and Behavior

Support: IITP Grant No.2017-0-00432

Title: Propose the new method for error detection in BCI system using Microstate

Authors: ***S.-K. KIM**, L. KIM;
Korea Inst. of Sci. and Technol., Seoul, Korea, Republic of

Abstract: Brain computer interface used to control robots and to study intuitive interaction between humans and robots. Motor-Imagery is a method of identifying a user's intention that appear when they imagine a certain movement. It has the advantage of being able to perform commands in the most intuitive manner to move a robot. However, its accuracy is low and results are different depending on the performance of users. Thus, we focus on the detection of error for improve MI performance. In many studies, used error-related potentials as error feature for detect. It is characterized by the negative potential over fronto-central regions that appears between 50~100ms and by the positive potential over parietal regions that occurs between 200~500ms after incorrect response. However, they were difficult to clearly detect, so we explored other features as a component of error. Microstate analysis provides a sparse feature of large-scale brain network activity. It also can be used both rest and task state. Using this, we proposed a new feature as appears error component. 10 subjects (6M; aged 26.6±2.91) asked to concentrate on visual cues and followed prompts to complete the corresponding MI. A trial included a preparation state (+, 3s), a concentrate state (auditory cue, 1s), an MI state (L/R hand grasping, 3s), a feedback state (correct/error robot control video, 2s), and a break (1.5s). 60 trials were performed per block, and this was repeated 5 times. We led the subjects into thinking that the feedback stimulus was presented in real time. In practice, 30% of all trials were configured to randomly generate error responses. We used data in feedback state to analyses. Using average epoch about correct or error, Top 5 microstates were calculated to best represent the correct/error epoch. In this result, rank 1 to 4 microstate are same between correct and error, however, 5th microstate (green in figure 1) is different between correct and error. In addition to, the microstate

occurs between 200~500ms and active in parietal region. Thus, we conclude the 5th microstate is component of error response.

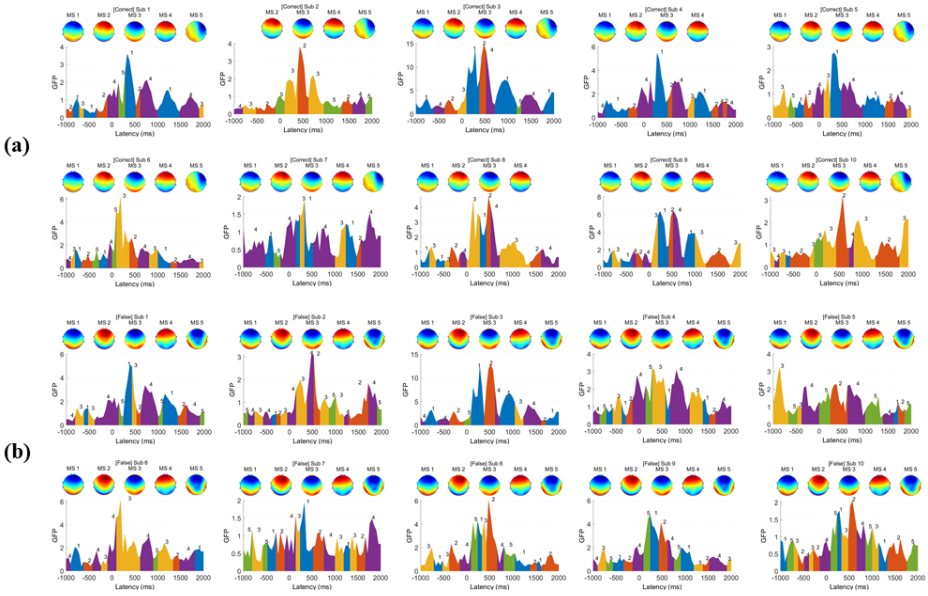

Figure1. The back-fitting graph using 5 microstates (a) Correct response about 10 subjects; (b) Error response about 10 subjects; GFP is Global field power

Disclosures: **S. Kim:** None. **L. Kim:** None.

Poster

790. Human Perception and Imagery III

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 790.19/BB71

Topic: H.02. Human Cognition and Behavior

Support: Natural Science Foundation of China grant (31230030)

Title: Orientation anisotropies compared in human psychophysics and two-photon imaging of macaque V1

Authors: ***S. GUAN**, X. ZHAO, S. TANG, C. YU;
Peking Univ., Beijing, China

Abstract: Humans are more sensitive to cardinal orientations than to oblique orientations. Whether V1 is responsible for this oblique effect remains controversial. Another form of orientation anisotropy is the superior processing of radial orientation compared to tangential orientation. To gain more insights into these orientation anisotropies, we measured

psychophysical orientation discrimination at these orientations, and reanalyzed two-photon imaging data from an earlier study (SfN2017), to compare the effects in human performance and macaque V1 responses. All the data were collected in parafovea (human: 3º; macaque: 2-4º), and two-photon imaging data were obtained from V1 superficial layers of four macaques.Psychophysics:Human orientation discrimination thresholds were lower at the cardinal orientations than oblique orientations for a Gabor presented on the right horizontal meridian or the lower vertical meridian, confirming the oblique effects. When the Gabor was centered at the lower-right or -left visual quadrant, superior orientation discrimination at radial orientations (lower-left 45º or lower-right 135º) was not observed when compared to performance at tangential orientations, failing to replicate the previous results. Two-photon imaging: Responses to a drifting Gabor at 6 SFs and 12 orientations were measured in six 850x850 μm^2 imaging windows, each at 150 and 300 μm depths, to produce 12 data sets. A total of 8798 cells' orientation tuning functions at the best SF were obtained. There were no more neurons tuned to cardinal orientations (0/90º ± 10º) than to oblique orientations (45/135º ± 10º) (19.5±0.9% vs. 22.0±1.3%, p = 0.31). The orientation tuning bandwidths between these two groups of neurons were not significantly different either (18.6±2.1 vs. 17.1±1.5 º , p = 0.19). However, there were significantly more neurons tuned to radial orientations than to tangential orientations (14.0±1.4 % vs. 8.0±1.0 %, p=0.01), but there were no significant differences in orientation tuning bandwidths (15.8±1.5 vs. 16.2±1.5 º, p=0.73) and response strengths (0.40±0.02 vs. 0.40±0.03, p =0.82). The population orientation tuning functions showed similar tuning bandwidths but less variations at radial orientations than at tangential orientations (19.9±1.2 vs. 21.1±1.4 º).Our two-photon imaging results from ~9000 neurons confirm that the oblique effect may not be represented in V1, at least not in parafovea. A radial-tangential anisotropy does show in V1 sub-neuronal population sizes and variations of population tuning. It is unknown why a radial-tangential anisotropy is absent in our psychophysical observations.

Disclosures: **S. Guan:** None. **X. Zhao:** None. **S. Tang:** None. **C. Yu:** None.

Poster

790. Human Perception and Imagery III

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 790.20/BB72

Topic: H.02. Human Cognition and Behavior

Title: Physiological activities in response to different airflows in an air-conditioned test room

Authors: *K. TAMURA[1], S. MATSUMOTO[1], Y. TSENG[2], T. KOBAYASHI[3], J. MIWA[4], T. HIRAO[5], T. OKAMOTO[1,2];
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[3]Mitsubishi Heavy Industries, LTD., Tokyo, Japan; [4]Mitsubishi Heavy industries, LTD., Tokyo, Japan; [5]Mitsubishi Heavy Industries Thermal Systems LTD., Tokyo, Japan

Abstract: Feelings of indoor thermal comfort can be influenced by airflow sensation. However, to our knowledge, few studies have investigated the physiological responses related to velocity and/or direction of airflow generated from an air-conditioning system. Hence, this study compared the physiological responses to different airflow conditions, directly or indirectly to the face, under similar temperature and humidity in an air-conditioned test room. Cooling and heating experiments were performed in seven healthy volunteers (4 females; age, 21–27 years). Participants performed cognitive tasks under two different airflow conditions: direct (DIRECT) or indirect (INDIRECT). Indoor thermal environments were controlled by draft control flaps (Mitsubishi Heavy Industries Thermal Systems LTD., Tokyo, Japan), which can prevent exposure to a constant airstream. Each task consisted of five sessions: resting, subjective evaluation of thermal sensation and affective states, time counting following time signals, time counting without any signals, and mental calculation. These five sessions were repeated thrice per condition. During the experiments, we recorded electroencephalography (EEG), electrocardiography (ECG), and additional physiological data. The experiments were approved by the local ethics committee of Kyushu University. All methods were performed in accordance with the approved guidelines.
The EEG theta band amplitudes in the frontal areas were higher in the heating-INDIRECT than in the heating-DIRECT condition. From this result, we can suggest that the participants could sustain higher attention in the heating-INDIRECT condition. For heart rate variability analysis, we calculated the ratio of the low frequency and high frequency (LF/HF) component as indices of autonomic nervous activity. The statistical testing of LF/HF showed a significant main effect of session in the heating-DIRECT but not in the heating-INDIRECT condition. Hence, autonomic nervous activity was normal in the heating-INDIRECT than in the heating-DIRECT condition. In conclusion, avoiding direct blowing in a heating environment helps maintain a stable mental state. This study is expected to contribute to understand the neuronal mechanism of airflow sensation and development of comfortable air-conditioning system.

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Poster

791. Human Working Memory: Mechanisms II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 791.01/BB73

Topic: H.02. Human Cognition and Behavior

Support: CUNY Graduate Center Doctoral Student Research Grant (round 12)

R56MH116007

Title: Maintenance strategy and task difficulty modulate delay activity and subsequent memory

Authors: *C. REICHERT PLASKA[1,2], A. ARANGO[2], K. NG[3], T. M. ELLMORE[2,1]; [1]Psychology, The City Univ. of New York, New York, NY; [2]Psychology, The City Col. of New York, New York, NY; [3]Neurosci., The CUNY Advanced Sci. Res. Ctr., New York, NY

Abstract: Working memory (WM) and subsequent long-term memory (LTM) may be facilitated by articulatory rehearsal (AR). There is a rich behavioral literature on AR for verbal stimuli, but few studies have examined the benefits of AR for complex novel visual stimuli. Neural delay period studies have largely failed to control for the use of AR, which makes activity patterns during maintenance difficult to interpret. Two studies examined changes in delay activity while participants maintained complex novel scenes and perceptually similar scrambled scenes. Forty-four participants completed a modified Sternberg Task. 64-channel scalp EEG was recorded during WM and long-term recognition. Participants either saw novel scenes (NS) that contained visual semantic information or phase-scrambled scenes (SS) that contained the same colors and spatial frequencies but lacked semantic information. Participants were instructed to generate a descriptive label (i.e. beach) and covertly rehearse the label (CR) or suppress rehearsal (AS, i.e. repeat "the") during the delay period. WM and LTM (10-mins later) performance were measured as proportion of correct trials. Artifact-corrected delay activity (temporal-spectral amplitude) was compared as a function of maintenance strategy (CR vs AS) and stimulus type (NS vs. SS) and was also correlated with performance on the WM and LTM tasks. Performance on the WM task for NS revealed that there was no significant difference in performance between CR and AS suggesting that CR did not provide a short-term behavioral advantage. There was also no long-term behavioral advantage on the delayed recognition task for CR. When task difficulty increased with SS, there was both a significant short-term advantage of CR over AS (85% vs 78% correct, $p<.001$) as well as a long-term advantage for images from the CR condition (71% vs 62% correct, $p<.001$). Comparison of sensor-level delay activity during the maintenance phase for NS and SS revealed two distinct patterns of neural activity. During rehearsal with NS, there was greater amplitude in the beta range in the right parietal and centromedial regions but it was not correlated with performance. For SS, greater amplitude was observed in the upper alpha and beta ranges across all sensors during CR and was significantly correlated with WM performance. Memory for difficult to remember phase-scrambled scenes benefited from rehearsal, whereas easy to remember intact scenes did not. Delay activity increased and correlated with subsequent memory in the former but not the latter suggesting that neural modulation during the delay period depends on both task difficulty and maintenance strategy.

Disclosures: C. Reichert Plaska: None. **A. Arango:** None. **K. Ng:** None. **T.M. Ellmore:** None.

Poster

791. Human Working Memory: Mechanisms II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 791.02/BB74

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant R56MH116007
NIH Grant SC2GM109346
CUNY ASRC Seed Grant (Round 4)

Title: A simultaneous EEG/fMRI study of scene working memory

Authors: *A. M. ARANGO[1], C. REICHERT PLASKA[1,2], J. ORTEGA[1], B. GOMES[2], G. SILVA[1], F. ANTARA[1], K. NG[3], A. SHEREEN[3], T. M. ELLMORE[1,2];
[1]Psychology, The City Col. of New York, New York, NY; [2]Psychology, The City Univ. of New York, New York, NY; [3]Neurosci., Advanced Sci. Res. Ctr., New York, NY

Abstract: Past studies show scene processing is supported by specialized neural circuitry and that scene memory is both high capacity and long-lasting. Less is known about the neural mechanisms supporting the encoding and maintenance of scenes in working memory (WM). 32-channel EEG was acquired simultaneously with BOLD-fMRI in 24 participants to map spatiotemporal activity patterns during a variant of the Sternberg WM paradigm. Participants viewed novel outdoor scenes during an encoding period followed by Fourier phase-scrambled stimuli with similar color and spatial frequency during a delay period. Scrambled scenes provided a perceptual baseline while participants maintained the scenes presented at encoding. Each participant completed 50 low- and 50 high-load trials presented in separate runs with order randomized and counterbalanced. Performance was above chance but did not differ between loads (low 87.37(26.15)%, high 77.54(28.07)%, paired t(23)=1.43, p=0.17).
Group paired t-test difference maps between encoding (ENC) and delay (DEL) were computed from BOLD fMRI data in AFNI. A posterior occipitotemporal network (consisting of right and left hippocampus and parahippocampal gyrus, right middle occipital gyrus) showed significantly greater activity (FDR=0.01) during ENC vs. DEL. A more anterior frontal-parietal network (consisting of left pre- and post-central gyrus, right angular gyrus, right and left inferior frontal gyrus, left and right middle frontal gyrus, left and right thalamus, left cerebellum, and right calcarine gyrus) showed greater activity during DEL vs. ENC.
Topographic voltage amplitude distribution maps were created from the simultaneously acquired EEG data using BESA and paired-t difference maps (ENC vs. DEL) were computed in BESA Statistics.
The low-load condition showed broad overlap with fMRI, with significant posterior ERP differences (ENC > DEL) over bilateral occipital and right centroparietal sensor locations

occurring as early as 106 ms and anterior ERP differences (DEL > ENC) at left frontocentral and temporal sensors occurring as early 134 ms.
The high-load condition showed overlap with fMRI, with significant posterior ERP differences (ENC > DEL) over centroparietal and centrooccipital sensors occurring as early as 76 ms and anterior ERP differences (DEL > ENC) over right frontocentral and temporal sensors occurring as early 210 ms.
The results show a posterior network is rapidly activated during scene encoding, with differences in a more anterior network appearing slightly later during maintenance. These findings add to our understanding of the neural dynamics for how scenes are encoded and maintained in WM.

Disclosures: **A.M. Arango:** None. **C. Reichert Plaska:** None. **J. Ortega:** None. **B. Gomes:** None. **G. Silva:** None. **F. Antara:** None. **K. Ng:** None. **A. Shereen:** None. **T.M. Ellmore:** None.

Poster

791. Human Working Memory: Mechanisms II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 791.03/BB75

Topic: H.02. Human Cognition and Behavior

Support: NIH R01-EY027925
NIH Grant F32-EY028438

Title: Tracking spatial working memory representations during distraction

Authors: *G. HALLENBECK[1], T. C. SPRAGUE[2], M. RAHMATI[1], K. K. SREENIVASAN[3], C. E. CURTIS[4];
[1]New York Univ., New York, NY; [2]Psychological and Brain Sci., Univ. of California, Santa Barbara, Santa Barbara, CA; [3]New York Univ. Abu Dhabi, Abu Dhabi, United Arab Emirates; [4]Psych & CNS, NYU, New York, NY

Abstract: A robust working memory (WM) system requires the maintenance of past but relevant information in memory against a continuous flow of newly incoming but irrelevant information. Recent reports conflict on how WM representations encoded in visual and parietal cortex are susceptible to interference (e.g., Bettencourt & Xu, 2016; van Moorselaar et al., 2017; Lorenc et al., 2018; Rademaker et al., pp2018). Here, we test how WM representations are affected by an intervening task by leveraging the robust ability to decode spatial WM representations from retinotopically organized visual field maps in human cortex. We measured brain activity with high-speed fMRI (1.33 Hz) while participants performed a memory-guided saccade task. On 30% of trials the delay was blank. The remaining 70% were dual-task trials where participants performed a challenging motion discrimination task within a small aperture appearing at

counterbalanced locations with respect to the WM target while remaining fixated. We used an inverted encoding model (Sprague & Serences, 2013) to reconstruct spatial WM representations across the delay interval in visual field maps defined in occipital, parietal, and frontal cortex. Performing the intervening task slightly reduced memory-guided saccade precision, indicating that the task was effective. In all visual field maps and with high fidelity, we could reconstruct the remembered location on trials with blank delays and in the epoch prior to the intervening stimulus on dual-task trials. However, the intervening task caused a temporary reduction in, but not loss of, reconstruction fidelity in all maps, accompanied by the ability to temporarily reconstruct the location of the intervening aperture. Before the end of the delay period, after distractor disappearance, reconstruction of the working memory representation recovered in visual, parietal cortex, and frontal cortex. Therefore, WM may be distractor-resistant because it is supported by a widely-distributed network of brain areas.

Disclosures: G. Hallenbeck: None. **T.C. Sprague:** None. **M. Rahmati:** None. **K.K. Sreenivasan:** None. **C.E. Curtis:** None.

Poster

791. Human Working Memory: Mechanisms II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 791.04/BB76

Topic: H.02. Human Cognition and Behavior

Title: Neural representations and temporal dynamics of rejection template in visual search

Authors: *W. WEN[1], Z. HUANG[1], S. LI[1,2];
[1]Sch. of Psychological and Cognitive Sci., Peking Univ., Beijing, China; [2]PKU-IDG/McGovern Inst. for Brain Res., Beijing, China

Abstract: To perform challenging visual search tasks, attention should be selectively allocated to task-relevant items through target promotion or distractor inhibition. Previous studies have suggested that the benefits of rejection template exist only if the to-be-ignored features remain unchanged (i.e., fixed-cueing condition) rather than change in a trial-by-trial basis (i.e., varied-cueing condition). To resolve the contradictory behavioural findings in fixed and varied distractor-cueing contexts, researchers have proposed that stable rejection template is essential in distractor inhibition and is created only under the fixed-cueing condition, whereas the varied-cueing context obstructed its formation. So far, there was little direct neural evidence shedding lights on the existence of rejection template or the underlying dynamics of its formation. By recording electroencephalography (EEG) of human participants, the current study investigated the neural representation of rejection template along with its temporal dynamics in both fixed-cueing and varied-cueing conditions in a typical visual search task. Participants were asked to locate the target and perform an orientation discrimination task. Before the search array onset,

they were informed of the color of the shapes where the target never appeared. In the matched distractor trials (75%), the cued color reappeared in the search array as the distractor color, while a randomly selected new color would be the distractor color in neutral trials (25%). Robust and persistent reconstruction of the to-be-ignored color from EEG signals in the fixed-cueing condition indicated the successful creation of rejection template. These neural representations could explain the overall significant behavioural suppression benefit. By contrast, there was a strong attention-related signal to the to-be-ignored color in the varied-cueing condition, as reflected by occipital lateral alpha oscillation and transient above-chance reconstruction after cue onset. Meanwhile, stronger frontal theta oscillation was found in the varied-cueing condition, suggesting the goal-directed disengagement from the to-be-ignored color as well as the rejection template transformation process. Finally, during the rejection template execution period, frontal-midline theta oscillation after search array onset positively correlated with individual behavioural suppression benefits in the varied-cueing condition. Overall, the current study demonstrated the neural signature of the rejection template as well as the distinctive neural dynamics underlying its formation and execution in visual search.

Disclosures: **W. Wen:** None. **Z. Huang:** None. **S. Li:** None.

Poster

791. Human Working Memory: Mechanisms II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 791.05/BB77

Topic: H.02. Human Cognition and Behavior

Title: Spatial working memory “precision” related to bump drift: Evidence from distraction

Authors: *J. F. O'RAWE, H.-C. LEUNG;
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Abstract: Fitting measurement models to continuous recall measures as an estimate for working memory precision has been fruitful in discriminating different computational models. However, under a simplified Gaussian drift model of working memory, the behavioral readout at the end of the retention interval combines not only variance from the precision of the actual memory representation, but also the variance due to drift in that representation across the time of the delay. We show that distraction, much like cueing, reduces spread in responses in the bump attractor model, as predicted by the simplified Gaussian drift model. This makes a unique prediction that in conditions of distraction, the location of the output (centered on the target, therefore bias) should be negatively correlated with the spread of the output. We collected data from 59 human subjects in a spatial working memory task which included manipulations of distraction. We presented a target dot stimulus along a circular array, followed by a distractor in ¾ of the trials (of varying distances from the target: 18 degrees, 36 degrees, 54 degrees) after a

variable delay (manipulation unrelated). Then after another variable delay the participants were probed with a free response to rotate a probe dot around a circle until it matched the remembered dot location. We found an increased location recall bias with increasing distance of distractors from the target. Importantly, we found that in 7/9 conditions of distraction, the location parameter was significantly negatively correlated with the spread parameter, while in 0/3 conditions without distraction showed this negative correlation. This provides another line of evidence demonstrating the importance of representational drift in the precision of working memory readout.

Disclosures: J.F. O'Rawe: None. **H. Leung:** None.

Poster

791. Human Working Memory: Mechanisms II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 791.06/BB78

Topic: H.02. Human Cognition and Behavior

Support: Whitehall Foundation (2017-12-73)
National Science Foundation (1736028)

Title: Prefrontal cortical aperiodic activity tracks the number of items held in short-term memory

Authors: *T. TRAN[1], B. VOYTEK[2,3,1,4];
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Abstract: Successful memory encoding is linked to decreased power in low-frequency neural activity and concomitant increased power in high-frequency activity across a wide network of temporal and frontal cortical regions. These changes have often been seen in the examination of individual memory items successfully maintained in short-term memory. However, it is not known to what extent similar changes in on-going, non-stimulus-evoked aperiodic activity might also track, over time, the contents of short-term memory as more and more items are maintained. To investigate this, we analyzed previously collected electrocorticographic (ECoG) recordings from 28 patients undergoing treatment for drug-resistant epilepsy. These patients performed a delayed free recall task in which multiple lists of serially presented words were provided, and after each list, patients were asked to recall as many words from the previous list as possible. From these recordings, we measured lateral temporal (LTL) and lateral prefrontal cortical (LPFC) aperiodic (1/f-like) slope using neural activity immediately preceding each word presentation. We hypothesized that the “flattening” of aperiodic slope over time would track the number of words currently being maintained in short-term memory. To test this, we calculated, for each patient, the difference in aperiodic slope between last- and first-available words per list.

Next, we examined the per-patient relationship between aperiodic slope difference values and recall percentages across lists. We found that aperiodic slope difference values from LPFC, but not from LTL, were positively correlated with list recall percentages consistently across patients. Specifically, increases in aperiodic slope values over time were indicative of more words memorized and subsequently recalled. These results demonstrate that the number of items maintained in short-term memory can be tracked using characteristics of on-going baseline aperiodic activity in the LPFC, and they also suggest that the degree to which prefrontal cortical neural populations can shift towards more asynchronous activity states has a direct effect on memory maintenance and capacity.

Disclosures: **T. Tran:** None. **B. Voytek:** None.

Poster

791. Human Working Memory: Mechanisms II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 791.07/BB79

Topic: H.02. Human Cognition and Behavior

Support: JSPS Grant 19700440

Title: New computer based training improves working memory and cognitive functions

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Abstract: How to maintain and improve cognitive functions in elder people is an important subject in cognitive psychology and mental health. Although a variety of training methods have been introduced, most of these could improve specific capacity only to achieve these tasks and do not improve overall cognitive capacity. We developed a new method to measure and improve working memory capacity and cognitive functions for elders. In this method, subjects need to solve problems that they frequently encounter in their real life (e.g., preparing food, planning a travel, or shopping). The problems that subjects want to solve can be selected by themselves depending on their interest and the parameters of problems (e.g., difficulty, time to solve the problem) can be changed easily by the experimenter and flexibly adapted to each subject's ability. In the present study, we examined effectiveness of this method by comparing the performance of this method with the performance of seven neuropsychological tests using Pearson's correlation coefficient. A stepwise multiple regression (SMR) analysis was also used to examine whether potential predictors were independently associated with the behavioral components of this method. Healthy elders performed this method and seven generally used neuropsychological tests. Correct performance rates of this method were significantly correlated

with those of mini-mental state examination (MMSE), category fluency test, digit span backward task, and trail making test. SMR analyses showed that neuropsychological capacities for trail making test B, MMSE, and category fluency test are closely related to the performance of this method. These results indicate that performance of our method requires working memory capacity, attentional control, and cognitive flexibility, and suggest that This method can be help to maintain and improve cognitive functions for elders.

Disclosures: S. Ichihara-Takeda: None. **K. Takeda:** None. **S. Funahashi:** None.

Poster

791. Human Working Memory: Mechanisms II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 791.08/BB80

Topic: H.02. Human Cognition and Behavior

Title: Exploring working memory in the DLPFC through direct stimulation

Authors: *P. S. ROLLO[1], O. WOOLNOUGH[1], K. J. FORSETH[1], N. TANDON[2];
[1]UTHSC at Houston, Houston, TX; [2]Vivian L. Smith Dept. of Neurosurg., Houston, TX

Abstract: Introduction: Cortical stimulation mapping (CSM) is a powerful research tool that allows researchers and clinicians to causally assign function to cortex in a way that eludes other collection modalities by allowing temporary disruption of local brain networks. Working memory is a crucial function as the short-term storage and manipulation of information involved enable so much of everyday human behavior. It has been extensively investigated using nonhuman primates as well as lesion and imaging studies in humans but the literature can benefit from stimulation work. Here we used CSM to localize regions of the brain that contribute to the process of working memory.
Methods: We collected data in 20 patients undergoing intra-operative language mapping using direct cortical stimulation (5-10mA, 50Hz, 2s). Working memory was evaluated with a battery of tasks including sentence repetition and digit manipulation. Digit manipulation was assessed by giving patients a list of three numbers, which patients were expected to repeat in reverse order. Stimulation sites were mapped onto a cortical model generated from the patient's MRI. The spatial extent of stimulation-induced depolarization modeled on the pial surface with a current spread model to generate subject-specific maps of memory disruption that were then projected onto a standard group atlas to produce a population-level representation.
Results: The stimulation yielded regions of sentence repetition disruption and regions of digit manipulation disruption. Sites of digit manipulation disruption were mostly confined to DLPFC, in agreement with the literature. However, these sites were distinct from the regions in which repetition was disrupted.
Conclusion: We have demonstrated DLPFC is essential to working memory providing evidence

of a new human population, separate from lesion and imaging studies. Additionally, we have shown the distinction between anatomically distinct regions for the storage and manipulation of information. These data serve to further validate the prevailing understanding of a divided system of working memory, separating storage and manipulation of information, while also providing causal evidence for where parts of those individual networks exist in the brain.

Disclosures: P.S. Rollo: None. **O. Woolnough:** None. **K.J. Forseth:** None. **N. Tandon:** None.

Poster

791. Human Working Memory: Mechanisms II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 791.09/BB81

Topic: H.02. Human Cognition and Behavior

Support: Universidad de Guanajuato

Title: Electroencephalographic features of middle aged women with high and low performance in a working memory test

Authors: *M. SOLIS-ORTIZ, E. GONZÁLEZ-PÉREZ;
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Abstract: Working memory is an executive function which is key for effective cognitive performance. This memory has shown deficits in middle aged women, although the results are inconclusive. An electroencephalographic (EEG) approach during the application of a working memory test and a discriminant analysis may aid in understanding these cognitive deficits, particularly in women who show high and low performance. The aim was to explore EEG features of middle-aged women through the execution of a test demanding working memory and to determine the predictor variables that best classify cases into the two groups. EEG activity was recorded through the execution of the Wisconsin Card Sorting Test in twenty-four middle-aged healthy women. The women were divided into a low execution group (n=10) and a high execution group (n=14), according to the number of completed categories of the test. Two completed categories were indicative of low performance. A stepwise discriminant analysis was performed to determine if participating women could be discriminated based on the following variables: delta, theta, alpha1, alpha2, beta1, beta2 absolute power, the number of completed categories, correct responses (trials), perseverative errors and test errors. The discriminant analysis showed that Wilks' lambda, as a test of discriminant function, was significant (lambda=0.101; X^2=36.71, p=0.001) and selected the four following variables as predictors of high and low performance: completed categories (F=54.27, p=.001), delta (F=48.57, p=.001), theta (F=40.41, p=.001) and alpha1(F=33.45, p=.001) power. These findings indicate that the calculated discriminant function based on the four predictor variables was useful for distinguish

membership to the high and low execution group during performance test, highlighting slow EEG activity.

Disclosures: M. Solis-Ortiz: None. **E. González-Pérez:** None.

Poster

791. Human Working Memory: Mechanisms II

Location: Hall A

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Program #/Poster #: 791.10/BB82

Topic: H.02. Human Cognition and Behavior

Support: Research Council of Norway 240389
Research Council of Norway 274996
Research Council of Norway 262762
NINDS grant R37NS21135

Title: Preservation of working memory capacity after orbitofrontal damage

Authors: *A. LLORENS[1,2,3], I. FUNDERUD[3], A. O. BLENKMANN[3], J. LUBELL[3], M. D. FOLDAL[3], S. LESKE[3], R. J. HUSTER[3], T. R. MELING[2,3,4], R. T. KNIGHT[1], A.-K. SOLBAKK[2,3,5], T. ENDESTAD[3,5];
[1]Dept. of Psychology, Helen Wills Neurosci. Institute, UC Berkeley, Berkeley, CA; [2]Dept. of Neurosurg., Oslo Univ. Hospital-Rikshospitalet, Oslo, Norway; [3]Dept. of Psychology, Univ. of Oslo, Oslo, Norway; [4]Service de Neurochirurgie, Hôpitaux Universitaires de Genève, Geneve, Switzerland; [5]Dept. of Neuropsychology, Helgeland Hosp., Mosjøen, Norway

Abstract: Orbitofrontal cortex (OFC) is implicated in multiple cognitive processes including inhibitory control, context memory, recency-judgment, and choice behavior. Despite an emerging understanding of the role of OFC in memory and executive control, its necessity for core working memory (WM) operations remains understudied. Therefore, we assessed the impact of OFC damage during a Recent Probes task (RPT) where subjects are asked to memorize a set of five letters and to indicate whether a probe letter was presented in set. Four conditions were created according to the response (yes / no) and the recency of the probe (presented in the previous trial set / in the current one). We compared behavioral and EEG responses between healthy subjects and patients with focal bilateral OFC damage (n=14). Even though OFC patients had prolonged reaction times to probes compared to controls across all conditions, the two groups showed the same core RPT recency pattern of slower response latency when the probe was presented in the previous trial. The within-group electrophysiological results showed no condition difference during letters encoding and maintenance. Indeed, the cluster-based permutation F-test made over the visual ERPs elicited by the visual presentation of the letters and over the four second of retention did not show significant cluster. In contrast, the same

analysis made over the ERPs observed after probe presentation showed distinct condition by group effects. Condition differences for controls occurred within the same time window (300-500 ms after probe presentation) and were observed in two distinct spatial clusters including right centro-posterior and left frontal electrodes, respectively. Both clusters showed ERPs difference elicited by the response effect and one cluster was also sensitive to the recency manipulation. Condition differences for the OFC group involved two other clusters, both encompassing only left hemisphere electrodes and occurring during two consecutive time windows (345-463 ms and 565-710 ms). Both clusters were sensitive to the response effect, but no recency effect was found despite the behavioral recency effect. Although the groups had different electrophysiological response, the maintenance of letters in WM, the evaluation of the context of the probe, and the decision to accept or reject a probed letter were preserved in our patient cohort. The results suggest that neural re-organization may contribute to intact response and recency judgment after OFC damage.

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Poster

791. Human Working Memory: Mechanisms II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 791.11/BB83

Topic: H.02. Human Cognition and Behavior

Title: Local DLPFC network causal measures predict working memory load

Authors: *D. P. DARROW[1], C. SAIOTE[1], A. HERMAN[1], Z. SHA[1], T. HENRY[1], M. C. PARK[2];
[2]Neurosurg., [1]Univ. of Minnesota, Minneapolis, MN

Abstract: Introduction: Working memory has been studied as a paradigm using EEG and fMRI. Frontal and parietal cortices have been identified as playing the most significant role underlying the neural basis for working memory centered on the prefrontal cortex. No intracranial studies in humans have reported on the spatial or temporal features associated with the N-back, a common working memory task. We evaluated the electrocortical event-related potentials and spectral activity during the N-back task during invasive recordings.
Methods: Four patients with pharmacoresistant epilepsy undergoing surgery for seizure localization completed N-back tasks with randomized degrees of load (0-, 1-, 2-, and 3-back) during a ten day stay in the epilepsy monitoring unit in a randomized order. Evoked-related potentials and spectral analysis were performed on a block-by-block basis.
Results: More than 800 individual time-locked epochs were completed by each patient resulting

in more than 48 blocks of 0-, 1-, 2-, or 3-back in equal proportions. Electrodes provided coverage over the medial and lateral prefrontal cortex, orbitofrontal cortex, hippocampus, and lateral temporal lobe in all patients. ERP analysis (permutation testing, cluster-based multiple comparison correction, $p<0.025$) revealed functionally selective effects of N-back load in the prefrontal cortex corresponding to DLPFC, and large but undifferentiated ERPs in the hippocampus. Spectral analysis revealed specific patterns of increased alpha/beta and gamma activity in prefrontal electrodes near the DLPFC with gradient representation of increasing back. Cross-validated SVM classification accuracies for task vs. baseline and load were found to be significantly above chance ($p < 0.0001$). Conclusion: We report analysis from the first intracranial recordings during the N-back working memory task. We found significant regional specificity for the task in the prefrontal cortex with task-dependent spectral differences most significant in gamma and alpha/beta bands. Event related potentials also demonstrated load specificity within the prefrontal cortex while large evoked-responses in the hippocampus dominated changes when compared to baseline.

Disclosures: **D.P. Darrow:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Abbot. **C. Saiote:** None. **A. Herman:** None. **Z. Sha:** None. **T. Henry:** None. **M.C. Park:** None.

Poster

791. Human Working Memory: Mechanisms II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 791.12/BB84

Topic: H.02. Human Cognition and Behavior

Support: Stony Brook University

Title: Spatial working memory precision across eccentricity and time

Authors: *L. JIANG, A. TSEGAI-MOORE, Y. LIU, H.-C. LEUNG;
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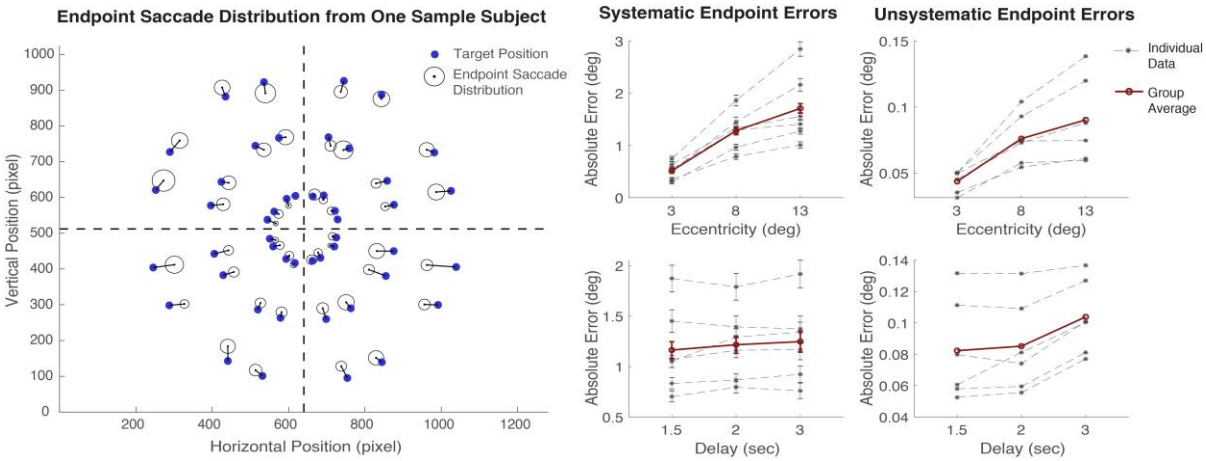
Abstract: How accurately target locations are represented and maintained in working memory remains unclear. Previous neurophysiology studies found weak or no clear topographic organization of spatial working memory representation in higher order regions, such as dorsolateral prefrontal cortex, while behavioral studies suggested both foveally-directed and quadrant-centered spatial distortions in the reproduction of spatial working memory. As most previous studies examined spatial working memory in one dimension (with targets arranged along a circle), the nature of working memory distortion across two-dimensional (2D) space remains to be determined. Here, we conducted a memory-guided saccade experiment to examine the variation in precision of spatial working memory recall across 2D space by varying target

eccentricity (3 to 13 degrees of visual angle) and delay duration (1.5 to 3 sec). Eye position was monitored and recorded from 6 participants. We calculated both systematic and unsystematic error of endpoint saccade to the to-be-remembered target location across trials for each individual. The figure shows the endpoint saccade distribution from a sample subject, and the systematic and unsystematic errors of individual data and group average. We found increases in both types of recall error with increasing target eccentricity, while only unsystematic error increases with increasing delay. Individual differences in both radial and angular bias of endpoint saccade were evident, though more participants showed memory-guided saccade biased toward the center of the quadrant and toward the fovea. Taken together, these findings indicate a reduced spatial working memory precision with increasing eccentricity and retention interval, suggesting the heterogeneity of working memory representation across space and time.



Disclosures: **L. Jiang:** None. **A. Tsegai-moore:** None. **Y. Liu:** None. **H. Leung:** None.

Poster

791. Human Working Memory: Mechanisms II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 791.13/BB85

Topic: H.02. Human Cognition and Behavior

Support: BFU2015-65315-R
RTI2018-094190-B-I00
SGR14-1265
SGR17-1565

Title: Parametric modulation of distractor filtering in visuospatial working memory

Authors: *D. BESTUE[1], A. COMPTE[1], T. KLINGBERG[2], R. ALMEIDA[3];
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[3]Stockholm Univ., Stockholm, Sweden

Abstract: Although distractor filtering is a fundamental component of working memory (WM), there are not many tasks where distractors are parametrically modulated both in the temporal and the similarity domain. Here, 21 subjects participated in a WM task where distractors could be presented prospectively or retrospectively at two different delay times (0.2 and 7s). Moreover, distractors were presented close or far away from the target. As expected, changes in the temporal and the similarity domain induced different distraction behaviours. In the similarity domain, we observed that close-by distractors induced an attractive bias while far distractors induced a repulsive one. Interestingly, this pattern of biases occurred both for prospective and retrospective distractors, suggesting common mechanisms of interference with the relevant target. This result is in line with a previously validated bump-attractor model where diffusing bumps of neural activity attract or repel each other in the delay period (Almeida et al, 2015). In the temporal domain, we found a stronger effect for prospective distractors and short delays (0.2s). As our experiment consisted of consecutive trials, we analyzed the effect of previous targets on current trial responses, or serial effects, showing that previous relevant information biased behaviour in a similar way as distractors did. The storage of irrelevant information reflected in different interference behaviours motivated an fMRI (3T) experiment to explore the storage of relevant (target), previously relevant (serial effects) and irrelevant (distractors) information in 3 candidate ROIs: visual cortex, IPS and PFC. Based on previous studies where sensory areas were not resistant to distractors (Bettencourt and Xu, 2016), we hypothesized that visual cortex would represent all stimuli while associative areas like IPS and PFC would subserve memory function in different ways for the increasingly relevant information. We test this by mapping parametric behavioral outputs to neurophysiological readouts (Ester et al, 2015) for the different distractor conditions and we explore the brain mechanisms storing information with increasing behavioural relevance. Taken together, our study opens the door to an integrative model of WM where different neural mechanisms and multiple brain regions are incorporated.

Disclosures: D. Bestue: None. **A. Compte:** None. **T. Klingberg:** None. **R. Almeida:** None.

Poster

791. Human Working Memory: Mechanisms II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 791.14/CC1

Topic: H.02. Human Cognition and Behavior

Support: NIMH R01-MH101478

Title: A non-monotonic relationship between working memory capacity and load-related increases in brain activity

Authors: *C. R. WALSH[1], J.-B. POCHON[2], K. D. ENRIQUEZ[2], H. TRUONG[2], A. LENARTOWICZ[2], S. K. LOO[2], C. A. SUGAR[2], C. E. BEARDEN[1,2], R. M. BILDER[1,2], J. RISSMAN[1,2];
[1]Dept. of Psychology, [2]Dept. of Psychiatry and Biobehavioral Sci., UCLA, Los Angeles, CA

Abstract: One fruitful functional neuroimaging approach for identifying regions involved in working memory (WM) has been to vary the number of to-be-maintained items and examine the degree to which activity increases as storage demands increase. Studies using delayed-match-to-sample paradigms are capable of isolating WM load effects during the encoding, maintenance, and response phases of a working memory trial. Whereas prior fMRI investigations have focused on documenting which brain regions exhibit load-dependent changes in brain activity, few studies have examined the relationship between individual differences in WM capacity and the expression of these WM load effects. In the present study, we collected an extensive battery of behavioral measurements of WM capacity from a large sample (N=170) of adult participants, who also underwent fMRI scanning while performing a delayed face recognition task. Each trial of the fMRI task involved the encoding of one face (low load) or three faces (high load), which needed to be maintained across a 7.5 s delay period followed by a match/nonmatch discrimination. General linear model analysis identified sets of prefrontal and parietal lobe regions exhibiting significant load-related increases during each task phase. We then split our sample into three groups (Low, Medium, and High Capacity) based on a composite measure of WM ability derived across ten behavioral tasks. When examining WM load effects across these subject groups, a striking pattern emerged. During the task phases when stimuli were present (i.e. encoding and probe phase), the magnitude of load effects increased markedly from Low Capacity to Medium Capacity subjects and then plateaued for High Capacity subjects. But during the maintenance phase (i.e. the delay period), we observed an inverted U-shaped relationship, such that Medium Capacity subjects showed greater load effects than either Low Capacity or High Capacity subjects. This pattern was highly consistent across regions, and suggests the search for strictly monotonic relationships between capacity and brain activity may be misguided. Low Capacity subjects may be unable to adequately increase frontoparietal delay period activity when challenged with high load, whereas High Capacity subjects may accomplish high load maintenance without the need for substantially elevated delay period activity. In contrast, the Medium Capacity subjects were the ones who engaged the most sustained activity of frontoparietal regions to succeed. Better understanding the nature of this relationship may support Research Domains Criteria (RDoC) efforts to relate neurocognitive markers of WM capacity to psychopathology.

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Poster

791. Human Working Memory: Mechanisms II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 791.15/DP14/CC2

ControlExtraData.DynamicPosterDisplay:
Dynamic Poster
Topic: H.02. Human Cognition and Behavior

Title: Neural systems supporting flexible top-down control over the priority of working memory representations

Authors: *J. M. SCIMECA, L. K. ROSS, M. D'ESPOSITO;
UC Berkeley, Berkeley, CA

Abstract: Control processes that can prioritize goal-relevant information in memory are critical to successful WM performance. However, the capacity, costs, and mechanisms of controlling priority within WM remain unclear and contentious. To address these gaps, we used semantic retrospective cues (retrocues) to indicate multiple high-priority items maintained in WM and assessed performance with a novel two-probe paradigm. First, we found converging evidence from behavior and computational modeling experiments that participants (N=136) can use semantic retrocues to prioritize multiple items in memory. We show that prioritization incurs clear costs to non-prioritized items, and that mnemonic prioritization is dissociable from task set preparation and spatial attention. These findings challenge recent theories proposing cost-free prioritization and a focus of internal attention with a one-item capacity, and instead suggest a flexible trade-off in priority between mnemonic representations that is under top-down control. Next, we used fMRI (N=20) to characterize the neural systems that support flexible prioritization within WM and to address ongoing debates regarding the contributions of frontoparietal (FP) and cingulo-opercular (CO) regions to mnemonic control. We first compared retrocue trials to neutral cue trials to identify transient activity at the retrocue versus sustained activity during the subsequent delay period. We found that both FP and CO regions are transiently recruited by retrocues. In contrast, sustained delay-period activity is reduced in CO regions following retrocues relative to neutral cues. There was differential recruitment of FP region when prioritizing items based on spatial versus non-spatial features, which occurred transiently at the retrocue and did not persist throughout the delay. However, there were persistent differences in visual sensory cortices when prioritizing a subset of items. Together, these findings support a model in which both FP and CO networks support an internally-directed attentional control process that can dynamically bias mnemonic representations in sensory cortices in favor of multiple high-priority items, and suggest that this selective bias is initiated by transient top-down control signals from frontoparietal regions.

Disclosures: **J.M. Scimeca:** None. **L.K. Ross:** None. **M. D'Esposito:** None.

Poster

791. Human Working Memory: Mechanisms II

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Topic: H.02. Human Cognition and Behavior

Support: NIH R01-EY019882
NIH R01-EY025275
NIH R01-MH110378
NIH P30-EY08126
NIH T32-EY007135

Title: Alpha-band activity finely tracks remembered locations within a visual hemifield

Authors: *D. W. SUTTERER, G. F. WOODMAN;
Psychology, Vanderbilt Univ., Nashville, TN

Abstract: Recent work (Foster et al., 2016, Sutterer et al., 2018) has shown that the topography of EEG alpha-band activity can be used to track remembered locations of objects. The locations in these demonstrations were presented around central fixation, and a well-known characteristic of alpha-band activity is that alpha power decreases contralateral to remembered stimuli and increases ipsilateral to remembered stimuli. Thus, an open question is whether tracking of remembered locations reflects relatively crude differences in alpha-band power across cerebral hemispheres or if alpha-band activity can more finely track remembered locations within a visual hemifield. To answer this question, we used a lateralized spatial estimation task and presented stimuli in a single hemifield (e.g., the left visual field). Human observers maintained fixation while remembering the location of one or two colored dots (blue or green) presented to the left of fixation. Dots were presented on a circle (radius of 4 degrees of visual angle) that was centered 6 degrees of visual angle to the left of fixation. We reasoned that if the large-scale difference of alpha-band responses across hemispheres enables tracking of remembered locations, we would be unable to track the precise location of each stimulus when stimuli were presented in a single hemifield. Alternatively, if alpha-band activity patterns can more finely track remembered locations, we would be able to track remembered locations even when they were presented in a single hemifield. By applying an inverted encoding model (IEM) to the topography of alpha-band activity on the scalp, we found that we were able to successfully estimate remembered locations for both one and two-item trials. In addition, we found that we could train the IEM on one-item trials and successfully recover the remembered location on two-item trials, suggesting that the format of alpha-band representations is similar when multiple items are maintained.

Together these results provide evidence that alpha-band activity tracks the precise location held in mind.

Disclosures: D.W. Sutterer: None. **G.F. Woodman:** None.

Poster

791. Human Working Memory: Mechanisms II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 791.17/CC4

Topic: H.02. Human Cognition and Behavior

Support: NIH R01-EY025648 (JG)
Alfred P. Sloan (JG)
NSF BCS-1632296 (AL)

Title: Competition between similar visual working memory items produces repulsion effects

Authors: *P. S. SCOTTI, Y. HONG, A. B. LEBER, J. D. GOLOMB;
Dept of Psychology, Ohio State Univ., Columbus, OH

Abstract: Competition between items in visual working memory results in poorer memory performance (Ahmad et al., 2017; Lewis-Peacock & Norman, 2014). Here we consider a particular type of memory error where subjects report a memory feature biased away from a reference or nontarget feature (e.g., reporting bluish-purple when presented with a purple target and red distractor). These repulsion effects have been well-established in visual working memory (e.g., Bae & Luck, 2017; Golomb, 2015; Golomb, L'Heureux, & Kanwisher, 2014) but theoretical accounts are debated. In a series of behavioral experiments, we consider an active competition framework where concurrent processing of working memory contents leads to increased reliance on relational information, such that memory items close in feature space become more distinct with increased competition. On each trial, subjects were instructed to simultaneously study two real-world objects for 1 second followed by a brief blank delay, and were then asked to report the color of one of the objects. The blank delay between study and test was 1 or 3 seconds, randomly intermixed. Repulsion effects were stronger for the 3-second compared to the 1-second condition. In a second experiment, we explored why repulsion was stronger at a longer delay. In addition to the 3-second blank delay condition, we tested another condition where, following a 1-second blank delay, a 2-second filler task was presented where subjects made a size judgment on two different objects. Hence, both conditions posed the exact same temporal delay between study and test, with the only difference being that the filler task was expected to disrupt the processing of the memory items and therefore interfere with active competition-based processes. Repulsion was indeed weaker for filler task trials compared to non-filler task trials. These results suggest that repulsion cannot be explained by temporal decay

(Barrouillet, De Paepe, & Langerock, 2012) or memory strength (Chunharas, Rademaker, Brady, & Serences, 2019). We suggest that an active competition framework can explain repulsion, a framework amenable to the neural processes of lateral inhibition (Johnson, Spencer, Luck, & Schöner, 2009) or off-target neuron tuning (Navalpakkam & Itti, 2007).

Disclosures: P.S. Scotti: None. **Y. Hong:** None. **A.B. Leber:** None. **J.D. Golomb:** None.

Poster

791. Human Working Memory: Mechanisms II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 791.18/CC5

Topic: H.02. Human Cognition and Behavior

Title: Decoding stimulus-specific features and task rule from the TMS-evoked response during a visual working memory task in humans

Authors: *M. WIDHALM[1], J. SAMAHA[2], N. ROSE[1];
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Abstract: Research has shown evidence for the reactivation of latent representations in working memory (WM) with transcranial magnetic stimulation (TMS) and simultaneously-recorded EEG (Rose et al., 2016, *Science*). The present study extends this work by examining the representational substrates of both stimulus-specific features and task rules in the retention and reactivation of latent WM.
First, we localized the TMS target site by applying single pulse (sp) TMS to left V1/V2 to localize phosphenes in the lower right visual field for each participant. In the ensuing WM task, one oriented grating was presented at the location of that individual's phosphene and another was presented in the opposite (left) hemifield at the same angle and distance from central fixation. These gratings were to be retained with two retro-cues and two recognition probes on each trial, such that one grating would be attended and the other unattended following each retro-cue. During the delay period following each cue, spTMS was applied to the retinotopically-localized site in left V1/V2 at 110% of phosphene threshold to target the sensory representation and assess direct effects on items presented in the right vs. left hemifield.
We used inverted encoding models to reveal if the specific orientation of the latent memory items could be reconstructed from the TMS-evoked response on simultaneously recorded EEG. Reconstruction was conducted using voltage from posterior channels that were contralateral to item presentation (i.e. left posterior channels for items presented on the right). While we found no reconstruction for the item on the left, the item on the right – which was directly targeted by TMS – showed robust reconstruction. This finding was replicated in a second experiment on different subjects. The second experiment also extended our findings by adding a DLPFC stimulation condition to allow comparison of stimulation site. A logistic regression classifier

trained and tested on delay period EEG was able to decode the task rule (attend left vs. right) using spectral power changes evoked before, during, and after both occipital and DLPFC TMS. In sum, not only can task rule be decoded from neural activity during the delay period of a visual working memory task, but TMS of retinotopic visual cortex also allows for reconstruction of stimulus-specific features.

Disclosures: **M. Widhalm:** None. **J. Samaha:** None. **N. Rose:** None.

Poster

791. Human Working Memory: Mechanisms II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 791.19/CC6

Topic: H.02. Human Cognition and Behavior

Support: ONR MURI (MURI N00014-16-1-2832)
NIMH grant (R01 MH111737)

Title: Information dynamics of input gating and output gating in visual working memory

Authors: *E. J. LEVIN, D. BADRE;
Cognitive, Linguistic, and Psychological Sci., Brown Univ., Providence, RI

Abstract: Visual working memory is a capacity-limited system that requires control processes to manage what information enters memory and to select what information guides a response. These control mechanisms are often conceptualized as gates, allowing transfer of information into or out of memory when the gate is open and prohibiting transfer when it is closed. Gating mechanisms are also important because they mediate the balance between the predicted utility of an item and our limited memory capacity (Chatham and Badre, 2013). For example, input gating proactively updates information to memory that is relevant (high priority) and filters information that is irrelevant (low priority). Output gating manages the contents of memory when relevance is known after encoding. The present experiment investigated whether the information content of working memory differs between input gating and output gating, and depending on the priority of items for the task. Participants performed a modified gating task previously developed by our laboratory (Chatham et al., 2014) across two fMRI sessions. In this task, participants had to maintain one or two orientation gratings over one or two delay periods, respectively. Participants were also presented with a higher-order context-cue that indicated which of the two orientations was relevant. This context-cue could either come first, putting task demands on input gating, or last, putting task demands on output gating. We then used an inverted encoding model (IEM) to assess the population-level tuning responses of working memory representations during input gating events and during output gating events in visual cortex (V1 and V2). We were able to reconstruct the orientation during the perceptual event as well as when the orientation was being

maintained over the delay period for both input gating and output gating events. We found that the reconstructions of relevant items in input gating conditions were narrower than the reconstructions for distractor items in input gating conditions, indicating better precision for the item that was higher priority. Further, we observed that items being maintained during output gating trials, in which the relevance was unknown, were reconstructed at a medium level of precision between the levels of high and low priority items. These results suggest that the precision of information held in working memory tracks priority, with higher-priority items maintained with more precision, and lower-priority items maintained with less precision.

Disclosures: E.J. Levin: None. **D. Badre:** None.

Poster

791. Human Working Memory: Mechanisms II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

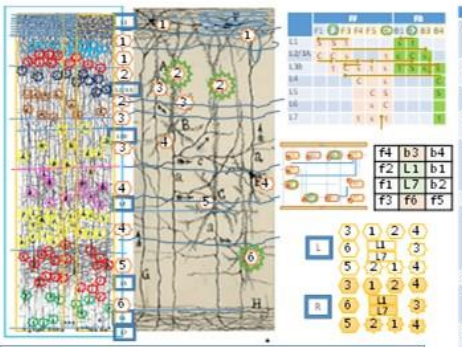
Program #/Poster #: 791.20/DP13/CC7

ControlExtraData.DynamicPosterDisplay:
Dynamic Poster
Topic: H.02. Human Cognition and Behavior

Title: Nematode and human brain architecture

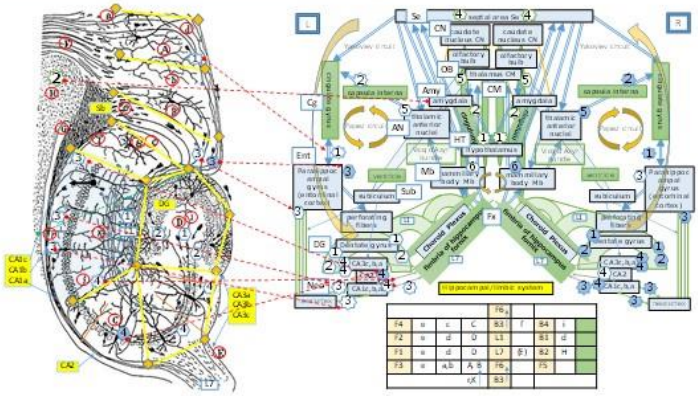
Authors: *M. OBAYASHI;
Metacube Co.,Ltd., Tokyo, Japan

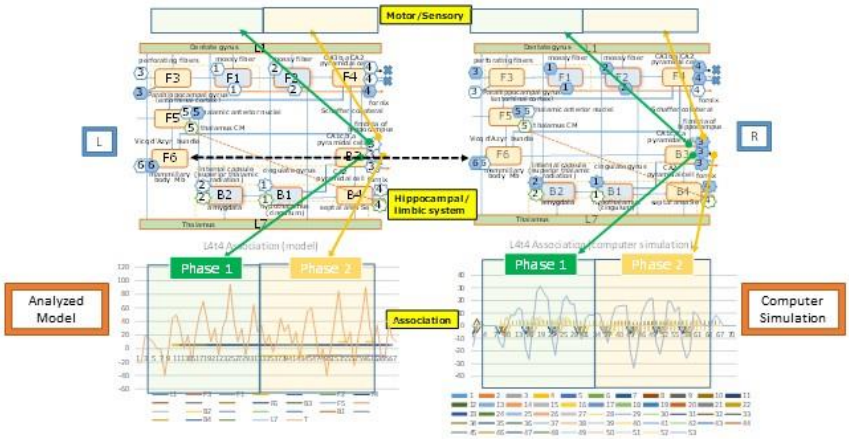
Abstract: A constitutive and theoretical model (hypothesis) of the brain, based on data for the nematode *Caenorhabditis elegans* as a model organism, is presented. Analysis of the nerve cell sketch of the hippocampus and cerebral cortex column by Ramón y Cajal is performed in detail, identifying each element of the neuron and glial cell in the core unit. In the memory model of the core circuit, the memory associated with time and space is dispersed and stored in the core circuit of the associative area and the motor/sensory area, spreading to the cerebral cortex. The memory determines whether or not the stimulus from the sensory neuron of the current sensor is similar to that of the past, and, as a whole, a pattern similar to the past memory is reproduced. At this time, the core circuit serves as a multilayered storage device (hierarchical associative memory), and can hold memory that recognizes time. As a result, the mechanism by which the hippocampal function synchronizes the firing patterns of neurons in the brain has been clarified. To date, it has been considered that *C. elegans* does not possess a central nervous system similar to the human brain structure. However, analysis of the *C. elegans* data from the viewpoint of the core circuit model suggests that the neural circuit is the basis of the human neural circuit, and it is presumed that all elements are retained and homologous. The findings strongly suggest that these structures are homologous between nematodes and humans, and are common in biological systems with brain framework.



	Assumed role
L1	Body of hierarchical memory (capture time series firing pattern of input F3) : Identify the firing level of layer.
L7	Body of inter-connective memory between L4t4 circuits
F3	Projection input (sensor neuron) : Associate time series firing patterns.
F1	Interneuron (maintains firing state of input F3 in short term)
F2	Interneuron (become familiar with inhibitory neuron) : Internal sync signal control : Phase adjustment in operation cycle
F4	Projection output (depending on F3, L1, F1, F2)
F5	Input from homogeneous neuron group (thalamus etc.) : As the origin of the indirect pathway. F5 has a role of quantitatively transmitting the firing status of F4 and B4 (of the previous phase) to B2.
F6	Clock input for synchronization
B2	Interneuron (amygdala etc.) : Internal sync signal control : Phase adjustment in operation cycle
B1	Interneuron (output adjustment) : Chemical adjustment for B4, etc.
B3	Clock output for synchronization
B4	Projection output (depending on L1, F5, B2, B1; which affected neighboring firing pattern)

FIG-1. Core unit L4t4 circuit





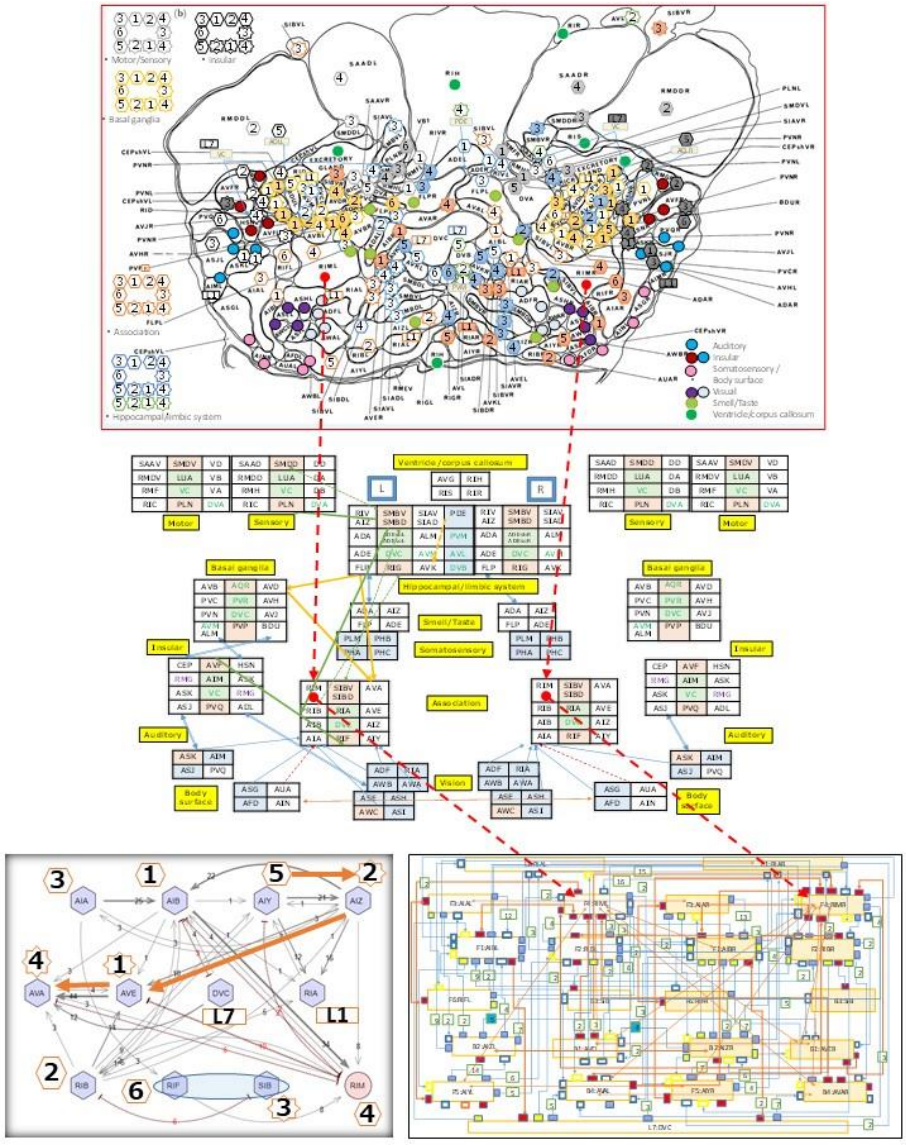


FIG-2. C. elegans mapping analysis

Disclosures: M. Obayashi: None.

Poster

792. Cognitive Aging II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 792.01/CC8

Topic: H.02. Human Cognition and Behavior

Support: DGAPA PAPIIT IG300608

Title: Factors that predict working memory maintenance and decline in older adults

Authors: *S. CANSINO[1], F. TORRES-TREJO[1], C. ESTRADA-MANILLA[1], M. PÉREZ-LOYDA[1], L. RAMÍREZ-BARAJAS[1], M. HERNÁNDEZ-LADRÓN-DEGUEVARA[1], A. NAVA-CHAPARRO[1], S. RUIZ-VELASCO[2];
[1]Lab. NeuroCognition, Nat Autonomous Univ. of Mexico, Mexico City, Mexico; [2]Applied Mathematics and Systems Res. Institute, Nat Autonomous Univ. of Mexico, Mexico City, Mexico

Abstract: The aging process is associated with the gradual decline of several cognitive functions, and working memory is particularly affected. Although the majority of older adults experience a deterioration of their working memory, some individuals maintain their working memory in older age and some suffer an extreme deterioration of their working memory. The purpose of the present study was to identify, among a total of 120 potential predictors, those that significantly contributed to these two extreme outcomes in working memory. A sample of 588 healthy adults was examined with the n-back task in the spatial and verbal domains using a 2-back level of difficulty. Individuals were classified as working memory maintainers or decliners if their discrimination level in the two domains was superior to the 80th percentile or inferior to the 20th percentile, respectively. The study is exploratory because as any cross-sectional experiment, the causal influence of the variables in the model cannot be confirmed. Logistic regression identified eight and six significant predictors of working memory maintenance and decline, respectively. High vocabulary scores and smoking more were significant predictors of working memory maintenance; however, in the opposite direction, these same variables predicted working memory decline. Both logistic models revealed that having a healthy cardiovascular system is an essential condition for preserving cerebrovascular functioning and, consequently, working memory. In the working memory maintenance model, lack of hypertension, lower consumption of cholesterol and moderate alcohol intake support this conclusion, while in the working memory decline model, decline is based on higher consumption of myristic acid. Another relevant consumption habit that predicted working memory decline was a lower consumption of vitamin D, which has a direct influence on brain areas supporting memory functions. Psychological traits and everyday activities were present in both models. We identified specific predictors involved in extreme an uncommon working memory performance in older age.

Disclosures: S. Cansino: None. **F. Torres-Trejo:** None. **C. Estrada-Manilla:** None. **M. Pérez-Loyda:** None. **L. Ramírez-Barajas:** None. **M. Hernández-Ladrón-deGuevara:** None. **A. Nava-Chaparro:** None. **S. Ruiz-Velasco:** None.

Poster

792. Cognitive Aging II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 792.02/CC9

Topic: H.02. Human Cognition and Behavior

Support: JSPS Grant-in-Aid for Scientific Research S 16H06325

Title: Musical instrument practice program improves verbal memory and neural efficiency in novice older adults

Authors: *X. GUO[1], M. YAMASHITA[2], M. SUZUKI[4], C. OHSAWA[5], K. ASANO[3], N. ABE[3], K. SEKIYAMA[2];
[1]Grad. Sch. of Social and Cultural Sci., Kumamoto Univ., Kumamoto, Japan; [2]Sch. of Integrated Advanced Studies in Human Survivability, Kyoto Univ., Kyoto-Shi, Japan; [3]Kokoro Res. Ctr., Kyoto Univ., Kyoto, Japan; [4]Dept. of Behavioral Neurol. and Neuropsychiatry, Osaka Univ., Suita, Japan; [5]Sch. of Music, Mukogawa Women's Univ., Nishinomiya, Japan

Abstract: Recent studies have reported that piano practice may improve cognitive function of older adults. However few studies on older adults have investigated the influence of instrumental practicing on neural efficiency during cognitive tasks. In addition, our previous study showed that playing keyboard harmonica might be beneficial to verbal memory of older adults. Therefore, in this study, we conducted a randomized controlled trial to further investigate the effects of musical instrument practice program using keyboard harmonica on cognitive functions and neural efficiency in older adults. Fifty-three musically naive healthy older adults (ages 61-85) were assigned to either the intervention group (n = 27), which received a 4-month keyboard harmonica classes or an untrained control group (n = 26). Cognitive measurements, and the brain activity (measured by functional magnetic resonance imaging) during a visual working memory task were administered before and after the intervention in both groups. Our results showed that intervention group significantly improved performance on the logical memory II test (a measure of delayed recall) as compared to control group. Moreover, after the 4-month intervention, the intervention group showed a reduction in brain activation in the middle frontal gyrus and superior parietal lobule, indicating less effort for the visual working memory task. Such intervention effects, increased neural efficiency together with improved memory performance, were consistent with the previous research on effects of multitask exercise intervention.

Disclosures: X. Guo: None. **M. Yamashita:** None. **M. Suzuki:** None. **C. Ohsawa:** None. **K. Asano:** None. **N. Abe:** None. **K. Sekiyama:** None.

Poster

792. Cognitive Aging II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 792.03/CC10

Topic: H.02. Human Cognition and Behavior

Support: Medel

Title: Cognitive performance of severely hearing-impaired older adults before and after cochlear implantation

Authors: *V. VAN ROMPAEY, E. ANDRIES, A. GILLES, V. TOPSAKAL, P. VAN DE HEYNING, G. MERTENS;
Antwerp Univ. Hosp., Edegem, Belgium

Abstract: Objective: To evaluate cognitive change in severely hearing-impaired older adults after cochlear implantation.
Study Design: Prospective, longitudinal cohort study with assessments before, and at 6 and 12 months after implantation.
Patients: Twenty older adults (median age: 71.5 yr).
Main Outcome Measures: Change in the Repeatable Battery for the Assessment of Neuropsychological Status for Hearing-impaired individuals (RBANS-H) total score and subdomain scores were used to assess cognitive evolution. In addition, change in best-aided speech audiometry in quiet (monosyllabic words) and in noise (Leuven Intelligibility Sentences Test [LIST]) was examined, as well as patient- reported measures of health-related quality of life (Nijmegen Cochlear Implant Questionnaire [NCIQ]), self-perceived hearing disability (Speech, Spatial, and Qualities of hearing Scale—12 [SSQ12]), sound quality (Hearing Implant Sound Quality Index—19 [HISQUI19]), and states of anxiety and depression (Hospital Anxiety and Depression Scale [HADS]).
Results: The RBANS-H total scores improved significantly after 12 months cochlear implant (CI) usage ($p < 0.001$). At subdomain level, significant improvements were observed in the immediate and delayed memory domain ($p < 0.005$ and $p < 0.002$, respectively), and to a lesser extent also in the attention domain ($p < 0.047$). Furthermore, speech perception in quiet and in noise improved significantly after 6 months and remained stable after 12 months. Similarly, a significant improvement was observed on all patient-reported measures after 6 months of CI usage. These results remained stable after 12 months, except for the HADS.
Conclusions: A significant improvement in overall cognition after 12 months of CI usage was established. However, future research is imperative to further disentangle possible practice effects from the effects of the cochlear implantation. The significant, positive effect of cochlear implantation on speech perception and patient-reported measures was confirmed.

Disclosures: **V. Van Rompaey:** 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.; Otonomy, Auris Medical, Medel. F. Consulting Fees (e.g., advisory boards); Cochlear. **G. Mertens:** 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.; Medel. **V. Topsakal:** 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.; Medel. **P. Van de Heyning:** 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.; Medel, Auris Medical. **E. Andries:** 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.; Medel. **A. Gilles:** None.

Poster

792. Cognitive Aging II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 792.04/CC11

Topic: H.02. Human Cognition and Behavior

Support: National Science Fund for Distinguished Young Scholars Grant 81625025
State Key Program of National Natural Science of China Grant 81430100
Fundamental Research Funds for the Central Universities Grant 2017XTCX04

Title: Reconfiguration of frontoparital and default network related to working memory aging

Authors: *C. YANG, J. FAN, C. LIU, J. XIA, Z. ZHANG;
State Key Lab. of Cognitive Neurosci. and Learning, Beijing Normal Univ., Beijing, China

Abstract: The human brain is well organized into a set of functionally specific networks to support higher cognitive operations and daily behaviors. Of these networks, the frontoparietal network (FPN) and the default network (DN) have been found to play crucial roles in working memory (WM), involving regions like dorsolateral prefrontal cortex (DLPFC), middle frontal gyrus (MFG), superior and inferior parietal gyrus (SPL/IPL) and precuneus as well as cingulate cortices (Anticevic et al., 2012; Rottschy et al., 2012). However, little is known about how the FPN and DN, as well as their interactions, are functionally linked to WM in old age. Thus, we have acquired N-Back WM task fMRI data (TR = 2s, TE = 30ms, 3mm voxel) from a community-based cohort of 273 old individuals (aged from 45 to 86, 121 females), and the task-

induced BOLD signals were processed with the approach of background connectivity to remove task-evoked activity (Al-Aidroos et al., 2012; Norman-Haignere et al., 2012), resulting a task state-related WM activity. We then defined FPN and DN based on Power's 264 atlas (Power et al., 2011), and estimated the within- and between-network background functional connectivity (bFC) through Pearson's correlations. The age-related alterations of bFC strength were explored with network-based statistic (NBS) (Zalesky et al., 2010), and their relationships to WM performance were evaluated by connectome-based predictive modeling (CPM) (Shen et al., 2017). Here, we observed widespread age-related decrease of bFC strength within both FPN and DN (FDR corrected $p < 0.05$), and but only bFCs identified within FPN could significantly predict individual WM accuracy rate ($r = 0.1867$, $p = 0.0018$, 5000 permutations). Furthermore, we also found age-related increase of bFC strength between these two networks (FDR corrected $p < 0.05$), mainly connecting brain regions like MFG, IFG, angular gyrus (AG) and medial superior frontal gyrus (mSFG), and when combined with the within-network bFCs in FPN and DN, the between-network bFCs could also predict WM performance ($r = 0.1825$, $p = 0.0023$, 5000 permutations). Taken together, these results implicated the reconfiguration of FPN and DN, with age-related weaken within-network bFCs and enhanced between-network bFCs, and these alterations have been significantly associated with individual WM in old age.

Disclosures: **C. Yang:** None. **J. Fan:** None. **C. Liu:** None. **J. Xia:** None. **Z. Zhang:** None.

Poster

792. Cognitive Aging II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 792.05/CC12

Topic: H.02. Human Cognition and Behavior

Support: RF1AG039103

Title: Mean cortical thickness predicts cognitive change in healthy aging

Authors: ***M. HOU**, M. A. DE CHASTELAINE, B. E. DONLEY, M. D. RUGG;
Ctr. for Vital Longevity and the Sch. of Behavioral and Brain Sci., Univ. of Texas at Dallas, Dallas, TX

Abstract: Cortical thickness has been related to cognitive function in healthy older adults in prior research. However, relatively little is known about the relationship between cortical thickness and longitudinal change in cognitive function. In the present study, we investigated the relationship between baseline cortical thickness and cognitive change over 3 years in 50 healthy older adults. Participants (age range: 63 - 76, mean age: 67.9, 25 female) were administered a neuropsychological test battery at Session 1, and were re-tested on the same battery after one month (Session 2) and again after 3 years (Session 3). T1-weighted whole brain images were

acquired at Session 1. Test performance across sessions was reduced to four constructs - labeled Memory, Speed, Fluency and Crystallized IQ - based on a principal component analysis applied to a larger sample tested at Session 1. To control for practice effects, mean performance across sessions 1 and 2 served as the baseline for assessment of change at session 3. Over three years, older adults showed significantly decline in Speed but not in other constructs. Controlling for chronological age, mean cortical thickness was negatively correlated with longitudinal change in Memory and Crystallized IQ. In addition, thickness was positively correlated with baseline scores in Speed and Fluency. Further analysis indicated that the correlations between cortical thickness and longitudinal change, and between thickness and baseline scores, did not significantly differ across the different cognitive constructs. Consequently, cortical thickness was negatively correlated with a composite longitudinal change score, and was positively correlated with a composite baseline score. These results suggest that cortical thickness is not only predictive of cognitive performance in older adults, but is also predictive of short-term cognitive change in this population. Furthermore, mean cortical thickness appears to capture variance shared across different cognitive domains.

Disclosures: **M. Hou:** None. **M.A. De Chastelaine:** None. **B.E. Donley:** None. **M.D. Rugg:** None.

Poster

792. Cognitive Aging II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 792.06/CC13

Topic: H.02. Human Cognition and Behavior

Support: NIH-NIDDK R01DK103902
Novo Nordisk, Inc.
Medtronics Inc.

Title: Dual task gait speed modifies the association between cardiovascular risk and visuospatial working memory in older adults

Authors: ***S. BUSS**[1], L. APONTE-BECERRA[1], J. TREVINO[1], R. E. MCGLINCHEY[2], C. B. FORTIER[2], V.-A. LIOUTAS[1], P. NOVAK[3], C. MANTZOROS[1], L. NGO[1], V. NOVAK[1]; [1]Beth Israel Deaconess Med., Boston, MA; [2]Geriatric Res, Educ, and Clin. Ctr. & Translational Res. Ctr. for TBI & Stress, VA Boston Healthcare Syst., Boston, MA; [3]Brigham and Women's Hosp., Boston, MA

Abstract: Background: Cardiovascular disease is a major risk factor for cognitive dysfunction and dementia. Some older adults with cardiovascular comorbidities show greater susceptibility to cognitive decline than others. Walking speed predicts 5-year survival and cardiovascular

mortality. Dual task (DT) gait speed, measured while preforming a working memory task, is related to attention and executive function. We hypothesize that subjects with faster DT gait speed are less vulnerable to the effect of cardiovascular risk factors on cognition.
Objective: To test if DT gait speed modifies the relationship between cardiovascular risk factors and cognitive performance.
Methods: 190 older adults (Mean ± SD, age: 65.6 ± 9.0 years, gender: 50% female) participated in the study. Visuospatial working memory was evaluated using the Paired-Associated Learning (PAL; total errors adjusted) test. The Framingham Risk Score (FRS, %) was used to measure 10-year cardiovascular mortality risk. Gait speed was assessed during DT walking (m/s). A general linear model using SAS 9.4 tested the effect of FRS, DT gait speed, and their interaction on PAL. Participants were divided into quartiles based on DT gait speed. Within each quartile, separate linear models were used to test the association between FRS and PAL.
Results: Baseline characteristics were obtained for PAL errors (32.2 ± 21.3), FRS (17.2 ± 9.6; intermediate risk), and DT gait speed (1.1 ± 0.2). Higher PAL error score was associated with higher FRS (β=1.8, $p<0.0001$) and slower DT gait speed (β=-3.4, $p=0.0002$). The slowest DT walking quartile (range: 0.4-0.9) had higher FRS (20.1 ± 9.3) and more PAL errors (41.1 ± 23.0). Higher FRS is associated with more PAL errors in the lowest DT quartile (β=1.02, $p=0.003$), but not in the second, third, or fourth quartiles.
Conclusion: High cardiovascular risk and slow DT gait speed predicted more errors during a task of working memory. Faster walking speed during DT is associated with a smaller impact of cardiovascular risk factors on cognitive performance. DT gait speed has potential as a simple and objective physiologic metric of brain resilience in patients with cardiovascular risk factors.

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Poster

792. Cognitive Aging II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 792.07/CC14

Topic: H.02. Human Cognition and Behavior

Support: The Center on Health, Aging, and Disability pilot grant

Title: Theta, alpha, and beta band oscillations related to value-directed strategic processing in cognitively normal younger and older adults

Authors: *L. T. NGUYEN[1], S. A. SHENDE[2], F. MARINI[3], D. A. LLANO[1,4,5], R. A. MUDAR[1,2];
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Abstract: Strategic processing allows for value-based preferential encoding of information. It involves an interplay between selective attention to relevant information and inhibition of irrelevant information, both of which are known to decline with age. However, behavioral studies using value-directed recall have found that strategic processing remains relatively stable with age. Examining underlying neurophysiological processes linked to value-directed processing may better clarify the effects of age. The current study examined EEG-derived event-related spectral perturbation (ERSP) power differences between 21 younger adults (13F; mean age: 22.2 ± 1.2 years; mean education: 15.8 ± 1.1 years) and 21 older adults (16F; mean age: 63.2 ± 6.5 years; mean education: 16.8 ± 2.3 years) in theta (4-8 Hz), alpha (8-12 Hz), and beta (12-30 Hz) bands, related to processing of high- and low-value information in a value-directed strategic processing task. The task used five word lists, each with a unique set of high- and low-value words presented one at a time while EEG was recorded. Participants were instructed to recall as many words as possible after each list with the goal of maximizing their score. Behaviorally, younger and older adults recalled significantly more high- than low-value words for the five lists, showing that older adults engaged in strategic processing similar to younger adults. Neurally, parietal alpha and beta bands showed differences between processing of high- and low-value information, with desynchronized alpha power for high-value words, and synchronized alpha and beta power for low-value words. Group differences were observed in the alpha band, with greater synchronized power for low-value words in older compared to younger adults. No significant effects were seen for frontal theta power. These findings suggest that alpha and beta bands index selective attention to high-value words and inhibition of low-value words. Importantly, alpha band differences between groups for low-value information suggests early neural changes in normal cognitive aging are observed in inhibitory processes linked to strategic attention and these alterations are not pronounced enough to show behavioral consequences. Such ERSP measures may be valuable for detecting and characterizing early neural changes in pathological cognitive aging, such as mild cognitive impairment.

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Poster

792. Cognitive Aging II

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Program #/Poster #: 792.08/CC15

Topic: H.02. Human Cognition and Behavior

Support: VA Grant IK2RX000956
VA Grant I01RX002619
VA Grant IK2RX000744
VA Grant I50RX002358

Title: Impact of a 12-week aerobic exercise intervention on interhemispheric inhibition and motor control in sedentary older adults

Authors: *J. OMAR[1], J. R. NOCERA[2], M. R. BORICH[2], B. A. CROSSON[3], L. KRISHNAMURTHY[4], V. KRISHNAMURTHY[3], K. MAMMINO[4], K. M. MCGREGOR[3]; [1]Neurosci. and Behavioral Biol., [2]Dept. of Rehabil. Med., [3]Dept. of Neurol., Emory Univ., Atlanta, GA; [4]Atlanta VA Med. Ctr., Atlanta, GA

Abstract: Previous cross-sectional work has shown there to be a general pattern of decreased interhemispheric inhibition and increased bilateral activation during a unimanual motor task in sedentary older adults as compared to aerobically active adults. The current study aimed to examine the impact of a 12-week aerobic exercise intervention on relateralizing motor function to a single hemisphere in sedentary older adults. Twenty-four participants were randomized into an aerobic spin cycling exercise group or a non-aerobic balance training group. Participants completed a pre- and post-intervention battery of motor control tasks and a pre- and post-intervention cardiovascular fitness assessment (estimated VO2max). Magnetic resonance images were acquired prior to and after the intervention and a block-design, right-hand motor task was used to evaluate interhemispheric cortical activation patterns. The aerobic exercise group showed significant improvements in their cardiovascular fitness as compared to the balance group. A significant decrease in bilateral primary motor cortex (M1) activity was not observed between the aerobic exercise group and the balance group. It was observed that those who completed the aerobic exercise intervention showed less left M1 and supplementary motor area (SMA) activity as compared to those who completed the non-aerobic balance intervention. Significant differences in motor performance were not observed between the groups although there was a trend of improved motor performance for those in the aerobic exercise condition as compared to those in the balance condition. In conclusion, the current study provides preliminary evidence indicating that a 12-week aerobic exercise intervention has the potential to alter cortical activation patterns. The present work also provides evidence suggesting that these changes in cortical activation patterns may be associated with clinically relevant improvements in motor functioning. Additional work is needed to precisely characterize the differential changes in cortical activation patterns between the right (ipsilateral) and left (contralateral) primary motor cortices after an acute aerobic exercise intervention and the rehabilitative significance associated with those changes.

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Poster

792. Cognitive Aging II

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Program #/Poster #: 792.09/CC16

Topic: H.02. Human Cognition and Behavior

Support: Arizona Alzheimer's Consortium, Department of Health Services
Evelyn F. McKnight Foundation
National Science Foundation Fellowship

Title: Context-dependent memory in cognitively-normal older e4 carriers and non-carriers

Authors: *J. M. PALMER[1,2], A. V. LAWRENCE[1,2], M. D. GRILLI[1,2], M. J. HUENTELMAN[3], J. S. TALBOOM[3], L. RYAN[1,2];
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Abstract: The ability to distinguish between highly similar objects requires the use of pattern separation or orthogonalizing information into distinct representations in the brain. Older adults generally perform worse on pattern separation tasks compared to younger adults by incorrectly identifying similar objects as ones seen previously. This suggests that older adults may have a decreased ability to create distinctive representations for objects with many overlapping features compared to younger adults. Context plays an integral role in recognition memory for objects, and the context in which an object is viewed can lead older adults to make even more similarity judgement errors. Older adults are more likely to make pattern separation errors (falsely recognizing similar objects as "old") when these similar objects are embedded in a context that was previously seen. Age-related impairment in pattern separation may therefore be a combination of a lack of utilizing details along with an over-reliance on the familiarity of the context in which an object is placed. Evidence suggests that changes in perirhinal cortex may be the neural mechanism underlying older adults' bias toward context familiarity. In contrast, preliminary data from our laboratory suggest that older adults who carry the APOE e4 allele are *less* likely to be influenced by the scene context during object recognition compared to older noncarriers. The e4 allele may confer a memory benefit that moderates older adults' susceptibility to rely on contextual familiarity, rather than object details. Participants were recruited from an existing pool in our laboratory. Older adults were carefully screened to exclude cognitive impairment. APOE status was determined from saliva by the Translational Genomics Institute in Phoenix, Arizona. Objects were embedded in semantically-related scenes and presented one at a time. Participants indicated whether each presented object was "new", "similar", or "different" compared to objects seen previously. Each object was either embedded in a context that was seen previously, a new context that had not been seen before, or on a white

background. Behavioral performance was compared between e4 carriers and noncarriers. Our results indicate that carriers and noncarriers do not differ on traditional recognition performance. However, consistent with our preliminary data, older e4 carriers were less susceptible to the influence of repeated contexts. The results suggest that the presence of the e4 allele may provide a memory benefit to older adults because carriers may not be biased toward relying on the scene context.

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Poster

792. Cognitive Aging II

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Program #/Poster #: 792.10/CC17

Topic: H.02. Human Cognition and Behavior

Support: "Research and development of technology for enhancing functional recovery of elderly and disabled people based on non-invasive brain imaging and robotic assistive devices" of NICT
KAKENHI grant number 18H05302

Title: EEG microstates in young and elderly people

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Abstract: Background: Recently, many experts in electroencephalogram (EEG) have focused on EEG microstates (Lehmann et al., 1987). EEG microstates are known as the four spatial patterns of EEG topographies. Each microstate can be analyzed according to the duration and occurrence. Previous studies, for example, have suggested that the effect of aging on EEG microstates. Many studies have aimed to determine the mechanism underlying the aging-induced deterioration of cognitive function and how this could be improved. However, only a few studies report the relationship between aging and EEG microstates. Therefore, the aim of this study was to compare the features of EEG microstates between young and elderly people, in accordance with the brain functional connectome. Method : We measured the resting-state brain activity of EEG from 25 subjects (Young:10, Elderly:15). The sampling frequency was 500 Hz. The data was further down sampled to 100 Hz and filtered to 2-20 Hz. The microstates were defined as follows.1. When the dispersion of EEG data from each channel peaked, the topography of EEG was saved.2. The topographies were clustered into 4 patterns by k-means method.3. The

topographies of original EEG data were compared with 4 topography patterns, and we chose the one with the most resemblance as labels.4. The labels were analyzed in terms of the occurrence and duration. Results : There were significant differences in occurrence of microstate class labeled C and D between young and elderly subjects. Young subjects had more occurrence of microstate C versus elderly subjects. However, elderly subjects had a greater occurrence of microstate D versus young subjects. In microstate A and B, there was no significant difference between the two groups. Discussion : The significant difference in the occurrence of microstate C and D between young and elderly people is congruent with some previous studies. Additionally, schizophrenic patients have fewer occurrences of microstate D versus healthy people (Hernandez et al., 2015). We may see a shared deterioration of cognitive function between people with aging and schizophrenia. Further studies should investigate the relationship between EEG microstates and cognitive function.

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Poster

792. Cognitive Aging II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 792.11/CC18

Topic: H.02. Human Cognition and Behavior

Title: Age related modulation of microsaccade rate in rapid serial visual presentation

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Abstract: Development of innovative technologies for the elderly to enable an independent life of high quality has become an urgent need in Japan. Therefore, the effects of aging on vital functions should be evaluated. Many regions in the human brain play functional roles in visual information processing, and the effect of visual dysfunction on the quality of life has shown to be more severe compared to those by dysfunction of other senses (Fischer et al. 2009). This indicates that the effects of aging on visual functions should be clarified. In this study, we analyzed microsaccades, which are small involuntary shifts in visual fixation, in rapid serial visual presentation (RSVP) tasks to examine the association between the subjects' age and the microsaccade characteristics. A total of 100 subjects, aged 20 to 60 years, participated in the study. Subjects were instructed to maintain a stationary gaze on a 10 Hz RSVP of alphabetical characters displayed at the center of a liquid crystal display screen. To control the subjects' focus of attention by changing the contrast of the target characters, we conducted 3 experimental tasks: (1) high contrast task (HC), (2) low contrast task (LC), and (3) no contrast task (NC) as a control. The eye movements were measured using an EyeLink CL system (SR Research, Ontario,

Canada) at a sampling frequency of 2000 Hz. Microsaccades were detected using an order-statistic time-window analysis (Ohtani et al. 2016). The results showed that the proportion of correct target detection in HC or LC significantly correlated with the subjects' age (HC: $r=-0.60$, $p<0.01$; LC: $r=-0.72$, $p<0.01$). The microsaccade rates showed rebound following inhibition in response to the onset of targets in HC and LC, which reflected the state of covert attention (Laubrock et al. 2005). The time taken to attain peak microsaccade rate after target onset was longer in LC compared to that in HC and increased with age (HC: 560 ms in 20-29 years, 663 in 30-39, 746 in 40-49, 745 in 50-59, and 948 in 60-69; LC: 582 in 20-29, 749 in 30-39, 753 in 40-49, 952 in 50-59, and 945 in 60-69). These results suggest that the need of attentional resources to increase in cognition with age, and thereby, delay the inhibition of microsaccades.

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Poster

792. Cognitive Aging II

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Topic: H.02. Human Cognition and Behavior

Support: JSPS KAKENHI Grant Number JP17H05920
JSPS KAKENHI Grant Number JP18KT0035
JSPS KAKENHI Grant Number JP19K14489

Title: Resting state functional connectivity patterns in older adults after the PICMOR intervention program: A preliminary report

Authors: *H. SUGIMOTO[1], T. KAWAGOE[2], M. OTAKE-MATSUURA[1];
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Abstract: We developed an intervention program, named Photo-Integrated Conversation Moderated by Robots (PICMOR), to improve cognitive functions in older adults. The PICMOR program is characterized by a moderated group conversation with robotic supports, in which participants are encouraged by robots to make a speech using photos they took beforehand, listen to others' talks, ask questions to others, and answer questions from others. The time allocated to each participant is equalized between talking and listening by robots to balance between inputs and outputs of information during the conversation. To examine the effect of PICMOR on cognitive functions in older adults, we conducted a randomized controlled trial (RCT), in which sixty-five healthy community-dwelling older adults were randomly allocated to the intervention group (INT) and the control group (CONT). Thirty-two participants assigned to INT took part in the PICMOR program once a week for 12 weeks, while thirty-three participants assigned to CONT took part in a free conversation program, in which they enjoyed a group conversation

without photos and robotic supports. Before and after the RCT, multiple neuropsychological data were acquired from all participants. In addition, resting state fMRI (rsfMRI) data were collected from 31 participants in INT and 30 participants in CONT only after the RCT due to our technical circumstances. In neuropsychological data, the increase in the score of a phonological verbal fluency task (PVFT) through the RCT was significantly larger in INT than in CONT. Based on the findings from a meta-analytic fMRI study, in which the left inferior frontal gyrus (LIFG) and middle frontal gyrus (LMFG) consistently show significant activation in PVFT, we analyzed the rsfMRI data by comparing the functional connectivity (FC) patterns with these language-related regions between INT and CONT. Results showed that the FC between the LIFG seed and the right temporal pole (RTP) in INT was significantly higher than that in CONT, whose strength was positively correlated with the PVFT score in INT. In contrast, the FC between the LMFG seed and the posterior cingulate cortex and precuneus, which are probably in the default mode network (DMN), was significantly lower in INT than in CONT. These findings may suggest that PICMOR has a beneficial effect on language production, and that the enhancement is related to the enhanced FC between the LIFG and semantic-related RTP and the suppressed FC between the LMFG and DMN. Further investigation will be done to confirm the possible effect of PICMOR on the brain network related to language production through pre-post analysis on rsfMRI data of the future RCT study.

Disclosures: H. Sugimoto: None. **T. Kawagoe:** None. **M. Otake-Matsuura:** None.

Poster

792. Cognitive Aging II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 792.13/CC20

Topic: H.02. Human Cognition and Behavior

Title: Heterogeneous functional and structural degradation of category-selective regions in the ventral visual cortex during normal aging

Authors: *Z. ZUO, Z. ZUO, N. LIU;
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Abstract: Accumulated evidence has shown that the function and structure of the ventral visual cortex degenerate during normal aging. However, the ventral visual cortex is a heterogeneous collection of functionally specialized cortical regions. For example, functional magnetic resonance imaging (fMRI) studies have revealed several discrete regions in the ventral visual cortex, which respond more strongly to one visual category relative to others, so-called category-selective regions. It is unclear whether age-related changes are uniform across these category-selective regions or not. To address this question, we examined how the functional and structural

properties of category-selective regions are affected by aging. In the present study, 20 young adults (mean age of 24.75 years) and 20 old adults (mean age of 62.45 years) were enrolled. First, we identified regions in each subject that were selective for faces, places, and objects, and calculated the category selectivity in each of these regions. Then, structural properties for these category-selective regions were measured by quantitative MRI. By comparing the category selectivity and structural properties of these regions between the young and old subjects, we found that both the function and structure of category-selective regions degraded during normal aging. Importantly, such aging-related changes exhibited heterogeneous patterns across different kinds of category-selective regions. Specifically, the degradation was most pronounced in place-selective regions and, to a less extent, in face-selective regions, while no significant degradation was found in object regions. Therefore, our results demonstrated that the aging-related changes in both functional and structural domains in the ventral visual cortex are highly heterogeneous, with different category-selective regions showing different degrees of degradation. It implies that the degradation of the ventral visual cortex during normal aging exhibits a complex pattern that may be related to functional segregation of regions.

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Poster

792. Cognitive Aging II

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Topic: H.02. Human Cognition and Behavior

Support: R01-AG058853
P20-GM103653
P20-GM113125
P20-GM103446

Title: Healthy aging and stiffness of the brain, hippocampus, and hippocampal subfields

Authors: *P. L. DELGORIO[1], L. V. HISCOX[1], F. SANJANA[1], A. M. DAUGHERTY[2], M. D. J. MCGARRY[3], H. SCHWARB[4], C. R. MARTENS[1], C. L. JOHNSON[1];
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Abstract: Magnetic resonance elastography (MRE) is a noninvasive medical imaging technique that can quantitatively assess brain viscoelastic mechanical properties to provide sensitive measurements of neural tissue health. Previous work has shown that global brain (GB) tissue stiffness decreases with healthy aging due to neurodegeneration, and aging effects on regional stiffness, such as in the hippocampus (HC), may be related to cognitive decline. We aim to

understand how HC stiffness changes with age, and, for the first time, how stiffness of individual HC subfields (HCsf) are differentially affected by age. Twenty-eight healthy subjects (22-74 years) were imaged on a 3T Siemens Prisma MRI scanner with a protocol including: (1) MRE scan at a 1.25 mm isotropic resolution with 50 Hz vibration; (2) T_1-weighted MPRAGE scan at 0.9 mm isotropic resolution; and (3) high-resolution T_2-weighted hippocampus scan at 0.4x0.4x2.0 mm^3 resolution. Whole-brain maps of stiffness were estimated from MRE data using a nonlinear inversion algorithm (NLI). FreeSurfer 6.0 was used to segment the bilateral HC and bilateral HCsf (dentate gyrus/CA4 (DG-CA4), CA1, and subiculum (SUB)) from T_1- and T_2-weighted images. Individual regional volumes were registered to MRE space. GB ($r^2 = 0.815$, $p < 0.001$) and HC ($r^2 = 0.364$, $p = 0.004$) stiffness exhibited quadratic relationships with age. In older adults (>50 y, n=16), GB and HC stiffness exhibited strong, linear decreases with age (GB: $r = -0.841$, $p < 0.001$; HC: $r = -0.674$, $p = 0.004$), while in younger adults (<50 y, n=12), GB and HC stiffness did not significantly correlate with age (GB: $r = -0.075$, $p = 0.818$; HC: $r = 0.299$, $p = 0.345$). Stiffness of each individual HCsf in the older group also displayed significant linear correlations with age (DG-CA4: $r = -0.692$, $p = 0.003$; CA1: $r = -0.588$, $p = 0.017$; SUB: $r = -0.695$, $p = 0.003$). To examine differential trajectories of HCsf stiffness with age, we also normalized each HCsf by whole HC stiffness. Normalized DG-CA4 ($r = -0.630$, $p = 0.009$) and CA1 ($r = 0.521$, $p = 0.038$) significantly correlated with age (though in different directions), while normalized SUB ($r = 0.179$, $p = 0.506$) did not exhibit a significant relationship with age. This suggests that, compared to whole HC stiffness, CA1 stiffness declines slower with age while DG-CA4 stiffness declines faster. Overall, our results confirm previous reports of brain softening with increasing age, especially in older adults. Notably, we also report that the stiffness of individual HCsf exhibit different rates of decline indicating a differential sensitivity of HCsf integrity to aging. Future analyses may use MRE of the HCsf to probe memory performance and impairment in aging.

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Poster

792. Cognitive Aging II

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Topic: H.02. Human Cognition and Behavior

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McKnight Brain Research Foundation

State of Arizona
Arizona DHS

Title: Mediation of age and hippocampal volume by temporal lobe white matter hyperintensities differ in relation to APOE e4 status in healthy older adults

Authors: *E. J. VAN ETTEN[1,6], P. K. BHARADWAJ[1,6], G. A. HISHAW[2], T. P. TROUARD[3,6], G. E. ALEXANDER[1,4,5,6,7];
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Abstract: While white matter hyperintensities (WMH) have been associated with hippocampal atrophy, less is known about how the regional distribution of WMH may differentially affect hippocampal volumes in healthy aging. Apolipoprotein E (APOE) ε4 carriers may be at an increased risk for WMH and greater hippocampal atrophy. The present study sought to investigate whether regional WMH mediate the relationship between age and hippocampal volume and whether this relationship is moderated by APOE ε4 status in healthy aging. A cohort of healthy adults (n=192, 94F/98M, mean±sd age=70.5±10.1, mean±sd Mini-Mental State Exam=29±1.2, APOE ε4 status (yes/no) = 59/133), 50 to 89 years of age were included. T1-weighted 3T volumetric MRIs were obtained and processed using Freesurfer (v5.3) software to obtain hippocampal volumes averaged across hemispheres. WMH in the four cerebral lobes were computed using T1 and T2 FLAIR scans and a lesion segmentation toolbox (Schmidt et al., 2012) with Statistical Parametric Mapping (SPM12). Total intracranial volume was computed for each participant using SPM12 to adjust hippocampal and WMH volumes for differences in head size. Mediation analyses were conducted with PROCESS macro software (Hayes, 2012) on SPSS, using bootstrap resampling with 10,000 iterations to produce bias corrected 95% confidence intervals. Temporal lobe WMH significantly mediated the relationship between age and average hippocampal volume, and this effect was moderated by APOE ε4 status (-.02 (SE=.01), 95% CI, [-.04, -.003]. APOE ε4 carriers, but not non-carriers, showed negative indirect effects of age on hippocampal volume through temporal lobe WMH (APOE ε4 carrier: -.02 (SE=.01), 95% CI, [-.03, -.003]; APOE ε4 non-carrier: .00 (SE=.01), 95% CI, [-.01, .02]). These findings remained significant after additionally adjusting for sex, years of education, and hypertension status. There were no significant mediation effects for frontal, parietal, and occipital lobe WMH, with or without covariates. The results indicate that the effects of aging on hippocampal volume are mediated by WMH regionally localized to the temporal lobes and that this effect depends on APOE ε4 carrier status. Together, these findings suggest that differences in hippocampal volumes observed in the context of healthy aging may be in part related to the influence of APOE ε4 on WMH and associated vascular mechanisms. Further research is needed to evaluate how regional WMH may influence other neuroanatomical effects of brain and cognitive aging.

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Poster

792. Cognitive Aging II

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Program #/Poster #: 792.16/CC23

Topic: H.02. Human Cognition and Behavior

Support: NIH NIA Grant R01AG047972

Title: Layer specific arteriovenous compliance in aging and age related cognitive slowing

Authors: *D. ABDELKARIM[1], D. SIVAKOLUNDU[2], M. P. TURNER[3], Y. ZHAO[4], K. WEST[5], H. LU[7], B. P. RYPMA[6];
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Abstract: As humans age, their vasculature becomes stiffer and less responsive to vasoactive stimuli. This stiffening, however, is not equal throughout all levels of vasculature. The levels of cerebral vasculature start with pial arteries just outside the parenchyma, from which penetrating arteries descend into brain tissue. These penetrating arteries then multifurcate into smaller arterioles and then into even smaller capillaries. At each level, the vascular structure is distinct, and the biological factors that contribute to aging and age-related vascular pathology impact each level in different ways. We hypothesize that these level-specific effects mediate age-related changes in brain function and cognition. In this study, we sought to ascertain whether differences in vascular reactivity across layers of cortex contribute to processing speed differences between younger and older adults. We used a measure called arteriovenous compliance (AVC), derived from the arterial cerebrovascular reactivity (CVR_a) and venous cerebrovascular reactivity (CVR_v), in different cortical layers to see if the reactivity across layers corresponded to the processing speed changes characteristic of aging. Relationships between AVC and processing speed were stronger in younger adults than in older adults. The results implicate neural-vascular coupling dysfunction in age-related cognitive slowing.

Disclosures: D. Abdelkarim: None. **D. Sivakolundu:** None. **M.P. Turner:** None. **Y. Zhao:** None. **K. West:** None. **H. Lu:** None. **B.P. Rypma:** None.

Poster

792. Cognitive Aging II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 792.17/CC24

Topic: H.02. Human Cognition and Behavior

Support: 5 T32 AG 96-35
AG034613

Title: Age-related impairments for maintaining separate memories for highly similar experiences in mice and humans

Authors: *B. S. KOLARIK, A. A. KEISER, S. M. STARK, M. A. WOOD, C. E. STARK; Univ. of California Irvine, Irvine, CA

Abstract: Aging brings about structural and functional changes in the hippocampus, which lead to impairments in the ability to encode and maintain memories for competing stimuli. Failures of pattern separation, a hippocampal computation that allows highly similar inputs to be represented distinctly, with minimal overlap, may underlie this impairment. Here, we hypothesized that age-related memory impairments are, in part, driven by a decrease in the ability to separate and maintain distinct memories for similar experiences. To test this hypothesis, we developed parallel tasks for both mice and humans that evaluate memory for similar experiences. In experiment 1, both young (9 week) and old (18 month) mice learned objects in two locations (A-B). Later, one of the objects was moved to a new location (A-C). At test, mice were presented with objects in 4 locations (A-B-C-D) and exploration time for each items was quantified, with longer exploration times expected for novel object-location pairings. In contrast to younger mice, older mice showed no preference for any of the object-locations, including the novel object (D), suggesting that older mice generalized the object-location pairings without separating the original and updated experiences into distinct events. In contrast, younger mice showed a preference for the novel object-location, indicating that they were able to maintain memories for the experience of both the original (B) and updated (C) locations. In experiment 2, we tested younger (18-24y) and older (60-80y) human participants on their ability to maintain separate memories for two similar experiences, using images of everyday objects in a continuous recognition paradigm. Later, some images were repeated, along with new items and highly similar lures. At test, participants were presented with two similar images simultaneously and responded with which images they had seen previously (original, lure, both or neither). There were no age-related differences in performance for repeated or new items, however on those trials where both images had been previously seen, older adults were significantly less likely to indicate that they had seen both, suggesting that they had a single memory, dominated by the most recent event, where younger participants are able to maintain two distinct memories for

highly similar events. Thus, across two experiments in both mice and humans, we find evidence that aging impairs the ability to separate and maintain memories for two highly similar, overlapping experiences, likely resulting from failed pattern separation and increased pattern completion processes, which leads to a more generalized memory representation.

Disclosures: B.S. Kolarik: None. **A.A. Keiser:** None. **S.M. Stark:** None. **M.A. Wood:** None. **C.E. Stark:** None.

Poster

792. Cognitive Aging II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 792.18/CC25

Topic: H.02. Human Cognition and Behavior

Support: National Science Foundation Graduate Research Fellowship Grant DGE-1746060
Arizona Alzheimer's Research Consortium
Evelyn F. McKnight Foundation

Title: Interactive effects of sex and BDNF Val66Met polymorphism on cognition in older adults

Authors: *S. MATIJEVIC[1], M. ELIAS[1], M. J. HUENTELMAN[2], L. RYAN[1];
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Abstract: Brain-derived neurotrophic factor (BDNF) promotes synaptogenesis and neurogenesis, and may play a critical role in supporting plasticity mechanisms underlying hippocampal-dependent memory. The BDNF gene Val66Met polymorphism contributes to individual variation in BDNF secretion, as carriers of the Met allele have abnormally reduced BDNF levels. Consequently, the Met allele has been shown to negatively influence hippocampal function, and in turn, episodic memory. This has implications for cognitive aging, given the susceptibility of the hippocampus to age-related damage and dysfunction. Indeed, the Met allele has been linked to enhanced memory deficits in older adults. To a lesser degree, BDNF has been implicated in the relationship between age and other cognitive domains, such as executive functioning. Evidence from the animal literature indicates that BDNF protein expression may differ by sex, as estrogen appears to regulate BDNF expression in the brain. Sex may therefore moderate the relationship between the Met allele and cognitive performance. The present study thus aims to characterize how the interactions between age, sex and the BDNF Met allele affect memory and executive function performance in older adults.
Neuropsychological testing and genotyping was carried out for 268 cognitively normal older adults (mean age = 72.27, ages 60-90). Participants with a BDNF Met/Met or Val/Met genotype were classified as Met allele carriers. Memory and executive function composite scores were

calculated from the neuropsychological test data (Glisky & Kong, 2008). Univariate GLMs were run to assess interactions and main effects of age, sex and BDNF Met carrier status on the composite scores.
For the memory composite scores, significant effects were found for Age ($F = 22.73$, $p < 0.001$), Sex ($F = 36.32$, $p < 0.001$), and the three way interaction between Sex, Carrier status, and Age ($F = 5.038$, $p = 0.026$). Females scored higher than males. While this difference increased with age among the Met non-carriers, it lessened among the carriers, as the memory composite scores negatively correlated with age only in the carrier females and non-carrier males. For the executive function scores, the effects of Age ($F = 9.95$, $p = 0.002$) and Sex x Carrier status interaction ($F = 6.61$, $p = 0.011$) were statistically significant. Male carriers performed better than both non-carrier males and carrier females.
BDNF carrier status is shown to interact with sex to influence both memory and executive function performance. These results suggest that the presence of the met allele may be less detrimental for males than for females, and perhaps even beneficial in regards to executive functioning.

Disclosures: **S. Matijevic:** None. **M. Elias:** None. **M.J. Huentelman:** None. **L. Ryan:** None.

Poster

792. Cognitive Aging II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 792.19/CC26

Topic: H.02. Human Cognition and Behavior

Support: NIH R01 AG034613

Title: Age-related changes in gray and white matter neurite density and diffusion within hippocampal subfields and the medial temporal lobe reflect memory performance

Authors: *H. RADHAKRISHNAN, S. M. STARK, C. E. L. STARK;
Univ. of California, Irvine, Irvine, CA

Abstract: Data from both human and animal models support the hypothesis that age-related alterations in hippocampal connectivity (e.g., fornix and perforant path) contribute to age-related memory decline. Recent advances in diffusion weighted imaging (DWI) have given us the ability to have a far more comprehensive view of these microstructural changes. In particular, Neurite Orientation Dispersion and Density Imaging (NODDI) lets us study diffusion not only in white matter, but in gray matter as well, letting us determine whether microstructural changes in gray matter also correlate with memory decline. We performed diffusion weighted imaging and structural MRI on 25 young (20-39; 12M) and 26 older (60-84; 11M) healthy adults. We used both fixel-based analysis and NODDI analyses to identify age-related changes in the medial

temporal lobe. Using the well-established age-related change in diffusion within the fornix, we first replicated this effect using an analysis of fiber orientation distributions via spherical deconvolution (MRTrix3), demonstrating that the overall fornix fiber density (FD) linearly decreases with age while fiber cross-section (FC) of the fornix linearly increases. We also found that fornix FD and FC were correlated with cognitive performance on the Rey Auditory Verbal Learning Test (RAVLT) and Mnemonic Similarity Task (MST). We then applied the NODDI model to the fornix and found that Free Water Volume Fraction (FISO) significantly increased with aging. Turning to diffusion within gray matter, we observed that the local neurite density index (NDI) increased with age (indicating more hindered gray matter diffusion) in the dentate gyrus (DG), CA1, and subiculum. We also observed that FISO decreased in all grey matter segments of the medial temporal lobe (save the entorhinal cortex) in stark contrast to its relationship with white matter. More importantly, we observed that the FISO (which was modulated by age) was significantly correlated with RAVLT scores in only the DG and the CA1, further supporting the idea that structural modulations in these regions primarily contribute to cognitive deficits in the aged population. These results not only shed more light into system-wide changes in tissue types, but also demonstrate that DWI is evolving into a tool to study more than just white matter changes, and might be in a unique position to resolve structural differences in gray matter more effectively.

Disclosures: H. Radhakrishnan: None. **S.M. Stark:** None. **C.E.L. Stark:** None.

Poster

792. Cognitive Aging II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 792.20/CC27

Topic: H.02. Human Cognition and Behavior

Support: Scientific Research Network on Decision Neuroscience Grant awarded to DVS [Subaward of NIH R24-AG054355 (PI Samanez-Larkin)]
College of Liberal Arts at Temple University (DVS)
NIH grant R21-MH116422 (DVS)

Title: Age-related reductions in functional connectivity in social brain systems during an economic trust task

Authors: *N. M. HENNINGER[1], V. KELLY[2], K. HACKETT[2], D. S. FARERI[5], S. KATTA[2], L. J. TEPFER[2], C. REECK[3], T. GIOVANNETTI[2], E. C. BEARD[4], J. DENNISON[2], B. MUZEKARI[2], D. F. DESALME[2], R. KINMARTIN[2], A. LANG[2], J. M. CIPRIASO[2], E. HUNTER[2], C. MORRISON[2], D. V. SMITH[2];
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Temple Univ., Philadelphia, PA; [4]Ctr. for Neural Decision Making, Dept. of Psychology, Temple Univ., Philadephia, PA; [5]Psychology, Adelphi Univ., Garden City, NY

Abstract: Positive social interactions are often built upon trust and reciprocity, signals which facilitate learning about others and maintaining close relationships. We have previously demonstrated that neurocomputational representations of reciprocity vary with respect to our relationship with an interaction partner (De Quervain et al., 2005; Delgado, Frank, & Phelps, 2005; Fareri & Delgado, 2014; Fareri, Chang, & Delgado, 2012; King-Casas et al., 2005). However, given that the nature of our relationships and susceptibility to social influence change across the lifespan, an important outstanding question is how decisions to trust close and unknown others change between young and older adults. To address this issue, we sought to characterize the relationship between decisions to trust familiar and unfamiliar others when sharing money, and whether there is a difference in this process based on age. We recruited 32 participants (20 younger adults, ages 20 - 35; 12 older adults, ages 65 - 80). Participants performed an economic trust game in an fMRI scanner in which they were presented with decisions to share (i.e., invest) money (up to $8 on a given trial) with either a same-sex friend (who also attended the session), a same-sex and age-matched stranger (confederate), or a computer (task based on Fareri, Chang, & Delgado, 2015). Participants received feedback on each trial as to whether the person they were sharing with chose to reciprocate or not. We found that participants shared more money with friends in comparison to computers ($t(31)=4.31$, $p<.001$), and also shared more money with friends than strangers ($t(31)=3.00$, $p<.001$). However, this social network effect did not interact with age ($F(31)=1.48$, $p=.223$). Replicating our prior work, we found that reciprocated trust (relative to unreciprocated trust) evoked activation in the ventral striatum. This study extends our prior work by demonstrating that younger adults (compared to older adults) exhibited enhanced functional connectivity between the fusiform face area and precuneus (cluster-defining threshold of $Z > 3.1$, FWE = 0.05, corrected). Taken together, these results demonstrate that cognitive aging is associated with alterations in functional connectivity within social brain systems. Understanding how social decisions involving trust and social closeness change across the lifespan main help shed light on the mechanisms that increase vulnerability to financial fraud in older adults.

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Poster

792. Cognitive Aging II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 792.21/CC28

Topic: H.02. Human Cognition and Behavior

Support: NIH Aging 5R01AG048076

Title: Individual differences in neural differentiation during episodic encoding predict associative retrieval in putatively healthy older adults

Authors: *M. B. HARRISON[1], V. A. CARR[4], N. CORSO[1], G. DEUTSCH[1], C. FREDERICKS[1], S. GUERIN[1], W. GUO[5], M. HUNT[1], M. JAYAKUMAR[6], J. JIANG[2], G. A. KERCHNER[3], A. M. KHAZENZON[1], C. LITOVSKY[7], E. C. MORMINO[8], A. NADIADWALA[1], S. SHA[1], N. J. TANNER[1], M. THIEU[6], A. N. TRELLE[1], A. D. WAGNER[1]; [2]Psychology, [1]Stanford Univ., Stanford, CA; [3]Stanford Univ., San Francisco, CA; [4]Psychology, San Jose State Univ., San Jose, CA; [5]Psychology, Univ. of Oregon, Eugene, OR; [6]Columbia Univ., New York, NY; [7]John Hopkins Univ., Baltimore, MD; [8]Neurol. and Neurolog. Sci., Stanford, Stanford, CA

Abstract: The magnitude of age-related episodic memory decline varies across older adults, raising fundamental questions about the causes of individual differences in memory late in the lifespan. One factor that is hypothesized to contribute to diminished memory in older adults is dedifferentiation — that is, a reduction in the specificity of cortical patterns that represent event features during encoding. To investigate the relationship between dedifferentiation at encoding and subsequent associative retrieval, the Stanford Aging and Memory Study collected high-resolution fMRI data while putatively 'healthy' older adults (N=100; age 60-88; CDR=0) encoded words paired with either a face or a place. Following encoding, participants encountered studied and novel words, and indicated whether they recalled the associate that had been paired with the word (face or place), whether they recognized the word as old in the absence of associative recall, or whether they perceived the word as new. FMRI analyses on data from targeted regions of interest entailed computing neural pattern similarity across encoding events, yielding measures of within-category similarity and between-category similarity. First, we explored whether neural differentiation (within category similarity > between category similarity) varied with age. Analyses revealed that differentiation declined over the later decades of life, with an age-related decrease (a) for faces in angular gyrus (p=0.01) and parahippocampal cortex (PHC) (p=0.001), and (b) for places in ventral temporal cortex (p=0.0001) and PHC (p=0.004). Second, we explored whether individual differences in neural differentiation partially account for differences in memory performance. Analyses revealed that, after controlling for age, neural differentiation in PHC was associated with better associative memory for places (β =3.59, p=0.03). Finally, a meditation analysis revealed that the relationship between age and associative memory was significantly mediated by neural differentiation for places in PHC($F_{(2,97)}$=6.58, p=0.002). These results suggest that cortical neural differentiation during encoding contributes to both age-related and individual differences in episodic memory late in the lifespan.

Disclosures: M.B. Harrison: None. **V.A. Carr:** None. **N. Corso:** None. **G. Deutsch:** None. **C. Fredericks:** None. **S. Guerin:** None. **W. Guo:** None. **M. Hunt:** None. **M. Jayakumar:** None. **J. Jiang:** None. **G.A. Kerchner:** None. **A.M. Khazenzon:** None. **C. Litovsky:**

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Poster

792. Cognitive Aging II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 792.22/CC29

Topic: H.02. Human Cognition and Behavior

Support: CONACYT 828873

Title: Cognitive reserve over different life stages in association with cognitive performance in healthy elderly

Authors: *C. GARCÍA-CAMACHO, T. VILLASEÑOR-CABRERA, M. JIMÉNEZ-MALDONADO, F. JÁUREGUI-HUERTA, J. RUÍZ-SANDOVAL;
Univ. De Guadalajara, Guadalajara, Mexico

Abstract: Cognitive reserve refers to factors that generate protection and favors recovery against brain injury or cognitive decline. This reserve arises through the life course and the activities that integrate it could vary such as its frequency.*Objectives:* To investigate if there's a life stage associated with the acquisition of more cognitive reserve and to identify the protective activities associated with a better cognitive performance during elderly.*Methods:* Descriptive, transversal and retrospective study. We included 61 healthy subjects ranging from 60 to 70 years old. People with a history of substance abuse, psychiatric disorders or traumatic brain injury were excluded. Cognitive function was measured with the Montreal Cognitive Assessment (MoCA), Phonological Fluency (PF), Digit Span and Vocabulary subtest (WAIS-IV). Cognitive reserve was obtained with Cognitive Reserve Questionnaire (CRC) and protective activities frequency was investigated with the Escala de Reserva Cognitiva y Envejecimiento (ERC).*Results*: The mean age was 63.9 y.o (SD=3.0), 73.8% were women. The average for education was 12.8 years (SD=5.2). 41% of analyzed subjects were retired, 36% still working and 23% never had formal job. The mean MoCA score was 25.3 points (SD=1.6), Digit Span subtest's average score was 9.3 points (SD= 2.1), Vocabulary subtest's score was 9.8 points (SD= 1.9), and mean Phonological Fluency was 13.6 words per minute (SD=3.4). 3.3% of the subjects evidenced low range cognitive reserve, 11.5% had a middle-low range, 47.5% had a middle-high range and 37.7% had a high range cognitive reserve. The stage of life where more cognitive reserve activities were reported was the late stage (41-60 y.o) (M=58.5, SD=9.1), followed by middle stage (21-40 y.o) (M=57.9, SD=10.4) and finally the early stage (first 20 years of life) (M=46.9, SD=13.7).Some daily activities like economy management, housework and basic technology use are present in all life stages; meanwhile academic activities or advanced technology use are more present on mid and late stages. Regarding hobbies, the most frequent activities during all life

stages are reading, watching television, listening music and exercise. Social interaction with diverse generations was the most frequent social activity in all life stages.*Conclusion*: Our results evidenced a strong association between high cognitive reserve and better cognitive performance in healthy subjects. The activities most frequently reported were those related to day-by-day functioning, knowledge acquisition, hobbies and practice of social skills. No differences were seen between life stages when correlated to generating activities.

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Poster

792. Cognitive Aging II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 792.23/CC30

Topic: H.02. Human Cognition and Behavior

Title: Resveratrol, a calorie restriction mimetic for the treatment of Alzheimer's disease: A preclinical investigation

Authors: *V. BENADE[1,2], P. JAYARAJAN[1], N. KRISHNADAS[2], V. KAMUJU[1], S. GANDIPUDI[1], R. NIROGI[1];
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Abstract: The major barrier in understanding Alzheimer's disease (AD) is a lack of knowledge about the etiology and pathogenesis of neuronal degeneration. Research in recent years accrued considerable data indicating the possible involvement of increased oxidative stress and free radicals in the pathogenesis of neuron death in AD. Tissue injury itself can induce reactive oxygen species (ROS) generation. Although, it is not known whether free radical generation is a primary or secondary event to other initiating causes, they are harmful and part of a cascade of events that can lead to neuronal death, suggesting that therapeutic efforts aimed at removal of ROS or prevention of their formation may be beneficial in AD. Resveratrol is a polyphenol found in red wines and in various plants, including grapes, berries and peanuts. Various *in vitro* and *in vivo* studies demonstrated antioxidant properties of resveratrol in addition to its other biological attributes, like anti-inflammatory activities, anti-platelet aggregation effect and anti-atherogenic property. Additionally, studies have provided insights into the effect of this compound on the life span of yeasts and flies, implicating the potential of resveratrol as an anti-aging agent. Due to the antioxidant and anti-aging properties, resveratrol has a potential in the treatment of age-related neurodegenerative disorders and in the current preclinical investigation resveratrol was evaluated as a potential treatment approach for AD. Rats were treated with Aluminium chloride (AlCl3; 10 mg/kg, i.p.) for 20 days for induction of oxidative stress leading

to neurodegeneration. Animals were treated with resveratrol (10, 15 and 30 mg/kg, p.o.) in parallel to AlCl3. Control group of rats received either saline alone or AlCl3 alone. Animals were subjected for evaluation in object recognition task followed by assessments of biomarkers (Malondialdehyde, glutathione, BDNF and SIRT-1 expression). Impaired cognitive abilities were observed in rats treated with AlCl3 alone; however resveratrol produced significant improvement in the cognitive performance at the highest dose tested. Similarly, oxidative stress evaluated through the measurement of malondialdehyde, glutathione was increased in animals treated with AlCl3, and resveratrol produced decrease oxidative stress. SIRT-1 and BDNF expression were found to be increased after the treatment of resveratrol. Results from current studies indicate potential benefits of resveratrol in the pharmacotherapy of AD through improvement of anti-aging properties.

Disclosures: **V. Benade:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **P. Jayarajan:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **N. Krishnadas:** A. Employment/Salary (full or part-time):; Manipal Academy of Higher Education. **V. Kamuju:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **S. Gandipudi:** 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

792. Cognitive Aging II

Location: Hall A

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Program #/Poster #: 792.24/CC31

Topic: H.02. Human Cognition and Behavior

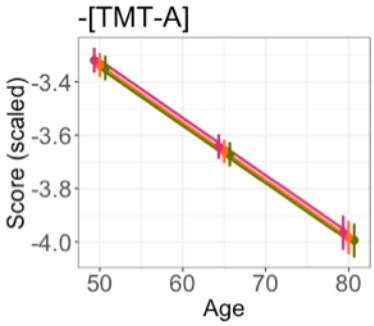
Support: NRF-2017R1D1A1B03033949

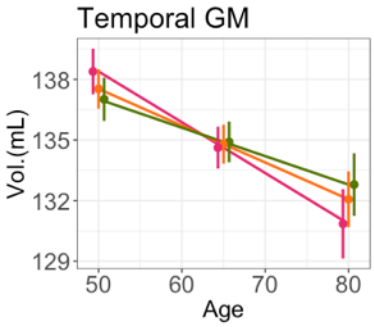
Title: Association between telomere and brain in large population study

Authors: *R. E. KIM[1], C.-H. YUN[3], R. THOMAS[4], I. BAIK[5], C. SHIN[2];
[1]Korea Univ., Ansan, Korea, Republic of; [2]Korea Univ., Seoul, Korea, Republic of; [3]Bundang Seoul Natl. Univ. Hosp., Bundang, Korea, Republic of; [4]Harvard Univ., Boston, MA; [5]Kookmin Univ., Seoul, Korea, Republic of

Abstract: Objective Prior studies have found a possible association of telomere attrition with small brain volumes and decreased cognitive function. This study is to access whether telomere length, as an indicative of a potential modifier of brain aging, interacts with age for brain volume and cognitive performance in mid-to-late adulthood. Prior studies have found a possible association of telomere attrition with small brain volumes and decreased cognitive function. **Methods** The present study investigated 1831 cognitively normal individuals. All subjects and data used in this study were derived from the Ansan Korean Genome Epidemiology Study. In

total, 5 brain sub-regions from magnetic resonance imaging and 15 cognition tests were analyzed with relative telomere length (TL) groups. **Conclusions** Telomere length seems related to both brain volume and cognitive function. In addition, longer TL may indicate relative protection from cognitive decline associated with aging. Our data sets the state for longitudinal analysis of TL effects on brain aging.





Disclosures: **R.E. Kim:** None. **C. Yun:** None. **R. Thomas:** None. **I. Baik:** None. **C. Shin:** None.

Poster

792. Cognitive Aging II

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Support: KCDC Grant 2011-E71004-00
KCDC Grant 2012-E71005-00
KCDC Grant 2013-E71005-00
KCDC Grant 2014-E71003-00

Title: Impact of apolipoprotein E and depression symptom on cognitive decline and white matter alteration in healthy aging adults

Authors: *H. AHN[1], R. KIM[1], S. KIM[1], C. SHIN[1,2];
[1]Inst. for Human Genomic Study, Col. of Med., Korea Univ., Seoul, Korea, Republic of; [2]Dept. of Intrnl. Med., Korea Univ. Ansan Hosp., Ansan, Korea, Republic of

Abstract: Introduction: The E4 allele of apoliprotein E (APOE) is the major genetic risk factor for Alzheimer's disease (AD). Previous studies have reported synergetic interaction between depressive symptoms and APOE E4 on risk of developing incident AD and mild cognitive impairment (MCI). Although significant relationships between depression symptoms and incident AD and MCI were observed in E4 carriers, the neurocognitive decline of this relationship in healthy aging adults was not fully reported. The aim of this study was to investigate the cognitive decline and possible cerebral modification of white matter integrity on depression symptom in APOE E4 and E3 carriers using diffusion tensor imaging (DTI).
Methods: A cohort of 2213 cognitively normal elderly adults from Korean Genome Epidemiology Study were evaluated. All participants underwent a brain MRI scanning and a comprehensive neuropsychological test battery that included memory and executive function measures. Participants were also asked to answer questions on the Beck Depression Inventory (BDI) to measure levels of depressive symptoms. Participants were divided in to one of four group base on result from BDI and genomic testing: depressed E4 carrier (n=80), non- depressed E4 carrier (n=386), depressed E3 carrier (n=364), and non-depressed E3 carrier (n=1483). The T1 weighted images were acquired in addition to 16 diffusion weighted images in a 1.5T MR scanner. The imaging data were processed using FSL´s Diffusion Toolbox; Tract Based Spatial Statistics (TBSS).
Results: A linear regression analysis showed that depressed subjects with APOE E4 carriers showed significantly lower Digit Symbol Test score ($p = 0.004$) and Trail Make Test score ($p = 0.013$) compared with non-depressed subjects who were also E3 carriers. Whole-brain WM integrity was analyzed using non-parametric t-tests and permutations. The results showed significant difference between depressed APOE E4 carriers and non-depressed APOE E3 carriers in multiple area such as frontal part of the right Inferior fronto-occipital fasciculus, bilateral superior longitudinal fasciculus, and right corticospinal tract regions ($p < 0.05$).
Conclusions: We found synergetic interaction between APOE genotype and depression symptom on executive function and white matter alteration. These findings provide an evidence for the high risk of developing incident AD and MCI in depressed adults with E4 carriers.

Disclosures: H. Ahn: None. **R. Kim:** None. **S. Kim:** None. **C. Shin:** None.

Poster

792. Cognitive Aging II

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Topic: H.02. Human Cognition and Behavior

Support: FONDECYT 1190958
FONDECYT 11171061

Title: Visuospatial/executive function in mild cognitive impaired patients correlate with performance in the visible-platform stage of a virtual navigation task

Authors: *N. K. ROGERS[1], C. SANMARTIN[2,3], D. P. PONCE[2], J. VALDÉS[2], M. I. BEHRENS[2];
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Abstract: Amnestic mild cognitive impairment (aMCI) is recognized as a prodromal stage of Alzheimer's disease (AD). The hippocampus is recognized as an important structure compromised in AD, as observed in early disturbances in memory in aMCI and AD patients. Changes in spatial navigation have also been described in virtual Morris Water Maze (vMWM) navigation tasks. Correlations between vMWM performance and other cognitive functions besides memory, such as visuospatial and executive functions, have only been previously reported in younger population (Korthauer et al., 2017). The role of these functions in vMWM performance of MCI and AD patients has not been previously characterized, in spite of evidence supporting that visuomotor integration is impaired both in cognitively healthy elderly population and early stages of dementia. Our aim was to investigate the correlation between scoring of the visuomotor/executive sub-items of the Montreal Cognitive Assessment (MoCA) and performance in a vMWM-like navigation task. We recruited 38 patients (20 healthy controls and 18 patients with aMCI diagnosis. Montreal Cognitive Assessment (MoCA) and Clinical Dementia Rating were used as tools for diagnosis. There was no significant epidemiological differences between groups in age, sex, comorbidities and educational level. Spatial navigation was tested through a three-staged version of a vMWM of increasing complexity; stage one has a visible platform and stages two and three describe predominantly egocentric and allocentric spatial navigation, respectively. A main component named "Efficiency score (ES)" was extracted with Principal Component Analysis (PCA). aMCI patients had an overall worse vMWM performance when compared with healthy controls (ES = 0.2479434 vs -0.2754926 AU, $p < 0.001$ t-test), observed in the first two stages. Age was an independent variable for overall vMWM performance in controls but not in aMCI patients. aMCI patients performed worse in the visuospatial/executive (VE/E) MoCA-sub-item score (3.5 vs 4.65 points, $p < 0.05$ t-test) (Total

MoCA score was 20.6 in aMCI vs 28.6 points in controls, p <0.0001, t-test). The VE/E score was significantly correlated with the overall performance in the vWMW for all subjects, even when normalized by age (pearson's correlation, r=0.3999 p<0.05). aMCI patients vMWM's performance in stage1 (visible platform test) also significantly correlated with VE/E scoring (pearson's correlation, r=0.5093 p<0.05), while in control patients it did not.

Disclosures: **N.K. Rogers:** A. Employment/Salary (full or part-time):; Departamento de Neurociencia, Universidad de Chile, Instituto de Neurocirugía Asenjo, Santiago de Chile. **C. SanMartin:** A. Employment/Salary (full or part-time):; Centro de Biología Integrativa, Universidad Mayor, Santiago de Chile, Departamento de Neurología y Neurocirugía, Universidad de Chile. 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.; FONDECYT 11171061. **D.P. Ponce:** A. Employment/Salary (full or part-time):; Centro de Investigación Clínica, Hospital Clínico de la Universidad de Chile. **J. Valdés:** A. Employment/Salary (full or part-time):; Departamento de Neurociencia, Universidad de Chile. **M.I. Behrens:** A. Employment/Salary (full or part-time):; Departamento de Neurociencia, Universidad de Chile, Centro de Investigación Clínica, Hospital Clínico de la Universidad de Chile, Departamento de Neurología y Neurocirugía, Universidad de Chile, Clínica Alemana, Santiago de Chile.

Poster

792. Cognitive Aging II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 792.27/CC34

Topic: H.02. Human Cognition and Behavior

Support: SFB (Sonderforschungsbereich) 779, Project A7, Deutsche Forschungsgemeinschaft

Title: The role of the dopaminergic and noradrenergic system in episodic memory

Authors: ***Y.-J. YI**[1,2], F. LÜSEBRINK[2], D. HÄMMERER[1], O. SPECK[3], E. DÜZEL[1]; [1]German Ctr. for Neurodegenerative Dis., The Inst. For Cognitive Neurol. and Dementia Res., Magdeburg, Germany; [2]Fac. of Med., [3]Fac. of Natural Sci., Otto-von-Guericke-Universität Magdeburg, Magdeburg, Germany

Abstract: A large body of evidence suggests that progressive cell loss in midbrain and brainstem neuromodulatory structures is significantly implicated in age-related decline in memory function, and they are among the first structures affected in dementia. However, it is currently unclear how a functional decline of noradrenergic and dopaminergic brain structures relates to altered memory capacities. To address this question, our project will use memory-encoding paradigms

tailored to assess the involvement of dopaminergic and noradrenergic modulation. Specifically, a reward-and-punishment and oddball paradigms are used to potentially induce cerebral DA and NA release. We hypothesised that the reward-associated stimuli would show a higher hit rate than the others during the delayed recall phase. Twelve subjects performed 4 tasks throughout 2 sessions. In the first session, they performed a reward task where the subject was asked to classify scene pictures into two categories and was given either a reward or punishment depending on the counterbalanced contingency condition. Afterwards, an immediate recall memory test and an oddball task with face stimuli followed. During the first session, 3-Tesla structural and functional magnetic resonance imaging scans (MRI), concurrent pupil dilation, which is a proxy indicator for NA activity, and behavioural indicators such as reaction time, recall accuracy, and recall confidence were collected. After a 2-hour break, participants performed a delayed recall test; only behavioural and pupillometric data were collected. Behavioural data analyses of memory tests show that the hit rate of the punishment-associated stimuli was higher. Moreover, pupil dilation for punishment-associated stimuli during delayed recall was significantly larger. Pupil dilation was larger for the oddball condition than standard condition. More data are required for robust analyses and further conclusions. Based on the final results after further data collection, the main study using 7-Tesla MRI and concurrent MRI-positron emission tomography will be conducted to assess functional correlates of reward-related dopamine release and high resolution structural and functional imaging of the noradrenergic system. The results are expected to contribute to obtaining a more comprehensive view of altered neuromodulatory systems in the context of healthy ageing and shed light on how it manifests in altered episodic memory.

Disclosures: Y. Yi: None. **F. Lüsebrink:** None. **D. Hämmerer:** None. **O. Speck:** None. **E. Düzel:** None.

Poster

793. Physiological and Cognitive Factors Associated With Healthy Aging

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 793.01/CC35

Topic: H.02. Human Cognition and Behavior

Title: The effects of cardiovascular risks on task switching in healthy older adults: An fMRI study

Authors: *S. QIN[1], C. BASAK[2];
[2]The Ctr. for Vital Longevity, [1]Univ. of Texas at Dallas, Dallas, TX

Abstract: Arterial plasticity and physical fitness, both factors of cardiovascular risk, have been independently associated with older adults' fMRI activations during executive functions. However, no fMRI study has investigated the combined effects of these two factors on executive

functions related brain activations in older adults. In the current fMRI study, we examined not only the separate, but also the combined, effects of these two cardiovascular risk factors on brain activations during task switching in healthy older adults. A hybrid design task switching paradigm (Basak et al., 2018; Nashiro et al., 2018) was used, allowing examination of both sustained (global switch cost, GSC) and transient (local switch cost, LSC) activations. Sixty healthy older adults (M_{age}=70) were recruited for this study, and their data were compared to existing fMRI task-switching data from 28 younger adults (M_{age}=21). Arterial plasticity was measured by pulse pressure (systolic - diastolic blood pressure). Physical fitness was measured by metabolic equivalent (MET) of VO_2Max. Whole-brain group contrasts were conducted in older adults to examine the separate and combined effects of the two risk factors in GSC and LSC. Older adults with low arterial plasticity and low MET showed reduced suppression of default mode regions (e.g. bilateral lingual gyrus), than those with lower cardiovascular risk for GSC. Older adults with low MET showed increased activation for GSC in the left inferior frontal gyrus (IFG) than those with high MET. Furthermore, increased GSC activations in the left IFG was associated with worse task performance in older adults. Older adults with 2 risk factors showed reduced suppression in default mode regions and increased left IFG activation compared to older adults with lesser number of risk factors (0 and 1). Additionally, we examined task-sensitive regions of interest for GSC and LSC, defined from previously published studies (Basak et al., 2018; Nashiro et al., 2018). Older adults with low plasticity showed diminished neural modulation for transient task switching (LSC) in the left post central gyrus, compared to high plasticity old. Across all analyses, older adults with low cardiovascular risk (high plasticity, high fitness, and with 0 risk factor) showed similar activation patterns compared to younger adults. Such results suggested that high cardiovascular risk was associated with both maladaptive overactivation and reduced task-sensitive activation in healthy older adults.

Disclosures: S. Qin: None. **C. Basak:** None.

Poster

793. Physiological and Cognitive Factors Associated With Healthy Aging

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 793.02/CC36

Topic: H.02. Human Cognition and Behavior

Support: Swedish research council
Knut and Alice Wallenberg foundation
StratNeuro Karolinska

Title: Striatal iron modulates neural signatures of working memory

Authors: *A. SALAMI[1,2], G. KALPOUZOS[2];
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Abstract: Intracellular non-hem iron in the brain is involved in numerous biological processes, such as neurotransmitter synthesis, synaptic plasticity, and myelination, which are crucial for early life development. However, elevated iron content in old age has found to be deleterious for brain cells because of triggering oxidative stress. Given previous evidence for the association between iron and cognitive measures, it is plausible that such an association varies across different age groups. Moreover, iron content could directly impact brain activity via astrocytic dysfunction: the astrocytes, cells where iron concentration increases with aging, are involved in the neurovascular coupling on which the blood oxygen level-dependent (BOLD) signal measured with functional MRI (fMRI) relies. Here we investigated age-related differences in brain iron content and their associations with differences in working memory and concomitant alterations in brain activation across the adult lifespan. We found that striatal iron was negatively associated with working memory (but also episodic memory and processing speed) in the older group, whereas positive associations (for episodic memory and processing speed and a trend level for working memory) were found in the younger group. Critically, a significant pattern revealing positive and negative associations of striatal iron to BOLD response during working memory in the striatal-cortical circuit was observed in younger and older adults, respectively. Taken together, striatal iron was related to working memory ability and associated BOLD response in an age-dependent manner, and future research needs to shed light on a mechanism behind the age-varying relationship.

Disclosures: A. Salami: None. **G. Kalpouzos:** None.

Poster

793. Physiological and Cognitive Factors Associated With Healthy Aging

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 793.03/CC37

Topic: H.02. Human Cognition and Behavior

Support: Mueller Family Charitable
State of Arizona DHS in support of the Arizona Alzheimer's Consortium
Flinn Foundation
NIH-NIA Grant R01-AG041232
NIH-NIA Grant R01-AG049465-05

Title: Web-based study of forty-one thousand women reveals factors associated to cognitive enhancement during menopause

Authors: *J. S. TALBOOM[1,2], A. K. HABERG[3], M. D. DE BOTH[1,2], M. A. NAYMIK[1,2], I. SCHRAUWEN[1], C. R. LEWIS[1,2], A. L. SINIARD[1], S. F. BERTINELLI[1], C. HAMMERSLAND[1], A. J. MYERS[4], M. HAY[5,2], C. A. BARNES[5,2], E. GLISKY[5,2], L. RYAN[5,2], M. J. HUENTELMAN[1,2];

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Abstract: Recently, our web-based cognitive study of over 75,000 individuals between the ages of 18-85 (www.mindcrowd.org) revealed that women's paired associates learning (PAL) performance was significantly higher at the fifth decade of life. Coinciding with this timepoint in a woman's life is menopause, marked by a cessation of ovarian hormones. Numerous studies have linked ovarian hormones and their cessation at menopause to cognitive changes in women. To evaluate potential links between menopause and cognition in our cohort, we developed a ten question menopause survey. Survey questions asked women about their contraceptive and hormone therapy use as well as if they had undergone an oophorectomy or hysterectomy. To date, over 7,130 women have completed the survey. We found the number of years that women reported using contraception was significantly associated with lower PAL performance (b=-0.034 word pairs/year of contraception, p=0.017). This effect was found after controlling for age, education, and several other factors related to PAL performance. This finding is in line with prior animal work linking contraception exposure to lower cognitive performance. This study helps further bridge the gap between animal and human studies and highlights the translational impact of contraception on cognition.

Disclosures: J.S. Talboom: None. **A.K. Haberg:** None. **M.D. De Both:** None. **M.A. Naymik:** None. **I. Schrauwen:** None. **C.R. Lewis:** None. **A.L. Siniard:** None. **S.F. Bertinelli:** None. **C. Hammersland:** None. **A.J. Myers:** None. **M. Hay:** None. **C.A. Barnes:** None. **E. Glisky:** None. **L. Ryan:** None. **M.J. Huentelman:** None.

Poster

793. Physiological and Cognitive Factors Associated With Healthy Aging

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 793.04/CC38

Topic: H.02. Human Cognition and Behavior

Support: PHFoundation

Title: Neurophysiological and neurocognitive correlates of obstacle avoidance behavior in older adulthood

Authors: *I. R. FLINT[1], A. R. WAARA[2], K. M. TREWARTHA[1,2];
[1]Dept. of Cognitive and Learning Sci., [2]Dept. of Kinesiology & Integrative Physiol., Michigan Technological Univ., Houghton, MI

Abstract: The objective of this research is to identify the neurophysiological and neurocognitive correlates that contribute to older adults' ability to make rapid evasive actions in response to sensory feedback during an ongoing movement. Rapid motor corrections allow us to make evasive actions, avoid knocking over objects in cluttered workspaces, and navigate around other people in crowded rooms. In the current research, we recorded electroencephalographic (EEG) signals while 18 older adult participants (*M* = 72.4, *SD* = 5.5 years old) and 18 young adult participants (M = 20.4, SD = 1.5 years old) used a robotic manipulandum (Kinarm, BKin Technologies) to correct for unpredictable visual "cursor shifts" while reaching for visual targets and avoiding visible haptic obstacles. Upon contact between the participants' cursor and the obstacles the robot applied a repulsive force to the hand, simulating a collision with a physical obstacle. On each trial the cursor briefly disappeared behind a rectangular occluder positioned in front of the start position, and emerged either unperturbed, or shifted by a small, medium, or large distance to the left or right of a straight line to the target. We focused our analyses on the behavior during the large jump condition, which uniquely required participants to switch hand paths around the outside of the obstacles, instead of between them, to be most efficient. Too assess neurocognitive correlates, we administered a battery of perceptuomotor, processing speed, and executive control tasks. We show that for older adults processing speed and executive control are significant predictors of the frequency of obstacle collisions. Additionally, when successfully navigating around the outside of the obstacles on large jump trials, movement times were predicted by measures of executive functioning in the older adults. To assess EEG correlates, we computed event-related potentials (ERP) associated with responses to the cursor shifts and conducted frequency analyses of the EEG data taken during the obstacle avoidance task. The results of this study add to the growing literature examining the neurophysiological impact of aging on adaptive motor behavior, as well as our understanding of the nature of neurocognitive contributions to rapid feedback control.

Disclosures: I.R. Flint: None. **A.R. Waara:** None. **K.M. Trewartha:** None.

Poster

793. Physiological and Cognitive Factors Associated With Healthy Aging

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 793.05/CC39

Topic: H.02. Human Cognition and Behavior

Support: NIH R56AG060052

Title: Physical fitness as a protective factor against age related declines in executive processes of working memory: A fMRI study on cue predictability, updating and switching

Authors: *C. BASAK[1], P. SKOLASINKA[3], S. QIN[2];
[1]Ctr. for Vital Longevity, [2]Univ. of Texas At Dallas, Dallas, TX; [3]Ctr. for Vital Longevity, Univ. of Texas at Dallas, Dallas, TX

Abstract: Everyday cognition critically depends on working memory, the ability to maintain information and adaptively update it. An important function of working memory is not just to retain the information in a capacity-limited short-term store, but the executive processes that control the information. This study is designed to determine the age-related differences in brain activation during these executive processes, and whether physical fitness could protect against age-related declines in some, if not all, of these processes. Although fitness is associated with changes in brain activations in older adults during executive processes of dual tasking and inhibition, these studies lacked data from younger adults, the functional control, to help interpret the fMRI results. Moreover, they did not investigate fitness effects on brain activations related to the executive processes of working memory.
We investigated fMRI activations using a hybrid blocked and event-related design 2-Match task. Three different types of executive processes were evaluated during working memory: cue-predictability (Predictable vs. Unpredictable), updating, and switching. We recruited 48 adults: Young, Low Fit Old (LF) and High Fit Old (HF); *n=12* in each group. LF and HF older adults differed significantly in physical fitness [measured by Metabolic Equivalent of VO_2Max, MET]. Young adults, compared to old, had higher accuracy. Importantly, higher fitness in old was associated with higher accuracy ($r = .519$, $p = .004$).
Whole-brain fMRI analyses identified distinct brain regions associated with predictable cues, unpredictable cues, and updating. Moreover, results from older adults showed increased activations in R SMG during predictable condition for LF, not HF. This increased activation in LF is maladaptive, because higher activity in R SMG in old was correlated with worse performance in predictable condition ($r=.35$). For updating, however, HF showed increased activations in R frontal cluster (DLPFC, IFG) and the precuneus. Moreover, increased activation in the precuneus during updating was correlated with higher accuracy ($r = .49$, $p = .008$). We conclude that physical fitness might play an important role in preserving executive processes, esp. updating information, and its related brain functions among older adults. Patterns of neural modulation in response to increased updating demands were similar across HF older adults and young. In contrast, increased activity in LF, compared to HF and Young, is deemed maladaptive.

Disclosures: C. Basak: None. **P. Skolasinka:** None. **S. Qin:** None.

Poster

793. Physiological and Cognitive Factors Associated With Healthy Aging

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 793.06/CC40

Topic: H.02. Human Cognition and Behavior

Support: 5I01CX000501 (VA CSRD)

Title: Cingulate function in typical cognitive aging

Authors: R. J. BERTHIAUME[1], S. M. NYABWARI[2], J. T. LEE[3], *J. V. PARDO[4];
[1]Biosci., [2]Continuing Educ., Univ. of Minnesota, Minneapolis, MN; [3]Cognitive Neuroimaging Unit, [4]Dept. Psychiatry, Univ. of Minnesota, Minneapolis Veterans Hlth. Care Syst., Minneapolis, MN

Abstract: The anterior cingulate cortex (ACC) undergoes marked changes in metabolism that correlate with declining executive function during typical cognitive aging. In contrast, although the posterior cingulate cortex (PCC) is among the first regions to undergo hypometabolism and amyloid deposition in early Alzheimer's disease, its metabolism is relatively stable with typical aging. The ACC and PCC are themselves densely interconnected anatomically and functionally. Here, we analyze publicly-available and published data from ADNI (A); Pardo et al. *Neuroimage* 35:1231 (2007) (B); Andrews-Hanna et al. *Neuron* 56: 924 (2007) (C); and Goyal et al. *Cell Metab* 25:353 (2017) (D) to examine cingulate function during aging. All subjects were cognitively intact; some (A-C) had amyloid imaging. The ACC showed a much greater metabolic decline than the PCC during aging. The smaller sample (N = 46) with wider age range (18-91) in B produced highly significant aging-related declines in the ACC but not in the PCC. The larger sample beginning at age 55 years in A showed significant decline in both ACC and PCC metabolism, but the correlation with age for the ACC was significantly greater than for the PCC. The large N (over 200) in A enabled identifying statistically ACC metabolism as a mediator between executive function and aging. The ACC and PCC functional connectivity (C) from BOLD timeseries did not change under age 35 years but declined precipitously after 60 years even when amyloid negative as reported previously in B. Aerobic glycolysis (D) in both ACC and PCC declined markedly from young adulthood to age 50 years without change afterward. This did not occur in control regions such as primary sensory cortices. Static intersubject connectivity (i.e., correlation between ACC and PCC metabolism across subjects within a sliding window for age) was grossly constant in young adulthood but declined with further aging. Thus, the ACC shows marked decline in metabolism and AG in young to middle adulthood, while in later life there appears a dissociation. ACC/PCC functional connectivity remained stable in younger adults but declined in later older adulthood. The results highlight dissociations in ACC and PCC function with aging. The decline in ACC metabolism and AG does not appear related to disconnection between the ACC and PCC.

Disclosures: R.J. Berthiaume: None. **S.M. Nyabwari:** None. **J.T. Lee:** None. **J.V. Pardo:** None.

Poster

793. Physiological and Cognitive Factors Associated With Healthy Aging

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 793.07/CC41

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant AG-036848
NIH Grant AG-036818
NIH Grant AG-056535

Title: Frontostriatal white matter connectivity declines with age and predicts cognition and dynamic BOLD modulation

Authors: *C. E. WEBB, D. A. HOAGEY, K. M. RODRIGUE, K. M. KENNEDY;
Ctr. for Vital Longevity, The Univ. of Texas at Dallas, Dallas, TX

Abstract: Frontostriatal circuitry is important for several regulatory activities, with dorsal prefrontal - dorsal striatal pathways specifically involved in aspects of cognitive control. The prefrontal cortex and striatum are among the structures most sensitive to effects of aging, yet the study of the pathways connecting these regions is limited. White matter connections are particularly vulnerable to aging, thus knowledge of frontostriatal pathway aging will be beneficial to understanding age-related and individual differences in cognitive control, as well as the function of these important gray matter regions. Here, we sought to examine age effects on frontostriatal white matter connections, and associations with both executive function performance and dynamic range of blood oxygen level dependent (BOLD) modulation to task difficulty. In a lifespan sample of 169 healthy adults aged 20-94 we used deterministic tractography to isolate a dorsal prefrontal - dorsal striatal white matter pathway. Frontostriatal fractional anisotropy (FA), a measure of the directionality of water diffusion, decreased linearly with age, while diffusivity metrics (mean, axial, and radial diffusivity) increased in a quadratic fashion across the lifespan. Frontostriatal diffusivity (but not FA) was associated with poorer executive function performance and this negative association strengthened with increasing age. Because age-related degradation of white matter likely influences the efficiency of communication between gray matter regions connected by white matter structure, we then examined whether age-related alterations of frontostriatal white matter connectivity were associated with functional modulation of BOLD activity in response to increasing working memory load on a digit n-back task. Whole-brain analysis results indicated an association between frontostriatal mean diffusivity and functional BOLD modulation selectively in the striatum. This association was moderated by age, such that younger and middle-aged individuals showed reduced dynamic range in response to increased difficulty as a function of increasing frontostriatal diffusivity. These findings illustrate that age-related alterations in frontostriatal

white matter negatively impact both executive function and dynamic range of functional modulation to cognitive challenge. Executive function performance showed sensitivity to frontostriatal aging across the age span, whereas frontostriatal effects on the ability to flexibly modulate striatal BOLD activity were apparent earlier in the lifespan, highlighting the importance of capturing brain changes occurring in middle adulthood.

Disclosures: C.E. Webb: None. **D.A. Hoagey:** None. **K.M. Rodrigue:** None. **K.M. Kennedy:** None.

Poster

793. Physiological and Cognitive Factors Associated With Healthy Aging

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 793.08/CC42

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant P01AG14449
NIH Grant P30AG010161

Title: Longitudinal fluctuations in memory and executive function correlate with Alzheimer's disease pathology in non-cognitively impaired elderly

Authors: *M. MALEK-AHMADI[1], S. E. PEREZ[2], E. J. MUFSON[3];
[1]Banner Alzheimer's Inst., Phoenix, AZ; [2]Dept Neurobio., [3]Neurobio., Barrow Neurolog. Inst., Phoenix, AZ

Abstract: Although the use of within-subject measures to characterize changes in cognition is increasingly prevalent, few studies have investigated whether these measures of cognition correlate with hallmark Alzheimer's disease (AD) neuropathology. Previous work by our group found that higher subject-level variability between cognitive domains is associated with increased tau containing neurofibrillary tangles (NFTs), but not with beta-amyloid (Aβ) neuritic plaques (NPs) or diffuse plaques (DPs). Longitudinal studies indicate that higher NP and NFT burdens are associated with an increase in the rates of antemortem cognitive decline, however the degree to which year-to-year fluctuations in cognition are associated with AD neuropathology remains an underinvestigated area. Here we investigated whether antemortem within-subject fluctuations in cognition correlate with post-mortem measures of AD neuropathology. Longitudinal cognitive data from 106 non-cognitively impaired (NCI) subjects from the Rush Religious Orders Study were analyzed. Average age at baseline was 76.38±6.13 years and average age at death was 84.27±5.58 years. The average length of follow-up was 7.62±4.75 years and the average post-mortem interval was 7.12±6.93 hours. Females comprised 48% (n = 51) of the sample. Intrasubject standard deviation (ISD) values derived from episodic memory and executive function composite scores were calculated for each subject. Negative

binomial (NB) regression models were used to assess the association between cognitive ISDs and AD neuropathology (NPs, DPs, and NFTs) while adjusting for age at death, sex, education, and APOE ε4 carrier status. Episodic memory ISDs were not associated with DP (β = 0.60, 95% CI (-1.52, 2.72), p = 0.58) or NP load (β = 0.18, 95% CI (-1.97, 2.33), p = 0.87), but were significantly related to NFT load (β = 1.39, 95% CI (0.30, 2.48), p = 0.01). Executive function ISDs were not associated with DP (β = 1.07, 95% CI (-1.57, 3.71), p = 0.43) or NFT load (β = -0.52, 95% CI (-1.91, 0.47), p = 0.87), but were significantly related to NP load (β = 2.94, 95% CI (0.28, 5.61), p = 0.03). ISDs did not correlate with subject-level slopes for episodic memory and executive function, indicating that higher ISDs were not the result of linear declines in cognition. These results show that year-to-year within-subject cognitive variability is associated with AD pathology severity in NCI older adults.

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Poster

793. Physiological and Cognitive Factors Associated With Healthy Aging

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 793.09/CC43

Topic: H.02. Human Cognition and Behavior

Title: EEG markers from a novel oddball task predicts subject's mental abilities, data from 443 adults

Authors: *J. DREO[1], D. SAKIC[2], Z. PIRTOSEK[2];
[1]Med. Faculty, Univ. of Ljubljana, Ljubljana, Slovenia; [2]Chair of Neurology, Fac. of Medicine, Univ. of Ljubljana, Ljubljana, Slovenia

Abstract: Due to population ageing, dementia-related expenses will rise in the coming decades. Even in the absence of disease-modifying therapy, developing cost-effective and non-invasive methods of diagnosing Alzheimer’s disease is essential to reduce health-care expenses. As part of a Slovenian research initiative aimed at early dementia detection (ADAM project) we performed 64-channel EEG recordings on 443 healthy elderly subjects in addition to conducting the Montreal Cognitive Assessment (MoCA). We designed an extremely short (3 min) novel oddball-like task that was intended to probe short-term memory recall. The subjects were instructed to pay attention to a series of images of several categories, some of which repeated while others did not. They did not need to perform any other task. EEG data was used to compute ERPs to different image types (repeats and non repeats). The resulting P3 (P300) potentials were compared between different image types and subjects with different cognitive (MoCA) scores. Sizable and significant changes were found in ERP latency, amplitude and, especially topographical distribution. These results indicate that our novel oddball task can offer

valuable objective insight into the cognitive performance of older adults and might point the way towards development of future EEG-based strategies to predict cognitive decline or dementia development.

Disclosures: J. Dreo: None. **D. Sakic:** None. **Z. Pirtosek:** None.

Poster

793. Physiological and Cognitive Factors Associated With Healthy Aging

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 793.10/CC44

Topic: F.04. Stress and the Brain

Title: The continuum from temperament to mental illness

Authors: *W. SULIS;
Psychiatry and Behavioural Neurosci., McMaster Univ., Hamilton, ON, Canada

Abstract: Background: Temperament and mental illness are thought to represent varying dynamical phases within a continuum of neurobehavioral regulation. This regulation primarily involves monoamine and cholinergic systems as well as opiate receptor systems. Trofimova has developed a taxonomy pf temperament (Functional Ensemble of Temperament model "FET") based upon linkaages between ensembles of regulatory systems and specific temperament traits. This model is sensitive to subtle alterations in neurobehavioral regulation and this is expected to show consistent and disease specific effects in the presence of various mental illnesses. This could in turn provide the basis for a new taxonomy of mental illness. Most popular models of temperament, being based heavily on emotionality traits, show very poor ability to discriminate between mental disorders. The main goal of this study was to examine whether the FET, which is based on modern neurophysiology and possesses an extensive set of non-emotionality traits provides better discrimination between Major Depression (MD), Generalized Anxiety (GAD) and Comorbid MD and GAD, in comparison to emotionality-based temperament models. **Methods**: Using the Structure of Temperament Questionnaire, the temperament profiles of 687 individuals (396 clients of private psychiatric and psychological practice, and 291 control subjects) were compared across four adult age groups (18-24, 25-45, 46-65, 66-84). **Results:** MD and GAD appear to be accurately distinguished by the traits of Motor Endurance and Motor Tempo (much lower values in depression), and Neuroticism (much higher value in anxiety). Comorbids can be distinguished based on a significant decrease in the traits of Plasticity, Intellectual Endurance, Sensitivity to Probabilities, and increased Impulsivity. These effects seemed independent of age and gender. **Conclusions**: The results suggest the benefits of including non-emotionality-related traits and the usefulness of a functional approach to both taxonomy of temperament and classification of mental disorders.

Disclosures: W. Sulis: None.

Poster

794. Novel Techniques of Biochemical Analysis

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 794.01/CC45

Topic: I.01. Molecular/ Biochemical/ and Genetic Techniques

Support: NIH Grant R01 MH115456
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P41 GM103712

Title: Quantitative MCell model shows competition and dynamic equilibrium within PDZ domain of PSD-95 at the postsynaptic density

Authors: *S. SAMENI[1], T. M. BARTOL, Jr[1], M. B. KENNEDY[2], T. J. SEJNOWSKI[1]; [1]Salk Inst. For Biol. Studies, La Jolla, CA; [2]Caltech, Pasadena, CA

Abstract: A major challenge in synaptic plasticity has been to understand how synaptic proteins that govern learning and information storage are regulated and to clarify the molecular mechanisms of plasticity. Although the existence of electron-dense structures known as postsynaptic densities (PSDs), comprising the key proteins that regulate synaptic plasticity and homeostasis have been studied for more than 60 years, it is still unclear how these structures are formed and regulated. We have made a stochastic computer model using MCell to simulate protein interactions in PSDs. We examined the competition among synaptic proteins including synGAP and AMPAR-TARPs for binding sites on PSD-95. SynGAP and PSD-95 are two of the most abundant PSD components. Their mutation has been linked to intellectual disability, autism and seizure. The competition for binding among these molecules leads to the formation of multiple equilibria within the PSD. A reduction of affinity of synGAP for PSD-95 shifts the balance to form a new equilibrium based upon the concentration and affinity of other components. In particular, the reduction of affinity of synGAP for PDZ 1 and 2 shifts the balance to form a new equilibrium with AMPAR-TARPs.

Disclosures: S. Sameni: None. **T.M. Bartol:** None. **M.B. Kennedy:** None. **T.J. Sejnowski:** None.

Poster

794. Novel Techniques of Biochemical Analysis

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The SRPBS and Brain/MINDS from AMED
The Mochida Memorial Foundation for Medical and Pharmaceutical Research

Title: *In vivo* imaging of alkynylated S-citalopram using surface-enhanced Raman scattering

Authors: *M. TANUMA[1], A. KASAI[1], K. BANDO[2], N. KOTOKU[3], K. HIGASHINO[1], Y. AGO[4], S. KAWATA[2], K. FUIJTA[2,5,6], H. HASHIMOTO[1,6,7,8];
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Abstract: Selective serotonin reuptake inhibitors (SSRIs) are the most used class of antidepressants, although they are known to have delayed onsets of clinical effects. Elucidating the distribution of SSRIs throughout the brain may provide insights into their precise mechanism of action. Here, in order to visualize SSRIs directly *in situ* at a high resolution, we combined the bioorthogonal alkyne tag with surface-enhanced Raman spectroscopy (SERS). Raman spectroscopy detects chemical compounds by detecting molecular vibrations of chemical bonds. Notably, the alkynyl group exerts a strong Raman peak in the silent region of the Raman spectrum and is therefore detected specifically. SERS amplifies spontaneous Raman scattering via the adsorption of chemical bonds to the surface of a nanoparticle. Focusing on the SSRI S-citalopram, we incorporated an alkynyl group by replacing the nitrile group at the C-5 position of the 1,3-dihydroisobenzofuran ring and chemically synthesized alkynylated S-citalopram. We

simulated its binding mode to the human serotonin transporter (hSERT) *in silico* and found that alkynylated S-citalopram bound to the hSERT similarly to S-citalopram. We then analyzed the brain transitivity of alkynylated S-citalopram by quantifying alkynylated S-citalopram in brain homogenates using liquid chromatography-tandem mass spectrometry. We found that alkynylated S-citalopram levels in the brain were not significantly different from S-citalopram levels. We also analyzed the serotonin release by alkynylated S-citalopram in the medial prefrontal cortex using brain microdialysis. We found that serotonin levels were not significantly different between alkynylated S-citalopram and S-citalopram administered mice. We then tested whether alkynylated S-citalopram can be detected with SERS *in vitro*. Alkynylated S-citalopram exerted a strong Raman peak in the silent region and was detected with a sensitivity of 400 pM. Finally, we performed SERS imaging on coronal mouse brain sections and successfully visualized alkynylated S-citalopram in the dorsal raphe nucleus. This study shows the combined alkyne tag and SERS imaging approach as a potent method for detecting low molecular drugs targeting the brain, and opens the door for the technique to be developed further to determine drug distribution.

Disclosures: **M. Tanuma:** None. **A. Kasai:** None. **K. Bando:** None. **N. Kotoku:** None. **K. Higashino:** None. **Y. Ago:** None. **S. Kawata:** None. **K. Fuijta:** None. **H. Hashimoto:** None.

Poster

794. Novel Techniques of Biochemical Analysis

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Program #/Poster #: 794.03/CC47

Topic: I.01. Molecular/ Biochemical/ and Genetic Techniques

Support: Nipissing University

Title: Depigmentation and clearing technique for planaria allowing optically accessible staining and fluorescence imaging of the complete worm

Authors: P. E. B. NICKERON[1,2], A. D. STILLAR[2], *M. J. SAARI[2];
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Abstract: Planaria, Dugesia Dorocephala, appear to be behaviourally sensitive to their social environment. In our hands, singly housed planaria show reduced activity and increased environmental “scanning” in comparison to group-housed planaria. Thus, they may serve as a potentially useful model for the examination of environmentally-mediated neural and behavioural plasticity. Previous studies have demonstrated their usefulness in the study of neural regeneration and toxicology studies, including exposure to alcohol during regeneration, among others. Classical histological techniques have offered effective means to characterize the

microscopic anatomy of developing and regenerating planaria. Although informative, cryosectioning and staining of serial sections represent an artifact-rich and labour-intensive methodology when attempting to reconstruct the three-dimensional (3D) microanatomy of whole organisms. Recent advances in whole-specimen clearing techniques have provided us with a platform wherein we can generate a whole-organism preparation that is optically accessible to laser-scanning fluorescence microscopy. We employed depigmentation techniques coupled with modified CUBIC clearing to generate optically accessible planarian worms that can be stained with conventional inorganic (vital) dyes. Worms stained with nuclear (DAPI) and neuronal (Nissl) stains can be mounted and 3D tile imaged, on a confocal microscope, revealing a detailed and comprehensive microanatomical view of the planarian nervous system. Conclusion: This depigmentation and clearing protocol mitigates a processing bottleneck in higher-throughput evaluation that is inherent to classical histological analysis. This protocol will be useful for the examination of neural plasticity of the planarian in numerous experimental models including environmentally mediated behavioural plasticity.

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Poster

794. Novel Techniques of Biochemical Analysis

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Support: NIH New Innovator Award DP2-HD075698
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NIHNS081981
NSF Career Award 1752506

Title: Carbon nanotube optical reporter maps changes in endolysosomal lipids

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Abstract: When lysosomes accumulate fat due to disposal problems, the accumulation can lead to toxic effects. This is found in a variety of lysosomal storage disorders, such as Niemann-Pick disease, which is an inherited condition of malfunctioning lipid metabolism. It is also implicated in cancer and neurodegenerative diseases. There are limited methods for detection of

accumulation of endolysosomal lipids, and it is particularly difficult to address *in vivo*. Many techniques provide lipid content quantification in organs, but there is limited specificity for individual organelles. Our lab has developed an optical reporter to detect endolysosomal lipid accumulation and fluctuations both *in vitro* and *in vivo*. Our optical reporter is composed of a photoluminescent carbon nanotube that responds to the accumulation of lipids by modulating the nanotube's optical band gap. The nanomaterial is made of short, singlestranded DNA and a single chirality, which allows it to localize exclusively to the endolysosomal organelle lumen. This is done without adverse effects to cell viability, proliferation, morphology, integrity, or function.

Near-infrared (NIR) fluorescence microscope was used to acquire the photoluminescence emission of single-walled carbon nanotubes, based on the intrinsic fluorescence of carbon nanotubes which have unique properties. The nanotubes were then added to Niemann-Pick disease model cells. We show detection of lysosomal lipid accumulation in Niemann-Pick type A/B (NPA/B) and Niemann-Pick type C (NPC) disease models, and primary cells from an NPC patient.

For *in vivo* models, the nanotubes are injected into the mouse via intravenous injections, and monitored noninvasively via NIR excitation/emission. We found hepatic lipid accumulation in the mouse model of NPA/B and NPC. We used the reporter to monitor lipid accumulation in KC endolysosomal organelles, and saw the effects of dietary intervention in non-alcoholic fatty liver disease and nonalcoholic steatohepatitis. This reporter has widespread implications for many disorders, such as monitoring lipid accumulation in neurodegenerative diseases such as Parkinson's and Alzheimer's disease.

Disclosures: L.E. Komer: None. **T.V. Galassi:** A. Employment/Salary (full or part-time):; Patent Agent at Wilson Sonsini Goodrich & Rosati. **P.V. Jena:** A. Employment/Salary (full or part-time):; LipidSense 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.; Photon Etc, paid consultant, Goldilocks Therapeutics, unpaid consultant. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); application no. US20170199126A1; title: Composition and method for monitoring lipid. **J. Shah:** None. **Y. Bram:** None. **A. Frankel:** None. **J. Park:** None. **J. Jessurun:** None. **D.S. Ory:** A. Employment/Salary (full or part-time):; Casma Therapeutics. 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.; consultant for Mallinckrodt Pharmaceuticals. **A. Haimovitz-Friedman:** None. **R.E. Schwartz:** None. **F.R. Maxfield:** None. **D.A. Heller:** A. Employment/Salary (full or part-time):; co-founder/officer of LipidSense Inc, co-founder/officer of Goldilocks Therapeutics Inc. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); application no. US20170199126A1; title: Composition and method for monitoring lipid. F. Consulting Fees (e.g., advisory boards); Oncorus Inc.

Poster

794. Novel Techniques of Biochemical Analysis

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 794.05/CC49

Topic: I.01. Molecular/ Biochemical/ and Genetic Techniques

Title: Imaging of neurotransmitters using AuNPs with laser desorption ionization mass spectrometry

Authors: *N. K. MCLAUGHLIN[1], K. STUMPO[2];
[1]Biol., [2]Chem., Univ. of Scranton, Scranton, PA

Abstract: Imaging of neuroactive molecules, specifically those with primary amines, are a challenge for mass spectrometry. The small molecular weight coupled with low abundance in biological tissues results in low ionization efficiencies. However, gold nanoparticles (AuNPs) as matrices in Laser-Desorption Ionization Mass Spectrometry (LDI-MS) have been established for ionization of biomolecules due to their flexibility in solvent preparation and salt tolerance. These properties may lend themselves to increased resolution for endogenous small molecular weight metabolites, such as neurotransmitters. Specifically, dopamine (DA), serotonin (5-HT), glutamate (Glu), gamma-Aminobutyric acid (GABA), Octopamine (OT), norepinephrine, (NE), acetylcholine (Ach), epinephrine(EPI) are of interest here. This study aims to advance the application of AuNPs of small neurogenic amines with LDI-TOF MS, including imaging MS techniques. Neurotransmitters were effectively ionized by 2 and 5 nm AuNPs. In addition to ionization of these small molecules, which is traditionally difficult, unique patterns of fragmentation has been observed with different sized AuNPs, with 2 nm AuNPs facilitating greater fragmentation. The mechanism for this phenomenon is still being investigated. NP-to-analyte ratio and laser power both factor into the incidence of fragmentation; complementary experiments are being conducted with attempts to enhance or diminish fragmentation. Because of the difficulty with traditional acid matrices, a comparison with DHB and CHCA will be done. These matrices self-ionize heavily and result in significant chemical noise in the m/z 150-300 range. This is problematic due to the fact that neurotransmitters often have masses in this area; for instance, the masses of DA, 5-HT, and GABA are 153, 176, and 147 Da, respectively. Imaging MS methods have thus far been optimized using AuNPs. Continuing experiments will evaluate limits-of-detection for each neurotransmitter, as well as further experiments using these molecules on biological tissue.

Disclosures: **N.K. McLaughlin:** None. **K. Stumpo:** None.

Poster

794. Novel Techniques of Biochemical Analysis

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Topic: I.01. Molecular/ Biochemical/ and Genetic Techniques

Support: NIDA Intramural Research Program (NIH)
P30 (P30 AR-070254) Rheumatic Disease Research Core Center

Title: A flow cytometry-based approach to study molecular alterations in synapses

Authors: *F. J. RUBIO[1], E. M. HILAIRE[1], P. V. SELVAM[1], C. A. MEJIAS-APONTE[1], S. ZHANG[1], R. CIMBRO[2], B. T. HOPE[1];
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Abstract: Learning plays a central role in cue-induced drug craving. Synapses that are activated during learning are thought to undergo long-lasting alterations to form a long-lasting engram encoding the memory. To identify and characterize these alterations in activated synapses, we first need to isolate them from the surrounding less activated synapses. Synapses can be isolated biochemically as synaptoneurosomes, which contain the presynaptic terminal attached to a resealed post-synaptic spine. Here we validated the use of flow cytometry using an optimized synaptoneurosome preparation to study molecular changes in candidate protein markers of activated synapses induced by drug administration. We first injected virus expressing yellow fluorescent protein (eYFP) into the medial prefrontal cortex (mPFC) to label presynaptic terminals in the striatum. We then administered one injection of 20 mg/kg of cocaine (IP) and harvested synaptoneurosomes from the striatum 0, 5, 10, 30 and 60 min later. After fixation with 0.1% PFA and permeabilization with 0.2% Tween-20, the synaptoneurosomes were stored at -80 °C in 5% DMSO and used later for immunolabeling. Within the gate chosen for synaptoneurosomes (eYFP-positive events), 60 or 80% of them were PSD95- or synaptophysin-positive for post-synaptic and pre-synaptic compartments, respectively. Different antibodies were used for analyzing candidate markers of synaptic activity, including Arc protein, CaMKII, phospho-CaMKII, ribosomal protein S6 and its phosphorylated form. We found time-dependent molecular alterations following cocaine administration, with the biggest alterations (4-fold) at 60 min for phospho-CaMKII and ribosomal protein S6. We will use these 2 protein labels as markers of activated synapses on activated (Fos-expressing) neurons associated with learning and cue reactivation in models of drug relapse. Further immunohistochemical analysis will be used to validate changes in these candidate proteins at the synapses.

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Poster

794. Novel Techniques of Biochemical Analysis

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Title: A high-loading drug delivery system with pH response based on magnetic nanomaterials modified by hyperbranched phenylboronic acid for glioma cell targeting treatment

Authors: H. SONG[1], Y. WANG[1], J. ZHANG[2], ***Y. LU**[1], R. GAO[2];
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Abstract: Glioma is the one of the most insidious and destructive type of brain tumor. The therapeutic effect is not satisfied by using surgery, radiotherapy and chemotherapy to treat glioma. Especially, the limited functionality of chemotherapy is due to the side effects to the normal glia cells. In this study, we have designed a novel hyperbranched phenylboronic acid (PBA) magnetic drug delivery system (DDS) capable of high drug loading, glioma targeting, and pH-responsive release to overcome the limited drug loading capacity of magnetic nanopharmaceuticals arising from the relatively large mass of the metal core. The preparation conditions, adsorption and desorption capability, and glioma cells targeting ability of the DDS were investigated in detail through chemical and biological experiments. The drug loading amount and thermodynamic fitting results of the DDS demonstrate its high drug loading capacity and multilayered adsorption process. The experimental results in U-87 MG malignant glioma cells confirm the glioma cells targeting and pH-responsive release properties of the DDS compared with primary cultured astrocytes. Moreover, the hemolysis assay shows that the DDS has good histocompatibility, which is a crucial prerequisite for *in vivo* experiments and further clinical application. The developed method could be an alternative solution for designing high-loading DDSs with a high-mass metal core and provides new perspective of thinking for studies on magnetic targeting, magnetic resonance imaging and magnetocaloric effects in glioma therapy.

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Poster

794. Novel Techniques of Biochemical Analysis

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Program #/Poster #: 794.08/CC52

Topic: I.01. Molecular/ Biochemical/ and Genetic Techniques

Title: Iterative direct expansion microscopy

Authors: *D. SARKAR[1], A. WASSIE[1], J. KANG[1], T. TARR[2], A. TANG[2], T. A. BLANPIED[3], E. S. BOYDEN[1];
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Abstract: While dense biomolecule-rich structures (such as synapses) support diverse biological functionsof importance in brain computation and pathology, visualization tags such as antibodies often cannot access biomolecules of interest in those crowded environments. Thus, visualization and deciphering of the nanoscale organization of such compact structures remains difficult. Here, we report a technology that not only allows nanoscale resolution imaging of intact tissues in ascalable way, but also offers a novel protein de-crowding effect allowing access of tags to individual biomolecules within densely packed structures, otherwise inaccessible.
This technology is the next generation of expansion microscopy, our technique for overcoming the diffraction limit of optical microscopy through physical magnification of biological specimens (Science (2015) 347(6221):543-548). While, in the original expansion microscopy(ExM) process, about 4.5x linear expansion and hence, a resolution of 60 nm (300 (diffractionlimit) / 4.5 (expansion factor)) was achieved, we recently demonstrated that, by iterating the expansion process (iExM), it is possible to obtain higher expansion factors (~20x) and higher resolution (300/20 ~15 nm) (Nature Methods (2017) 14, 593-599). However, in iExM, the biomolecules themselves were not retained during the process, but instead DNA strands were used to encode relative location information, which requires staining before expansion withDNA-conjugated antibodies.
Our new technology, which we call iterative direct expansion microscopy (idExM), not only allows iterative rounds of expansion leading to high expansion factors (up to 100 fold) and thus,excellent super resolution (<10 nm resolution) on ordinary microscopes, it retains the biomolecules throughout the whole process. Thus, the tags can be brought in to label the biomolecules after the expansion, when they are de-crowded from each other and more accessible to tags such as antibodies. We are now using idExM to visualize nanoscale details of highly complex and compact architectures in intact brain circuits.

Disclosures: D. Sarkar: None. **A. Wassie:** None. **J. Kang:** None. **T. Tarr:** None. **A. Tang:** None. **T.A. Blanpied:** None. **E.S. Boyden:** None.

Poster

794. Novel Techniques of Biochemical Analysis

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Topic: I.01. Molecular/ Biochemical/ and Genetic Techniques

Support: The Korea Goverment (MSIT) NRF-2017R1A2B2006896
The Grainger Foundation

Title: Enhanced sensitivity and selectivity in the detection of serotonin *in vivo* using N-shaped fast cyclic square wave voltammetry

Authors: H. SHIN[1,4], *Y. OH[1], C. PARK[4], Y. KANG[4], A. RUSHEEN[1], A. S. BARATH[1], K. E. BENNET[2], C. D. BLAHA[1], K. H. LEE[1,3], D. JANG[4];
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Abstract: Background: Serotonin is thought to be involved in numerous physiological processes underlying anxiety, impulsivity and compulsivity, mood, social behavior, and stress. *In vivo* microdialysis has been useful in establishing the role of serotonin in these disorders and others, but is constrained in both spatial and temporal measurement resolution. Conventional N-shaped fast scan cyclic voltammetry (N-FSCV) in combination with carbon fiber microelectrodes (CFM) has been shown to be able to detect serotonin *in vivo*, but has relatively low sensitivity and selectivity compared to microdialysis. Thus, there is a need to improve current voltammetric techniques in both sensitivity and selectivity to serotonin. Based on our previous studies using fast cyclic *square wave* voltammetry (FCSWV) for *in vivo* dopamine measurements, we have modified this technique to optimize the detection of serotonin *in vivo*. **Methods**: A series of large amplitude square-shaped potentials was superimposed onto an N-shaped waveform to provide cycling through multiple redox reactions within the N-shaped waveform to increase sensitivity and selectivity to serotonin. We electrically stimulated (0.35 mA amplitude, 60-90 Hz frequency, 2 ms biphasic pulse width for 2-5 sec) the medial forebrain bundle in the urethane (1.5 gm/kg i.p.) anesthetized rat (AP:-2.7, ML:+1.7, DV:-8.0) with a bipolar parallel electrode and recorded stimulation evoked phasic release of serotonin in the substantia nigra reticular (SNr) with a CFM (AP:-4.8, ML:+2.0, DV:-8.5). Pharmacological confirmation of serotonin was performed with escitalopram (ESCIT, 10 mg/kg i.p.), a serotonin selective reuptake inhibitor. **Results**: N-shaped fast cyclic *square wave* voltammetry (N-FCSWV) showed 3 times higher sensitivity to serotonin than conventional N-FSCV. In addition, N-FCSWV could differentiate serotonin from dopamine and 5-hydroxyindoleascetic acid. N-FCSWV was confirmed that the square waveform did not influence local neuronal activity, and it could monitor electrical stimulation evoked phasic release of serotonin in the rat SNr before and

after injection of ESCIT. **Conclusions**: Here, we introduce N-FCSWV as a novel *in vivo* voltammetric technique for serotonin measurement by combining large amplitude CSWV with a background subtraction method based on conventional N-waveform design. Application of a large amplitude square wave potential induced multiple redox chain reactions within a single square wave pulse resulting in increased sensitivity to serotonin.

Disclosures: H. Shin: None. **Y. Oh:** None. **C. Park:** None. **Y. Kang:** None. **A. Rusheen:** None. **A.S. Barath:** None. **K.E. Bennet:** None. **C.D. Blaha:** None. **K.H. Lee:** None. **D. Jang:** None.

Poster

794. Novel Techniques of Biochemical Analysis

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Program #/Poster #: 794.10/CC54

Topic: I.01. Molecular/ Biochemical/ and Genetic Techniques

Title: A high efficacy selection method for transfected cells utilizing recombinant isolectin B4-saporin

Authors: M. A. GALVAN, P. A. SHRAMM, R. BOUAJRAM, D. A. LAPPI, *L. R. ANCHETA;
Cytologistics, LLC, San Diego, CA

Abstract: Transfection protocols often rely on the use of antibiotics for the selection of transfected cells and has become the accepted approach for *in vitro* research and therapeutic applications. Antibiotics have several shortcomings such as cost, continuous use, and harmful effects -- even on the transfected cell population. In addition, selection pressures are often inefficient and fail to provide a population of cells that express the gene of interest (GOI) at high levels. We have used three separate GOI's to select for solely high-expressing transfectants using targeted toxin selection pressure. Normal Rat Kidney Cells (KNRK) were individually transfected to express green fluorescent protein (GFP), melanopsin or the low-affinity nerve growth factor receptor (p75) using an innovative new transfection delivery vector called pGEI. The results from various assays were utilized to visually determine the expression rate and pattern of the targeted toxin selection method. Melanopsin and p75 -- a photopigment and nerve growth factor, respectively -- were of great interest to express in our transfected cells as a means to study their role in the development and function of neurons. The delivery vector, pGEI, removes resident Galalpha(1-3)Gal epitopes from non-human mammalian cell surfaces. This residue is the target of recombinant Isolectin B4 - Saporin (IB4-SAP), a selective targeted toxin. IB4-SAP is extremely potent, with an EC_{50} in the low picomolar range for alpha-D-galactopyranoside expressing cells *in vitro*. The cells with the highest expression of the inserted vector, and therefore the GOI, will have these residues removed. Those that fail to express the

vector or do not express the vector in high enough amounts, will not have all the residues removed, and will be targeted and eliminated via IB4-SAP. This method of selection provides a means of purifying the highest-expressing transfected populations using a more cost-effective and time-saving approach.

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Poster

794. Novel Techniques of Biochemical Analysis

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 794.11/CC55

Topic: I.01. Molecular/ Biochemical/ and Genetic Techniques

Support: NIH R01 DA035281
NIH R01 DA035482
NIH R44 DA041967

Title: Nicotine and THC exposure in rats using JUUL®-related electronic cigarette devices

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Abstract: The popularization of electronic nicotine delivery systems (ENDS), including the JUUL® device, in recent years stimulates the need for preclinical models examining this method of drug delivery. The appearance of third-party refillable pods, which can be substituted for the nicotine containing JUUL® pods, , gives rise to the potential for this device to be used for the delivery of other psychoactive substances, most notably Δ9-tetrahydrocannabinol (THC). In the present study, nicotine and THC were administered to rats using a vapor inhalation system modified with an adapter for JUUL® vaporizers, to compare with prior results using a canister style ENDS device. Blood plasma levels of nicotine, cotinine and THC were measured to assess the efficacy of drug delivery. Adult male rats were implanted with intravenous catheters to facilitate blood draws within the inhalation chamber. Subjects were administered vaporized nicotine or THC during 30-minute vapor sessions. Blood samples (~500 µL) were collected from the catheters at sequential time points within session (t = 5, 15, 30 and/or 35 min). Plasma nicotine, cotinine, and THC levels were then quantified via liquid chromatography/mass

spectrometry (LC/MS) using an Agilent 1100 series HPLC system coupled with an Agilent MSD6140 mass spectrometer configured for selected ion monitoring [nicotine (*m*/*z* = 163.1), nicotine-d4 (*m*/*z* = 167.1), cotinine (*m*/*z* = 177.1), cotinine-d3 (*m*/*z* = 180.1), THC (*m*/*z* = 315.2), THC-d3 (*m*/*z* = 318.2)]. Nicotine blood plasma levels showed a time/cumulative dose-dependent increase across the 30-minute session, with a peak of 17.82 ng/mL (±0.92 SEM) at the t = 30 min. time point. Cotinine levels demonstrated a similar rise, increasing to 16.16 ng/mL (±3.62 SEM) at t = 35 min. THC analysis is currently in progress. Plasma drug concentrations observed with the JUUL® device are consistent with results previously observed in our laboratory using refillable canister style ENDS . These data confirm that physiologically relevant doses of psychoactive compounds can be delivered to rats via inhalation using JUUL® devices. Therefore it is possible to use JUUL® ENDS for preclinical studies of the psychoactive effects of nicotine or other drugs when delivered by vapor inhalation.

Disclosures: E.L. Harvey: None. **J.D. Nguyen:** None. **Y. Grant:** None. **T.M. Kerr:** None. **M. Cole:** None. **M.A. Taffe:** None.

Poster

794. Novel Techniques of Biochemical Analysis

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 794.12/CC56

Topic: I.01. Molecular/ Biochemical/ and Genetic Techniques

Title: Sox-based sensors for protein kinases and phosphatases for neuroscience discovery and drug development

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Abstract: Introduction: Protein kinases are a diverse group of 535 enzymes whose dysregulation lies at the center of many diseases including brain tumors, neuroinflammation and neurodegeneration. Although 50 drugs are approved, these are predominately ATP-competitive inhibitors. More recently, there is an expanded focus on inhibitors with different modes of action, where new tools are needed to effectively characterize mechanism of action and predict drug potency. Methods: We harnessed chelation-enhanced fluorescence by combining the sulfonamido-oxine (Sox) chromophore with high-throughput solid-phase peptide synthesis to create optimized peptide sensors for quantitative and homogenous detection of kinase and phosphatase activity. The same sensor can be monitored kinetically using fluorescence intensity (Ex/Em 360/485 nm) or in endpoint mode using Europium and time-resolved fluorescence (Ex/Em 360/620 nm). Results: We established a robust process to rapidly identify novel

optimized substrates based on physiological sequences. We identified highly-generic substrates for detection of 80 Tyr kinases and highly-selective substrates for quantitative detection in crude cell or tissue lysates including analysis of Protac-mediated degradation of kinases. The resulting panel of neuroscience-related sensors created for high-profile tyr kinases: EGFR & clinically-relevant mutants, Src, TEC-family (BMX, BTK, ITK, TEC, TXK) & TRKA-C, and, ser/thr kinases: AMPK (+/- AMP), CAMK2a, b, d (+/- Ca/Calmodulin), CDK5, GSK3b, LRRK2, MAP3Ks (DLK, Raf), MAPKs (ERK1/2, JNK1-3, p38a-d), MARK1-4, PKR (+/- RNA)/EIF2AKs, PKA, PKC (+/- Ca/lipid) & PKG (+/- cGMP), illustrates the broad applicability of our approach, including enabling the study of Tau phosphorylation and the role of LRRK2 in Parkinson's disease. In addition, we created CSox-based phosphopeptide sensors to monitor protein phosphatases with specificity for tyr (PTP1B, SHP1/2) or ser/thr (PP2A, PP2B, PP2C, PHLPP1/2). Conclusions: The generation of robust activity-based sensors for a range of neuroscience kinase and phosphatase targets opens new areas for discovery and drug development. The described kinetic assay format is ideal for elucidating drug mechanism of action, potency, and enzyme regulation, while the Red/endpoint format is ideal for HTS, SAR and profiling. Together, these formats can be applied across the entire discovery and drug development workflow, providing a quantum improvement in creating next generation protein kinase and phosphatase inhibitors.

Disclosures: E. Schaefer: None. **S. Cornell-Kennon:** None. **B. Lu:** None. **J. Fishman:** None. **E. Berg:** None. **B. Imperiali:** None.

Poster

794. Novel Techniques of Biochemical Analysis

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 794.13/CC57

Topic: I.01. Molecular/ Biochemical/ and Genetic Techniques

Title: rsCaMPARI: An erasable marker of neuronal activity

Authors: *F. SHA, A. S. ABDELFATTAH, R. PATEL, J. J. MACKLIN, E. R. SCHREITER; Janelia Res. Campus, Howard Hughes Med. Inst., Ashburn, VA

Abstract: Identifying and comparing active neuron ensembles underlying different complex behaviors is a key challenge in neuroscience. Recent tools such as CaMPARI have enabled the optical marking and selection of active neuron populations[1,2]. However, CaMPARI is based on the activity of a photoconvertible fluorescent protein whereby the marking is permanent and irreversible. These properties limit the utility of CaMPARI in samples where multiple snapshots of activity are desirable or where different activity profiles must be compared within the same sample. We sought to overcome these limitations by developing an erasable neuronal activity marker based on a reversibly switchable fluorescent protein. Here we introduce a new tool

named rsCaMPARI, a reversibly switchable calcium marker that enables spatiotemporal precise marking, erasing, and remarking of active neuron populations under widefield illumination. rsCaMPARI photoswitching kinetics are modulated by calcium concentration when illuminating with blue light, and the fluorescence can be recovered with violet light. We demonstrate the utility of rsCaMPARI for repeated marking and erasing of calcium activity in cultured neurons and freely swimming larval zebrafish.

1. Fosque, B. F. *et al*. Neural circuits. Labeling of active neural circuits *in vivo* with designed calcium integrators. Science **347**, 755-760, doi:10.1126/science.1260922 (2015).
2. Moeyaert, B. *et al*. Improved methods for marking active neuron populations. *Nat Commun* **9**, 4440, doi:10.1038/s41467-018-06935-2 (2018).

Disclosures: F. Sha: None. **A.S. Abdelfattah:** None. **R. Patel:** None. **J.J. Macklin:** None. **E.R. Schreiter:** None.

Poster

795. Anatomic Methods: Sample Preparation and Novel Probes

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 795.01/CC58

Topic: I.03. Anatomical Methods

Support: Research and Development Support from NSA Labs, Inc.

Title: Comparison of occlusion and staining techniques in rodents with induced cva injuries and the use and effectiveness of ischemia contrast stain

Authors: *S. O. AHMAD[1], K. BARILLIER[1], B. KINGSLEY[1], M. KUMNICK[1], J. BAUN[2], T. YORK[2], R. SWITZER, III[2];
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Abstract: The purpose of this methods project is to investigate the efficacy and implications of various methods of occlusion and staining techniques on Sprague-Dawley rats with a Middle Cerebral Artery Occlusion. Through a literature review, ten studies were identified for comparative analysis of factors including: animal information, occlusion method, length of time of occlusion, amount of time post-occlusion at which staining occurred, type of stain used and the outcomes of the study. Fluroro-Jade B, NeuN, Nissel, and Hematoxylin and Eosin were all used in one study respectively, and Cresyl-Violet was used in two of the studies. Our Method: Neurohistology Embedding, Sectioning & Staining Brains or spinal cords received at NeuroScience Associates were examined, then treated overnight with 20% glycerol and 2% dimethylsulfoxide to prevent freeze-artifacts. The specimens were then embedded in a gelatin matrix using MultiBrain®/ MultiCord® Technology (NeuroScience Associates, Knoxville, TN).

The blocks were rapidly frozen, after curing by immersion in 2-Methylbutane chilled with crushed dry ice and mounted on a freezing stage of an AO 860 sliding microtome. All sections were cut through the entire length of the specimen segment and collected sequentially into series of 24 containers. Ischemia Contrast stain - For Ischemia Contrast staining, sections are first mounted onto gelatinized (subbed) slides then stained with a modification of the Weil method for myelin. They are dehydrated through alcohols, then rehydrated and stained in Hematoxylin/ Ferric Ammonium Sulfate staining solution. They are then differentiated first in 2% Ferric Ammonium Sulfate, rinsed in deionized water rinses, and secondly in a Potassium Ferricyanide/ Sodium Borate solution.Unlike myelin staining, the gray matter is left dark in order to highlight ischemic areas. Following deionized water rinses, the slides are dehydrated in a standard alcohol series, cleared in xylene and coverslipped. Following serial ordering of the slides, rostral to caudal for each stain, the slides were numbered by permanent ink in the upper right corner. Results: Comparative analysis was performed using Ischemia Contrast Staining, Nissl and Hematoxylin staining with pixel distance and greyscale. The image and accompanying gray level range data show that the ICS stain is more capable of showing lesion areas (visually and through data acquisition) compared to HE and thionine: ICS data -- Min. gray value = 4.1, Max gray value = 112.4, Range = 108.3 Thionine data -- Min. gray value = 187.1, Max gray value = 241.0, Range = 54 H&E data -- Min. gray value = 142.6, Max gray value = 180.0, Range = 37.4

Disclosures: **S.O. Ahmad:** None. **K. Barillier:** None. **B. Kingsley:** None. **M. Kumnick:** None. **J. Baun:** None. **T. York:** None. **R. Switzer:** None.

Poster

795. Anatomic Methods: Sample Preparation and Novel Probes

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 795.02/CC59

Topic: I.03. Anatomical Methods

Support: MEXT/JSPS KAKENHI JP16H04663
MEXT/JSPS KAKENHI JP17K19451
MEXT/JSPS KAKENHI JP16H01426
Brain/MINDS from AMED JP18dm0207064
MEXT/JSPS KAKENHI JP18K19641
MEXT/JSPS KAKENHI JP18KK0259
MEXT/JSPS KAKENHI JP15H04266

Title: Multi-scale imaging from the whole brain level to the ultrastructure level by using a modified scales method

Authors: ***H. HIOKI**[1], K. YAMAUCHI[1], S. OKAMOTO[1], K. ISA[3], Y. ISHIDA[1], A. TAKENAKA[4], M. TAKAHASHI[1], J. HWANG[1], A. YOSHIDA[4], Y. UCHIYAMA[2], M.

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Abstract: An optical clearing method, ScaleS, provides stable tissue preservation and thus can be combined with electron microscopy (EM). However, there is still room for improvement on membrane integrity in the cleared samples. In the present study, we aim to establish a pipeline optimized for multi-scale imaging from macro- to nano-levels based on ScaleS technology. We first modified a ScaleS method, and succeeded in transparentizing 1-mm-thick brain slices of mice and marmosets within 14 hours without any change in tissue size. Even after fixation with glutaraldehyde (GA) of a high concentration (2%), the tissue transmittance was retained. Furthermore, by using EM, we observed that addition of GA contributed to preservation of ultrastructures in cleared brain tissue. The effect of fixation with GA on ultrastructures was investigated not only in mice but also in marmosets. Then, aiming at realizing successive LM/EM imaging, we developed an AAV vector expressing a fusion protein of EGFP and APEX2 (peroxidase enzyme). To deposit biotin molecules in APEX2 expressing cells, we performed tyramide signal amplification (TSA) method with brain slice immediately after fixation, and carried out ABC-DAB reaction after tissue-clearing and fluorescence microscopy. Now, we are trying successive LM/EM imaging by combining ScaleS technology with the AAV vector to achieve multi-scale imaging in large scale 3D structure.

Disclosures: H. Hioki: None. **K. Yamauchi:** None. **S. Okamoto:** None. **K. Isa:** None. **Y. Ishida:** None. **A. Takenaka:** None. **M. Takahashi:** None. **J. Hwang:** None. **A. Yoshida:** None. **Y. Uchiyama:** None. **M. Koike:** None. **T. Isa:** None. **T. Furuta:** None.

Poster

795. Anatomic Methods: Sample Preparation and Novel Probes

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Program #/Poster #: 795.03/CC60

Topic: I.03. Anatomical Methods

Support: Samsung Research Funding & Incubation Center of Samsung Electronics under Project Number SRFC-MA1601-08

Title: Scalable and isotropic expansion of tissues with simply tunable expansion ratio

Authors: *H.-E. PARK[1,3], D. CHOI[2], J. PARK[1], C. SIM[2], J. LEE[3,4], Y. LEE[5], Y. LEE[2], S.-Y. KIM[2,4];
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Abstract: Tissue expansion techniques physically magnify gel-embedded samples to enhance effective imaging resolution, but this costs signal dilution, imaging time and photobleaching. We introduce a hydrogel conversion-based expansion method, termed ZOOM, that allows for easy adjustment of the expansion ratio (up to 8-fold in a single expansion process) for individual needs, while simplifying expansion procedure, improving gel uniformity and preserving biomolecules for multi-round labeling. ZOOM can be flexibly applied to nanoscale imaging of subcellular details of cultured cells, brain tissues as well as exoskeletal *C. elegans*.

Disclosures: H. Park: None. **D. Choi:** None. **J. Park:** None. **C. Sim:** None. **J. Lee:** None. **Y. Lee:** None. **Y. Lee:** None. **S. Kim:** None.

Poster

795. Anatomic Methods: Sample Preparation and Novel Probes

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 795.04/CC61

Topic: I.03. Anatomical Methods

Title: New advanced tissue clearing method

Authors: *E.-S. LEE, G.-H. KIM, Y.-I. PARK, S.-I. GUM;
Binaree, Inc., Daegu, Korea, Republic of

Abstract: Conventional histology techniques are laborious and require tissue sectioning, which are barriers toward rapid three-dimensional (3D) visualization of organ structures. The recent development of potent tissue-clearing methods enables rapid 3D imaging of a mouse brain when combined with confocal and light-sheet fluorescence microscopy. In the past seven years, many tissue clearing protocols have spawned. However, a previous method requires expensive equipment and complicated processes, resulting in non-reproducible data. In addition, other methods make too toxic or soft cleared tissue to proceed next steps. Here, we introduce novel tissue clearing method named Binaree tissue clearing methods. Binaree method has simple processes, uses non-toxic solution and takes only 3 days to complete 1-mm thick mouse brain tissue clearing. The maintenance of endogenous fluorescence and single cell resolution within tissues using Binaree tissue clearing were much better than that of other tissue clearing method. In addition, Binaree tissue clearing allow immunostaining of more than 1 mm thick brain tissue. Our results support that Binaree tissue clearing method be a first choice, when you are looking for simple, non-toxic and reproducible clearing method.

Disclosures: **E. Lee:** None. **G. Kim:** None. **Y. Park:** None. **S. Gum:** None.

Poster

795. Anatomic Methods: Sample Preparation and Novel Probes

Location: Hall A

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Topic: I.03. Anatomical Methods

Support: Vascular Dementia Research Foundation
Synergy Excellence Cluster Munich
ERA-Net Neuron
German Federal Ministry of Education and Research via the Software Campus initiative

Title: Cellular and molecular interrogation of intact human organs

Authors: *S. ZHAO[1], M. I. TODOROV[1], R. CAI[1], H. STEINKE[2], E. KEMTER[3], E. WOLF[3], J. LIPFERT[4], I. BECHMANN[2], A. ERTÜRK[1];
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Abstract: The three dimensional (3D) imaging of intact adult human organs at cellular and molecular level is a high interest of biomedical sciences. However, standard histology for human tissues can routinely be applied only on micrometers thick tissue slices due to lack of scalable methods. Here, we introduce SHANEL, a highly scalable method that renders human organs transparent for cellular mapping. To demonstrate SHANEL's utility, we generated first transparent intact adult human brain and kidney, and performed 3D histology using antibodies and dyes in centimeters thick human tissues. We revealed structural details of sclera, iris and suspensory ligament in the human eye, as well as the vessels and glomeruli in the human kidney. SHANEL technology is also applicable on other large mammals including pigs. We mapped complex structures of EGFP expressing beta cells in > 10 cm size pancreas of transgenic pigs. Overall, SHANEL is a robust and unbiased technology to map the cellular and molecular architecture of intact human organs.

Disclosures: **S. Zhao:** None. **M.I. Todorov:** None. **R. Cai:** None. **H. Steinke:** None. **E. Kemter:** None. **E. Wolf:** None. **J. Lipfert:** None. **I. Bechmann:** None. **A. Ertürk:** None.

Poster

795. Anatomic Methods: Sample Preparation and Novel Probes

Location: Hall A

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Program #/Poster #: 795.06/CC63

Topic: I.03. Anatomical Methods

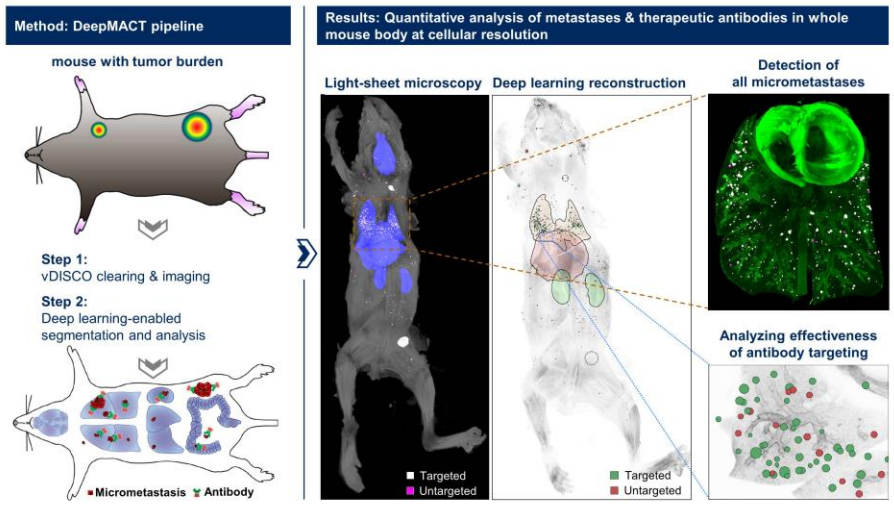
Support: Vascular Dementia Research Foundation
Synergy Excellence Cluster Munich (SyNergy)
ERA-Net Neuron (01EW1501A to A.E.)
Helmholtz-Center for Environment Health (grants to R.Z.)
German Federal Ministry of Education and Research via the Software Campus initiative

Title: Deep learning reveals cancer metastasis and therapeutic antibody targeting in the CNS and whole body

Authors: *C. PAN[1,2], O. SCHOPPE[3], A. PARRA-DAMAS[1], R. CAI[1,2], M. I. TODOROV[1,2], G. GONDI[4], B. VON NEUBECK[4], A. GHASEMIGHARAGOZ[1], M. A. REIMER[1], B. GARVALOV[5], B. MENZE[3,6], R. ZEIDLER[4,7], A. ERTÜRK[1,2,8];
[1]KUM-LMU Inst. For Stroke and Dementia, Munich, Germany; [2]Grad. Sch. of Systemic Neurosci. (GSN), Munich, Germany; [3]Ctr. for Translational Cancer Res. (TranslaTUM) & Dept. of Computer Sci., Munich, Germany; [4]Helmholtz Zentrum München, Res. Unit Gene Vectors, Munich, Germany; [5]Dept. of Microvascular Biol. and Pathobiology, European Ctr. for Angioscience (ECAS), Heidelberg, Germany; [6]Munich Sch. of Bioengineering, Tech. Univ. of Munich, Munich, Germany; [7]Dept. for Otorhinolaryngology, Klinikum der Univ. München, Munich, Germany; [8]Munich Cluster for Systems Neurol. (SyNergy), Munich, Germany

Abstract: Reliable detection of disseminated tumor cells and of the biodistribution of tumor-targeting therapeutic antibodies within the entire body including into the brain has long been needed to better understand and treat cancer metastasis. Here, we developed an integrated pipeline for automated quantification of cancer metastases and therapeutic antibody targeting in the whole-body including the CNS, named DeepMACT. First, we enhanced the fluorescent signal of tumor cells more than 100-fold by applying the vDISCO method (Cai et al., 2019, Pan et al.,2016) to image single cancer cells in intact transparent mice. Second, we developed deep learning algorithms for automated quantification of metastases with an accuracy matching human expert manual annotation. Deep learning-based quantifications in a model of spontaneous metastasis using human breast cancer cells allowed us to systematically analyze clinically relevant features such as size, shape, spatial distribution, and the degree to which metastases are targeted by a therapeutic monoclonal antibody in whole mice. DeepMACT can thus considerably improve the discovery of effective therapeutic strategies for metastatic cancer (Pan et al., 2019).

Reference: Pan C, Schoppe O⋯Ertürk A. Deep learning reveals cancer metastasis and therapeutic antibody targeting in whole body. Corresponding author. BioRxiv: https://www.biorxiv.org/content/10.1101/541862v1.
Cai R, Pan C⋯Ertürk A (2018, Nature Neuroscience, Cover article). Panoptic imaging of transparent mice reveals whole-body neuronal connectivity and skull-meninges connections.
Pan, C., Cai, R., Quacquarelli, F.P., Ghasemigharagoz, A., Lourbopoulos, A., Matryba, P., Plesnila, N., Dichgans, M., Hellal, F., and Ertürk, A. (2016 Nature Methods, Cover article). Shrinkage-mediated imaging of entire organs and organisms using uDISCO.



Disclosures: C. Pan: None. **O. Schoppe:** None. **A. Parra-Damas:** None. **R. Cai:** None. **M.I. Todorov:** None. **G. Gondi:** None. **B. von Neubeck:** None. **A. Ghasemigharagoz:** None. **M.A. Reimer:** None. **B. Garvalov:** None. **B. Menze:** None. **R. Zeidler:** None. **A. Ertürk:** None.

Poster

795. Anatomic Methods: Sample Preparation and Novel Probes

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 795.07/CC64

Topic: I.03. Anatomical Methods

Support: ITS/381/15

Title: Establishing an experimental protocol for making transparent brain for neurodegenerative disease research

Authors: *K. LEE[1], H. LAI[2], R. C. CHANG[1,3];
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Abstract: Until recently, different techniques have been developed to clear tissues to become transparent. However, to speed up the process, most of the methods involve many steps of chemical treatments or extreme temperature. This leads to several issues including fluorescent quenching, protein degradation, and distortion to tissue architecture due to swelling/shrinkage. While some techniques protect tissues by cross-linking them with acrylamide and epoxy monomers, these treatments are usually irreversible. Until now, there is no technique that can preserve tissues from exposing to many steps of chemicals or extreme temperature. Therefore, we have established a delipidation-based technique to preserves tissue structure without the use of any external monomer network.

In this study, we performed partial delipidation by adding OPTIClear, a refractive index (RI) matching solution, into SDS solution. We found that tissue clearing with SDS-OPTIClear not only reduced the required clearing time than usual SDS solution, but also showed less protein loss and no intense swelling/shrinkage.

We further demonstrated that tissues cleared with SDS-OPTIClear would have better antigen preservation, thus allowing better quality in immunohistochemical staining. Previously, it has been reported the failure of immunofluorescence staining with Iba-1, a marker of microglia, after SDS-treatment. Here, we demonstrated Iba-1 immunoreactivity in the hippocampus treated with SDS-OPTIClear and SDS solution. Under the same condition, tissues cleared with SDS-OPTIClear showed better morphology and deeper penetration depth compared to the one cleared with SDS. Immunohistochemical staining of other antigens such as ChAT and TOMM-20 showed that they had stronger signal and deeper penetration depth in tissues treated with SDS-OPTIClear.

Finally, we performed TO-PRO-3 staining on tissues and visualized under confocal microscopy before and after clearing such that the degree of distortion after clearing can be examined and quantified. While tissues cleared with SDS showed dramatic size change upon clearing and RI matching, SDS-OPTIClear did not trigger swelling effect. Tissue morphology was preserved throughout clearing and RI matching.

Taken together, we demonstrated that SDS-OPTIClear preserved better tissue morphology and architecture without the requirement of tissue embedding. This is a simple and cost-effective methodology. This allows us to investigate neurodegeneration with high resolution in a three-dimensional manner without intense swelling/shrinkage.

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Disclosures: K. Lee: None. **H. Lai:** None. **R.C. Chang:** None.

Poster

795. Anatomic Methods: Sample Preparation and Novel Probes

Location: Hall A

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Program #/Poster #: 795.08/CC65

Topic: I.03. Anatomical Methods

Support: SINTEF
Forskningsrådet

Title: Effects of omega-3 fatty acids in modulating the role of glia cells in synaptic plasticity in dementia

Authors: *D. SARAJ[1], S. ARYAL[2], T. EID[4], S. DAVANGER[3];
[1]Dept. of Mol. Med., [3]Anat., [2]Univ. of Oslo - Inst. of Basic Med. Sci., Oslo, Norway; [4]Dept Lab. Med., Yale Univ., New Haven, CT

Abstract: The effects of omega-3 fatty acids on brain function and ageing is currently of public interest, likewise the use of diet-based interventions to counteract age-related disorders. High intake of DHA and other omega-3 polyunsaturated fatty acids (n-3 PUFAs) have been described as protective against age-related cognitive decline, dementia and Alzheimer's disease. These molecules may act as endogenous anti-inflammatory mediators and are produced during the resolution phase of inflammation. Our aim is to investigate the possible role of omega 3 fatty acids in the prevention of Alzheimer's disease, through glial cell/synapse interactions. We will use omega-3 fatty acids as anti-neuroinflammatory agents to intervene with glial cell phagocytosis of synapses in the hippocampus and related regions of the cerebral cortex of young mice. We have initially fed young mice with a diet with or without the omega-3 fatty acids docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) for 5 months after weaning. This dietary intervention led to a 65 % increase in the concentration of DHA in whole brain synaptosomal phospholipids compared to the negative controls, while the corresponding increase in EPA was even higher (457 %). We observed increased concentrations of glutamate receptor subunits, including GluA1, GluA2, and NR2B, and synaptic vesicle proteins synaptophysin and synaptotagmin 1 in hippocampal synaptosomes of omega-3 fatty acid-fed mice as compared to the deficient group. In contrast, a decreased concentration of neuronal inositol 1,4,5-trisphosphate-receptor 1 (IP3-R1) was observed in the omega-3 fatty acid enriched group. Furthermore, omega-3 fatty acid enrichment increased the long-term potentiation (LTP) in stratum oriens of the hippocampal CA1 area, but not in stratum radiatum. The mice will also be investigated for cognitive/behavioural changes, astrocyte and microglial inflammatory activation patterns, and dendritic spine density. We will use the same intervention in a mouse model of Alzheimer's disease (5xFAD) with manifest Amyloid plaques.

Disclosures: D. Saraj: None. **S. Aryal:** None. **S. Davanger:** None. **T. Eid:** None.

Poster

795. Anatomic Methods: Sample Preparation and Novel Probes

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Program #/Poster #: 795.09/CC66

Topic: I.03. Anatomical Methods

Title: Ethanolic extract of garcinia kola (heckel) affects the histology of organs of the hypothalamic-pituitary-gonadal axis in adult Wistar rats

Authors: *A. U. OBI[1], P. U. NWOHA[2];
[1]Dept. of Anat. and Neurobio., Imo State Univ., Owerri, Nigeria; [2]Anat. and Cell Biol., Obafemi Awolowo Univ., Ile Ife, Nigeria

Abstract: This study was designed to evaluate whether or not the extract of *Garcinia kola* affects organs in the neuro-endocrine-reproductive axis in adult male Wistar rats. Four groups A, B, C and D (6 rats per group) of adult Wistar rats were used for this study. Group D, served as the control, had normal saline, while groups A, B and C formed the experimental groups and receivrd 500mg, 1000mg and 1500mg respectively of the ethanolic extract of *Garcinia kola* per kilogram body weight for four weeks. All groups were fed normal rat chow, and free access to tap water *ad libitum.* At the end of the second and the fourth week, three rats from each group were sacrificed; the hypothalamus, pituitary and the testis were harvested, fixed in formal saline, processed and stained with haematoxylin and eosin stains. Results of the study showed significant histological alteration in the organs of study of the 1500mg/kg group. These alterations presents more evident in the testis than in the hypothalamus. There was degeneration of the leydig cells, and the luminal spermatozoa. The present study suggests that exposure or consumption of *Garcinia kola* could alter the histology of organs in the hypothalamo-pituitary-gonadal axis in adult male Wista*r* rats.

Disclosures: A.U. Obi: None. **P.U. Nwoha:** None.

Poster

795. Anatomic Methods: Sample Preparation and Novel Probes

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 795.10/CC67

Topic: I.03. Anatomical Methods

Support: 1F31NS11184701

NIH-5R01MH110932
NIH-1UF1NS107659

Title: Multimodal measurement of neuron morphology, molecular identity, and connectivity using novel clearing and expansion technology

Authors: *F. Y. SHEN[1], H. CHENG[3], L. WALKER[1], K. FINOS[1], M. HARRINGTON[1], X. LI[4], D. CAI[2];
[2]Cell and Developmental Biol., [1]Univ. of Michigan, Ann Arbor, MI; [3]Cell and Developmental Biol., Univ. Of Michigan, Ann Arbor, MI; [4]Cell && Developmental Biol., Ann Arbor, MI

Abstract: A tremendous goal in neuroscience is to catalog all the different neuronal cell types in the brain. The difficulty is that neurons can be defined by many different criteria, including anatomical, molecular, and functional properties. Moving forward, it'll be fundamentally important to perform multimodal measurements of neuron properties to ameliorate conflicting definitions of cell types. To address this correspondence problem, we have developed a multi-round antigen preserving expansion (mapEx) protocol that can be combined with multicolor genetic labeling strategies (Brainbow) to simultaneously interrogate morphology, molecular identity, and connectivity in thick brain sections. The capacity for 3-4x linear expansion of the tissue specimen gives us the ability to perform "super-resolution" imaging to untangle densely labeled neurons and trace their neurites using nTracer, a custom ImageJ software. By optimizing the preservation of antigens in a hydrogel, we are able to carry out multiple rounds of immunostaining for Brainbow fluorophores and cell type markers. As a proof of concept, we demonstrate that mapEx can be applied to Brainbow labeled inhibitory neurons in the basolateral amygdala to correlate inhibitory neuron cell types with their morphologies and local anatomy network. Furthermore we show that Brainbow immunostaining can be combined with pre- and post-synaptic markers to measure synaptic connectivity between neurons. We envision mapEx combined with Brainbow to be a powerful tool researchers can use to perform multimodal analysis of neuronal structure, molecular identity, and connectivity.

Disclosures: F.Y. Shen: None. **H. Cheng:** None. **K. Finos:** None. **X. Li:** None. **D. Cai:** None.

Poster

795. Anatomic Methods: Sample Preparation and Novel Probes

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 795.11/CC68

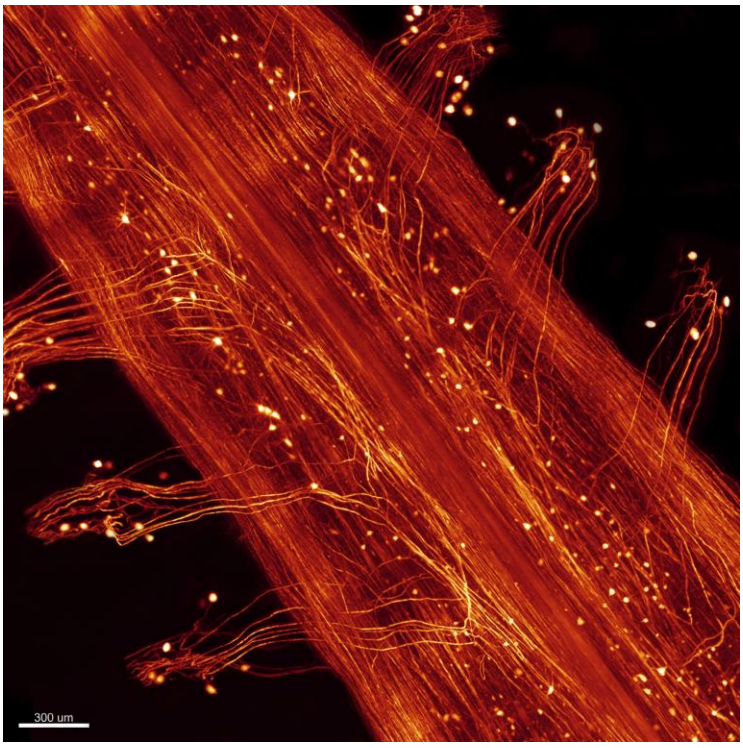
Topic: I.03. Anatomical Methods

Support: NIH/NIDCR R21 DE027928

Title: Tissue clearing of both hard and soft tissue organs with the PEGASOS method

Authors: D. JING[1], ***H. ZHAO**[2];
[1]Texas A&M Univ. Col. of Dent., Dallas, TX; [2]Texas A&M University, Col. of Dent., Dallas, TX

Abstract: Tissue clearing technique enables visualization of opaque organ and tissue in 3-dimension by turning tissue transparent. Current tissue clearing methods are restricted by limited types of tissue that can be cleared with each individual protocol, which inevitably led to the presence of blind-spots within whole body or body parts imaging. Hard tissues including bones and teeth are still the most difficult organs to be cleared. In addition, endogenous fluorescence loss remains to be a major concern for solvent based clearing methods. Here, we developed a polyethylene glycol (PEG) Associated Solvent System (PEGASOS), which rendered nearly all types of tissue transparent and preserved endogenous fluorescence. Bones and teeth could be turned to nearly invisible after clearing. The PEGASOS method turned the whole adult mouse body transparent and we were able to image an adult mouse head composed of bones, teeth, brain, muscles and other tissues with no blind areas. Hard tissue transparency enabled us to reconstruct intact mandible, teeth, femur or knee joint in 3-D. We were able to image intact mouse brain at sub-cellular resolution and to trace individual neurons and axons over a long distance. We were able to visualize dorsal root ganglions directly through vertebrae. Finally, we revealed the neural network distribution pattern in 3-dimension within the long bone marrow space. These results suggest that the PEGASOS method is a useful tool for general biomedical research.



Disclosures: D. Jing: None. **H. Zhao:** None.

Poster

795. Anatomic Methods: Sample Preparation and Novel Probes

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 795.12/CC69

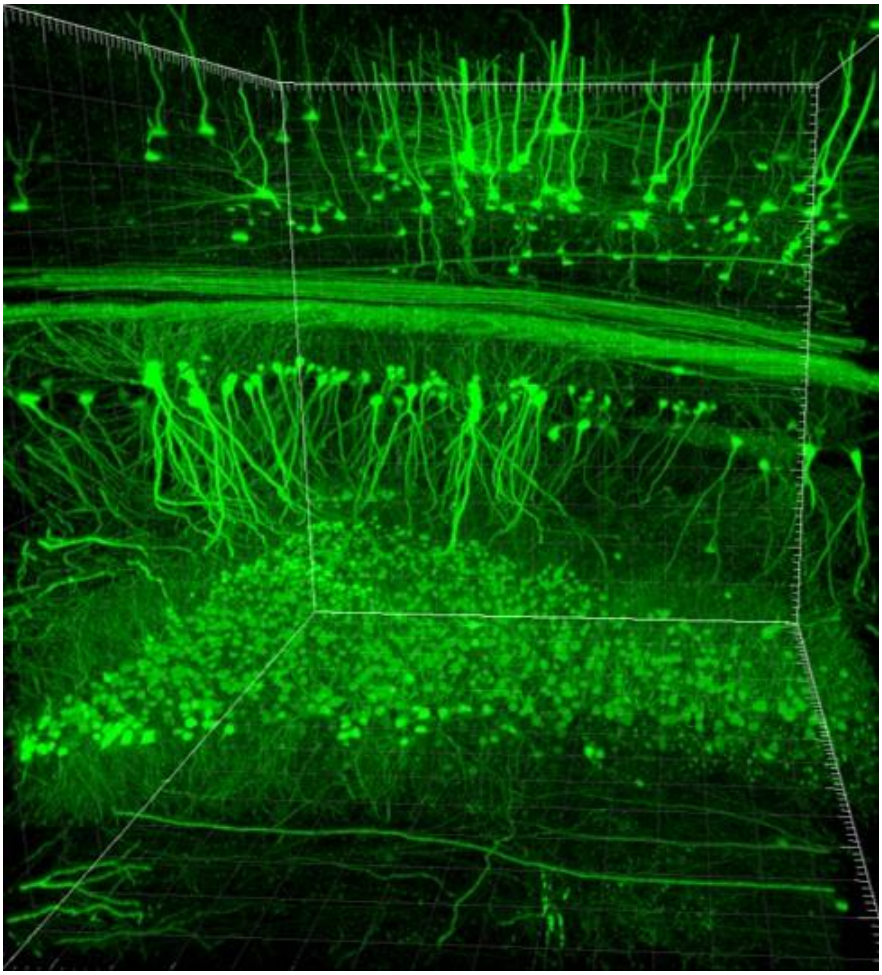
Topic: I.03. Anatomical Methods

Support: NIH/NIDCR R21 DE027928

Title: The second generation PEGASOS method: A new solution for high-resolution connectome mapping in large organs

Authors: *Y. YI[1], H. ZHAO[2];
[2]Dept. of Restorative Sci., [1]Texas A&M University, Col. of Dent., Dallas, TX

Abstract: Contradictions between resolution, working distance and optical aberration in deep region are major challenges for current tissue clearing methods during connectome mapping. To solve these problems, based on our previous PEGASOS tissue clearing method, we developed the second generation PEGASOS method (PEGASOS 2). PEGASOS 2 technique is a combination of block surface imaging and tissue clearing. The clearing process is composed of fixation, decalcification (for hard tissues), decolorization, delipidation, dehydration and clearing. Finally, the clearing medium could be conveniently converted into transparent gel embedding the sample from inside to outside. The gel formation embedding process improves the tissue strength by over 150 folds. Embedded tissues remain highly transparent and GFP fluorescence remains unchanged after gel formation. Images were acquired only for the superficial regions of the sample ranging from 200 micrometers to several millimeters depending on the objective working distance and resolution requirement. The embedded samples were sectioned to remove the superficial regions and exposed deeper regions were then imaged. Strong mechanical properties of the solvent gel prevent distortion from the cutting process. All stacks were stitched together with no noticeable discontinuity or distortion. The PEGASOS 2 method is applicable for all types of tissue including brain, bones, spinal cord of any size. It is also compatible with any objective disregarding their working distance. We used 40X 1.3NA confocal objective with 240 micrometer working distance to image brain (figure), vertebrae, bone and body trunk of over several millimeters thickness with nearly identical resolution throughout the entire sample. Projections of neural axons were clearly identified. In summary, PEGASOS 2 method provides a powerful tool for high-resolution connectome mapping of large organs composed of complex tissue types.



Disclosures: **Y. Yi:** None. **H. Zhao:** None.

Poster

795. Anatomic Methods: Sample Preparation and Novel Probes

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 795.13/CC70

Topic: I.03. Anatomical Methods

Support: NIH Grant R01-EB021018

Title: Chronic mouse imaging: From optical systems to functional ultrasound

Authors: *K. KILIÇ, J. TANG, E. ERDENER, S. SUNIL, J. T. GIBLIN, B. S. LEE, D. D. POSTNOV, A. I. CHEN, D. A. BOAS;
Biomed. Engin., Boston Univ., Boston, MA

Abstract: Functional ultrasonography (fUSG) of the brain is a recently introduced imaging technique in the neuroscience field. Power Doppler-based fUSG has shown promising results for imaging cerebral hemodynamics of the entire mouse brain with ~100 μm resolution. Microbubble tracking-based ultrasound localization microscopy (ULM) has the ability to map the microvasculature of the entire brain with ~10 μm resolution. The whole rodent brain imaging capabilitymakes fUSG a great tool for obtaining macro scale information complementary to most commonly used optical imaging techniques.The inclusion of macro-scale information can be critical in the study of functional changes due to aging, stroke, and neurodegenerative diseases. Chronic preparations make longitudinal studies possible and allow awake imaging that removes the confounds of anesthesia for functional imaging. Owing to variability in behavior among animals, performing multimodal and repeated measurements within the same subject is highly desirable and can lead to higher scientific rigor. Here we propose a chronic preparation method using polymethylpentene sealed cranial windows suitable for imaging with fUSG and optical methods such as optical coherence tomography, 2-photon microscopy, intrinsic optical signal imaging and laser speckle contrast imaging for a span of three to six months.

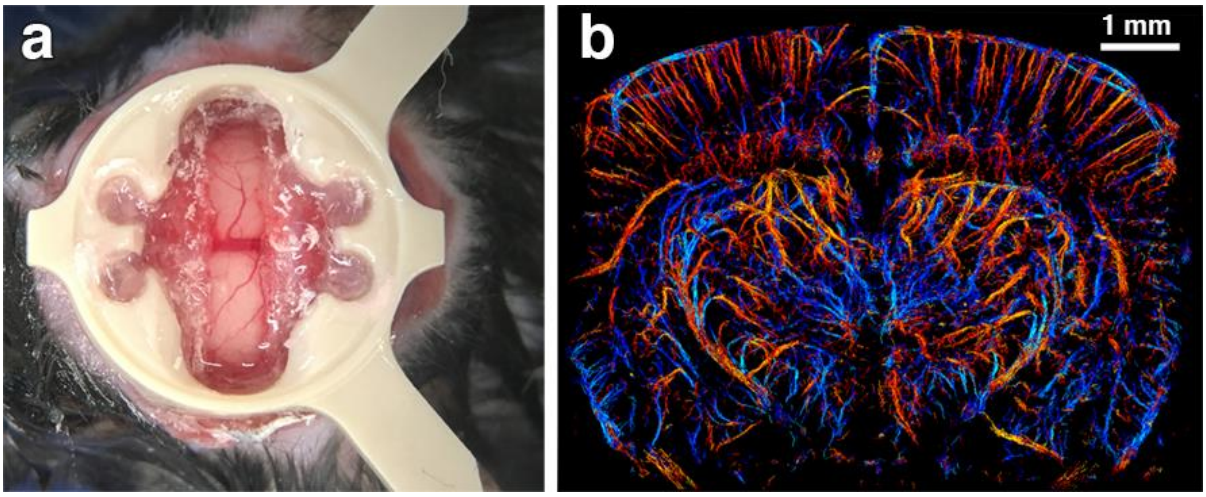


Figure: a) Example of an imaging window. B) Example of an ULM imaging.

Disclosures: **K. Kiliç:** None. **J. Tang:** None. **E. Erdener:** None. **S. Sunil:** None. **J.T. Giblin:** None. **B.S. Lee:** None. **D.D. Postnov:** None. **A.I. Chen:** None. **D.A. Boas:** None.

Poster

795. Anatomic Methods: Sample Preparation and Novel Probes

Location: Hall A

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Program #/Poster #: 795.14/CC71

Topic: I.03. Anatomical Methods

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the Science Fund for Creative Research Group of China Grant No. 61721092
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Title: Rapid aqueous clearing method for three dimensional mapping of intact organs

Authors: *J. ZHU[1,2], T. YU[1,2], Y. LI[1,2], J. XU[1,2], Y. QI[1,2], Z. CHEN[1,2], Y. YAO[1,2], Y. MA[1,2], P. WAN[1,2], X. LI[1,2], H. GONG[1,2], Q. LUO[1,2], D. ZHU[1,2];
[1]Britton Chance Ctr. for Biomed. Photonics, Wuhan Natl. Lab. for Optoelectronics, Huazhong Univ. of Sci. and Technol., Wuhan, China; [2]MoE Key Lab. for Biomed. Photonics, Collaborative Innovation Ctr. for Biomed. Engineering, Sch. of Engin. Sciences, Huazhong Univ. of Sci. and Technol., Wuhan, China

Abstract: Three dimensional (3D) imaging of large volume tissues at high resolution has become increasingly important in biomedical research. In recent years, tissue optical clearing technique has been proposed for imaging deeper inside tissues. Among various methods, aqueous-based clearing methods are known for good fluorescence preservation and scalable size maintenance. However, most of these methods suffer from either long incubation time or poor clearing performance. To address these issues, we developed a novel aqueous clearing method with reasonable incubation time, good clearing performance and robust compatibility, termed MACS. MACS can render intact organs and rodent bodies highly transparent in a relatively short time and possesses ideal compatibility with multiple fluorescent probes. Using MACS, we performed 3D imaging and reconstruction of the neural structures of transgenic whole adult brains and immunostained mouse embryos, as well as the neural projections throughout the whole brain labelled by viruses. We also visualized the vascular structures of various organs, including mouse brain, spinal cord, heart, spleen, small intestine, and generated 3D pathology of glomeruli tufts in healthy and diabetic kidneys by MACS and light-sheet microscope. We believe MACS can provide a powerful tool for 3D imaging and reconstruction of intact organs and is expected to facilitate the biomedical studies.

Disclosures: **J. Zhu:** None. **T. Yu:** None. **Y. Li:** None. **J. Xu:** None. **Y. Qi:** None. **Z. Chen:** None. **Y. Yao:** None. **Y. Ma:** None. **P. Wan:** None. **X. Li:** None. **H. Gong:** None. **Q. Luo:** None. **D. Zhu:** None.

Poster

795. Anatomic Methods: Sample Preparation and Novel Probes

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 795.15/CC72

Topic: I.03. Anatomical Methods

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NSFC Grant 81870934
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National Key Research and Development Program of China Grant 2017YFA0700501
Science Fund for Creative Research Group of China Grant 61721092
Fundamental Research Funds for the Central Universities, HUST Grant 2018KFYXKJC026

Title: Advanced solvent based clearing method for imaging whole organs

Authors: *T. YU[1,2], Y. QI[1,2], J. XU[1,2], P. WAN[1,2], Y. MA[1,2], J. ZHU[1,2], Y. LI[1,2], H. GONG[1,2], Q. LUO[1,2], D. ZHU[1,2];
[1]Britton Chance Ctr. for Biomed. Photonics, Wuhan Natl. Lab. for Optoelectronics, Huazhong Univ. of Sci. and Technol., Wuhan, China; [2]MoE Key Lab. for Biomed. Photonics, Collaborative Innovation Ctr. for Biomed. Engineering, Sch. of Engin. Sciences, Huazhong Univ. of Sci. and Technol., Wuhan, China

Abstract: Three-dimensional (3D) imaging of intact tissues at high resolution is becoming essential in life science researches. The conventional histological tissue analysis based on individual sections is rather valuable but often labor-intensive and prone to registration errors. The recently developed automated serial sectioning and imaging techniques, such as STP or fMOST, enabled high-throughput data acquisition but inevitably lead to sample destruction. Tissue optical clearing technique has been proposed as a distinct method for 3D imaging of large-volume tissues combined with multiple optical imaging techniques. In the past decade, kinds of optical clearing methods have been developed and contributed as powerful tools for deep biological imaging of various intact tissues. Organic solvent-based clearing methods, such as 3DISCO, present the advantages of high clearing efficiency and size reduction for imaging of large samples such as whole organs, and even whole bodies. However, 3DISCO results in a rapid quenching of endogenous fluorescence, which has impeded its application in many studies. Here, we propose an optimized method named FDISCO to overcome this limitation. FDISCO can effectively preserve the fluorescence of various fluorescent probes, including GFP, YFP and tdTomato, and it can also slow the quenching of multiple chemical fluorescent probes. It can

achieve a long storage time up to 1 year while retaining potent clearing capability. We applied FDISCO to clear various tissues, including mouse brain, spinal cord, kidney, skeletal muscle, and so on. Combined with light sheet microscope, we obtained high-resolution imaging and reconstruction of neuronal and vascular networks in different organs. Moreover, FDISCO is compatible with labelling by multiple viruses (RV, PRV, AAV) and enables fine visualization of neurons with weak fluorescence labelling in the whole brain. These results show that FDISCO is an effective alternative to the 3D mapping of whole organs and can be extensively used in biomedical studies.

Disclosures: **T. Yu:** None. **Y. Qi:** None. **J. Xu:** None. **P. Wan:** None. **Y. Ma:** None. **J. Zhu:** None. **Y. Li:** None. **H. Gong:** None. **Q. Luo:** None. **D. Zhu:** None.

Poster

795. Anatomic Methods: Sample Preparation and Novel Probes

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 795.16/CC73

Topic: I.03. Anatomical Methods

Title: Exploring the potential of sodium magnetic resonance velocity imaging for determining white matter fiber directionality

Authors: *Y.-A. CHEN, W.-Y. I. TSENG;
Inst. of Med. Device and Imaging, Natl. Taiwan University, Col. of Med., Taipei, Taiwan

Abstract: Efficient information transfer in the brain is supported by white matter tracts. Although diffusion weighted imaging allows the estimation of white matter fiber orientation, there is currently no non-invasive method of estimating the direction of fiber projection. Information on fiber directionality is indispensable for understanding brain connectivity because signal propagation is directional. Previous studies suggested correlation between the direction of current flow along the axon and the direction of axon projection. Because current is composed of moving electrolytes, some of which possessing NMR properties, we conducted simulations to explore the possibility of estimating fiber directionality using sodium magnetic resonance (MR) velocity imaging. To investigate the magnitude and direction of sodium drift under the influence of electric field, we built an axon model based on Hodgkin-Huxley equations and cable equation. Three types of ion channels are used to simulate action potential generation: Fast sodium channels, non-inactivating potassium channels, and fast-transient potassium channels. Since previous measurement results are obtained on peripheral nerves, we adjusted the parameters according to previous experimental results obtained on rat sciatic nerves. The half-width of an action potential generated by the axon model is 0.78 ms, and the conduction velocity is 80.075 m/s. Applying a 0.5-nA current stimulus induces saltatory conduction with a spatiotemporal voltage distribution similar to those observed using voltage-sensitive dye imaging.

Spatiotemporal distribution of electric field derived from the voltage distribution was used to compute the net electric drift of 80 sodium ions equally spaced along an 800-μm myelinated internode. The simulation results showed that, on average, an intracellular sodium ion moves 6.58×10^{-6} μm toward the axonal terminal during the passage of an action potential. Varying internodal length from 100 μm to 800 μm changes the drift pattern but not the order of magnitude of the drift distance. It was also found that the drift distance accumulates over multiple action potentials during T1 relaxation time. However, the order of magnitude of accumulated drift distance did not exceed 10^{-4} μm. The simulated drift velocities are far lower than the theoretical resolution limit of MR velocity imaging. In conclusion, the simulation results indicate that sodium MR velocity imaging is not feasible for estimating the direction of fiber projection.

Disclosures: Y. Chen: None. **W.I. Tseng:** None.

Poster

795. Anatomic Methods: Sample Preparation and Novel Probes

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 795.17/CC74

Topic: I.03. Anatomical Methods

Support: NIH Grant U24 NS109113
NIH Grant U01 NS099714
NIH Grant R24 NS092991

Title: Recombinant miniaturized antibodies for studying brain structure and function

Authors: *J. S. TRIMMER[1], J.-X. DONG[2], L. PALAO, III[2], C. DUMITRAS[2], B. GONG[2], K. D. MURRAY[3], S. BRIAND-SCHUMACHER[4], B. DREIER[4], A. PLÜCKTHUN[4], J.-C. MONTANARO-PUNZENGRUBER[5], R. SHIGEMOTO[5], R. SANDO[6], T. C. SUDHOF[6]; [1]Physiol. and Membrane Biol., [2]Neurobiology, Physiol. and Behavior, [3]Psychiatry & Behavioral Sci. and Ctr. for Neurosci., Univ. of California, Davis, Davis, CA; [4]Biochem., Univ. of Zurich, Zurich, Switzerland; [5]IST Austria, Klosterneuburg, Austria; [6]Mol. and Cell. Physiology/HHMI, Stanford Univ., Stanford, CA

Abstract: Antibodies (Abs) and related affinity reagents are widely research reagents used to label, isolate and manipulate the function of specific target molecules in complex experimental preparations including in vivo. We have pursued a multi-pronged approach to develop renewable recombinant Abs and related affinity reagents that exhibit specific binding to neuronal target proteins distinctly expressed in specific subcellular structures, cell types, circuits and/or activity states within the brain for use in diverse neuroscience research applications. We have converted a substantial portion of an existing library of mouse monoclonal antibodies (mAbs) into

recombinant form, allowing for their archiving in and dissemination from plasmid banks, and their reliable expression as defined recombinants. This also allows for their engineering into alternate forms more amenable to multiplex labeling applications, and their miniaturization into single chain variable fragments (ScFvs), which are ≈25 kD or 1/6 the mass of the intact parent mAb. We have also generated novel llama nanobodies (nAbs) against neuronal targets. nAbs are nanoscale antibodies derived from atypical heavy-chain only antibodies and represent one of the smallest (≈15 kD) autonomous antigen binding domains known. We have also isolated from highly diverse combinatorial libraries Designed Ankyrin Repeat Proteins or DARPins against neuronal targets. DARPins are small (≈14-18 kD) designer proteins of high affinity and specificity. While each of these binder classes has distinct and somewhat complementary properties, in general the small size, solubility and stability of ScFvs, nAbs and DARPins facilitates their functional expression in mammalian cells, allowing for their use as intracellular antibodies or intrabodies. Their small size also enhances the resolution of imaging obtained when they are used as immunolabels, and enhances their penetration into tissue, cells and subcellular compartments. We have developed ScFvs, nAbs and DARPins that function as intrabodies to deliver cargo to specific neuronal subcellular compartments to report on and/or manipulate neuronal function in vivo. We have also developed these as miniaturized nanoscale immunolabeling reagents to allow for higher resolution imaging of the molecular anatomy of neurons at the ultrastructural (immunogold-EM) and super-resolution scales, and to allow for enhanced penetration into brain tissue for correlative microscopy and whole brain imaging approaches.

Disclosures: **J.S. Trimmer:** None. **J. Dong:** None. **L. Palao:** None. **C. Dumitras:** None. **B. Gong:** None. **K.D. Murray:** None. **S. Briand-Schumacher:** None. **B. Dreier:** None. **A. Plückthun:** None. **J. Montanaro-Punzengruber:** None. **R. Shigemoto:** None. **R. Sando:** None. **T.C. Sudhof:** None.

Poster

795. Anatomic Methods: Sample Preparation and Novel Probes

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 795.18/CC75

Topic: I.03. Anatomical Methods

Title: A new application of fluorescent organosilica nanoparticles as an imaging tool

Authors: *N. YUASA, Y. FUJIKI, K. HASHINO;
Tokyo Chem. Industry Co., Ltd., Tokyo, Japan

Abstract: The novel type of organic silica nanoparticles, organosilica nanoparticles, has been developed by Nakamura and colleagues. These nanoparticles can be prepared in a single-step reaction and have good size control and dispersibility[1,2]. Organosilica nanoparticles are different

from common silica nanoparticles structurally and functionally. Organosilica nanoparticles have SH groups on the surface and inside, and it is possible to incorporate a fluorescent dye as internal functionalization. Because organosilica nanoparticles contain SH groups as surface functionalization, it is easy to modify their surface with antibodies and other protein molecules. We synthesized 100 nm fluorescent organosilica nanoparticles that are internally functionalized by fluorescein isothiocyanate (FITC) and then conjugated an anti-mouse IgG antibody, protein A, and streptavidin to these nanoparticles. The antibody, protein A, and streptavidin can be chemically modified while retaining their binding ability. It is possible to obtain high-resolution fluorescent images because these probes (i.e., fluorescent nanoparticle conjugates) have photoresistance; therefore, we applied these probes to immunofluorescence staining of mouse brain tissue sections and cultured neurons. We also discuss other biological applications, including *in vivo* imaging, and a whole mouse brain that is treated by a tissue-clearing technique.

References
1) Nakamura M *et al*., Size-controlled, one-pot synthesis, characterization, and biological applications of epoxy-organosilica particles possessing positive zeta potential. *Langmuir*. 2008, 24, 12228-34.
2) Nakamura M *et al*., One-pot synthesis and characterization of three kinds of thiol-organosilica nanoparticles. *Langmuir*. 2008, 24, 5099-108.

Disclosures: **N. Yuasa:** None. **Y. Fujiki:** None. **K. Hashino:** None.

Poster

795. Anatomic Methods: Sample Preparation and Novel Probes

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 795.19/CC76

Topic: I.03. Anatomical Methods

Support: Kakenhi
Sumitomo

Title: Cellular composition of the harbor porpoise (Phocoena phocoena) cortex

Authors: J. KASAI, T. MATSUSHIMA, ***N. PATZKE**;
Biol. Sci., Hokkaido Univ., Sapporo, Japan

Abstract: Toothed whales are commonly accepted to be the world's second most intelligent animals, with only humans displaying greater brainpower. Recently it has been proposed that this cognitive advantage of primates/humans is a direct result of higher neuronal density, and hence total number of neurons in the cerebral cortex in comparison to non-primate mammalian species with similar brain size. Moreover, it was demonstrated that the relationship between mass of cerebral cortex and the number of neurons has been shared between non-primate mammals,

following the same neuronal scaling rule, but differs from that in primates. Primates are characterized by an evolutionarily derived scaling relationship that results in more cortical neurons building a given cortical volume compared to non-primates. Thus, the question arises, if the presumable higher cognitive ability of toothed whales is also accompanied by higher cortical neuronal number as seen in primates or if the cortical neuronal number is as projected from the non-primate scaling rule. To test our hypothesis, we analyze the number of neurons in the cerebral cortex of the harbor porpoise (*Phocoena phocoena*), a small toothed whale (brain mass ca. 560g) using the isotropic fractionator technique. Our results demonstrate that while cortex of the harbor porpoise conforms to the universal non-neuronal scaling rule that applies to all mammals, including primates, it has a higher cortical neuronal number than one would predict from the non-primate cortical scaling rule. These results indicate that brain evolution of toothed whales might have been driven by increased information-processing demand imposed by complex social systems, which lead them deviate from other non-primate mammalian species.

Disclosures: J. Kasai: None. **T. Matsushima:** None. **N. Patzke:** None.

Poster

795. Anatomic Methods: Sample Preparation and Novel Probes

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 795.20/CC77

Topic: I.03. Anatomical Methods

Support: NIH Grant R21MH115680

Title: Development of an antibody-free staining method for the visualization of oxytocin receptors in tissue: Histochemical detection of a biotinylated ligand

Authors: *S. M. FREEMAN[1,2], M. C. PALUMBO[2], M. MUTTENTHALER[3], K. L. BALES[2]; [1]Dept. of Biol., Utah State Univ., Logan, UT; [2]California Natl. Primate Res. Ctr., Univ. of California, Davis, Davis, CA; [3]Inst. for Mol. Biosci., Univ. of Queensland, Brisbane, Australia

Abstract: Oxytocin (OT) can act as a potent neuromodulator in a variety of species to influence complex social behaviors, including social bonding, affiliation, and social reward. As a result, the OT system has been highly implicated in the biology and treatment of several psychiatric conditions that are characterized by deficits in sociality, including autism spectrum disorder. Because of this high translational potential for OT to benefit human health, it is crucial that research efforts focus on the fundamental neuroanatomy and physiology of the OT system in the brains of both animals and humans. Thanks to the suite of transgenic tools available, research in mice has contributed considerably to our understanding of the function of OT in the regulation of social behavior. However, non-mouse models are increasingly being used, including monogamous rodents as well as nonhuman primates. To complement the elegant behavioral

pharmacology being done in these species, rigorous neuroanatomical work is required to characterize the underlying neural circuits. Currently, the most reliable and widely available technique for the visualization of OT receptors (OXTR) in brain tissue is receptor autoradiography, but this method only resolves receptors at the gross anatomical level. The most common technique to visualize receptors on the cellular level is immunohistochemistry (IHC) but there are no reliable, commercially-available primary antibodies for OXTR. We have been working to advance the field of OT research by developing a novel method for the cellular staining of OXTR in brain tissue. This technique relies on the histochemical detection of biotin, which has been covalently bound to a selective OXTR ligand. Our biotinylated ligand is deamino-lysine vasotocin (dLVT), which is an analog of OT that binds selectively to OXTR. Here we report our progress in prairie vole brain tissue to develop this staining technique, which we call "autohistochemistry" because it combines the receptor-binding steps at the start of autoradiography with the deposition of a chromogenic stain at the end of immunohistochemistry. We have assessed the effects of the following variables in our optimization experiments thus far: tissue freezing methods, sectioning thickness, fixation strength/duration, the type and duration of blocking steps, signal specificity, and washing procedures. Our future work will combine our autohistochemistry method with IHC for tyrosine hydroxylase in the same tissue sections to demonstrate our ability to use a a double-labeling approach to detect OT-sensitive dopaminergic neurons, which will advance the study of OT neural circuitry in non-mouse organisms.

Disclosures: S.M. Freeman: None. **M. Muttenthaler:** None. **M.C. Palumbo:** None. **K.L. Bales:** None.

Poster

795. Anatomic Methods: Sample Preparation and Novel Probes

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Topic: I.03. Anatomical Methods

Support: The Michael J. Fox Foundation

Title: A novel radioligand for *in vitro* and *in vivo* alpha-synuclein imaging

Authors: *B. JANSSEN[1], Z. LENGYEL[1], C.-J. HSIEH[1], J. J. FERRIE[2], A. RIAD[1], K. XU[1], C. HOU[1], C.-C. WENG[1], W. E. KLUNK[3], C. A. MATHIS[4], E. J. PETERSSON[2], R. H. MACH[1]; [1]Radiology, [2]Chem., Univ. of Pennsylvania, Philadelphia, PA; [3]Psychiatry, Neurol., [4]Radiology, Univ. of Pittsburgh, Pittsburgh, PA

Abstract: The major pathological hallmark in synucleinopathies is α-synuclein (α-syn) fibril formation. Cellular localization and distribution patterns of α-syn aggregates differ between diseases, and therefore α-syn could be a useful marker for diagnosis and disease progression

(Kotzbauer *et al. Clin. Transl. Imaging* 2017). However, a successful ligand for α-syn imaging has yet to be developed. Recently, various antibodies have been shown to bind to α-syn differently in post-mortem brain tissue of Parkinson's disease (PD) patients (α-syn in Lewy bodies) versus that of multiple system atrophy patients (glial inclusions of α-syn; Peng *et al. Nature* 2018). This is in agreement with the identification of multiple binding sites (e.g. sites 2 and 9) in α-syn fibrils (Hsieh *et al*. *ACS Chem. Neurosci.* 2018), and highlights the importance of α-syn specific ligands, that may even be disease-specific. Aim of this study was to validate a hit-to-lead approach from molecular modeling to *in vitro* binding studies to identify new radioligands with high affinity for α-syn.
Based on *in silico* modeling data, **BJ-1-094** was synthesized and K_i values for two binding sites in α-syn fibrils were determined via competitive inhibition with [^{3}H]**tg-1-90b** (site 2) and [^{3}H]**BF-2846** (site 9). Radioiodination was performed to yield [^{125}I]**BJ-1-094**, which was then used to obtain K_d values in both α-syn and Aβ42 fibrils, and for *in vitro* autoradiography on brain sections of an 18-month old transgenic A53T mouse. In addition, binding studies on brain tissue homogenates of PD and Alzheimer's disease (AD) patients and control brain were executed, as well as an *ex vivo* biodistribution in normal balb/c mice.
K_i values for **BJ-1-094** for site 2 and site 9 were 5.2 nM (95% CI 3.2-8.6 nM) and 3.6 nM (95% CI 1.5-8.6 nM), respectively. K_d values of 0.48 ± 0.08 nM for α-syn fibrils and 2.47 ± 1.30 nM for Aβ42 fibrils were obtained using [^{125}I]**BJ-1-094**. Increased binding of [^{125}I]**BJ-1-094** was observed in regions with high α-syn antibody staining in A53T mouse brain. Binding of [^{125}I]**BJ-1-094** to PD tissue was elevated compared with control brain and showed 2-fold selectivity over AD tissue. [^{125}I]**BJ-1-094** entered mouse brain (6 ± 1 %ID/g at 2 min p.i.), and since **BJ-1-094** also bears a methyl group amenable to carbon-11 labeling, further *in vivo* studies with this ligand are ongoing.

Disclosures: B. Janssen: None. **Z. Lengyel:** None. **C. Hsieh:** None. **J.J. Ferrie:** None. **A. Riad:** None. **K. Xu:** None. **C. Hou:** None. **C. Weng:** None. **W.E. Klunk:** None. **C.A. Mathis:** None. **E.J. Petersson:** None. **R.H. Mach:** None.

Poster

795. Anatomic Methods: Sample Preparation and Novel Probes

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 795.22/DD1

Topic: I.03. Anatomical Methods

Title: Individually tailored segmentation method for distorted hypothalamus in craniopharyngioma patient

Authors: *M. LEE[1], A. HONG[4], J. LEE[2], J. KIM[3], Y. KIM[2], H. CHOI[1];
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Abstract: Introduction:
Segmentation of specific brain region contour is an essential process for neuroimaging study. Auto-segmentation and semi-auto-segmentation methods are developed for some brain regions. However, certain brain regions, such as hypothalamus, are difficult for segmentation due to low signal contrast. Another problem related to brain region segmentation is a distortion due to surgery or tumor. Therefore, segmentation of low signal contrast structure in distorted brain is a challenging process. The present study aimed to investigate the optimal methods for hypothalamus segmentation of craniopharyngioma patients who have underwent surgical removal.
Methods:
Seventy seven (43 male and 34 female) adult craniopharyngioma patients who underwent tumor removal surgery in Seoul National University Hospital between 2012 and 2017 were analyzed. Manual segmentation of hypothalamus in 3 tesla MRI images was carried out by two independent raters, well trained neuroimaging analyst and expert neurosurgeon. Segmentation was carried out in T1-weighted and T2-weighted MR images of 3mm thickness acquired at 3 Tesla, Sixty one patients' data was analyzed for method 1 and 77 patients analyzed in methods 2. Method 1: segmentation on T1-weighted images in order to established boundaries of hypothalamus. Method 2: segmentation was carried out based on T2-weighted images. Lateral borderline was individually tailored in order to adjust for their distortion level. And thalamus area was excluded.
Results:
Median of age and post-operative duration were 46 years (range: 18-76 years) and 37 months (range: 3-95 months). Pre-operative tumor size was 8142mm3, sd=11804. Hypothalamic volume of 61 segmented by method 1(m=631.73mm3, sd= 227.36) is larger than those by method 2(m= 507 mm3, sd=112.31), t=4.730, p<.001, but positively correlated, r=.412, p=.001. In method 2, hypothalamic volumes in 77 patients were 496.mm3, sd=114.83 in first rater, 497mm3, sd= 128 in second rater. Inter-rater correlation was excellent, r=.852, p<.001. Association between post-operative hypothalamus volume and clinical parameters, such as metabolic phenotype and surgical complications, are analyzed.
Conclusions:
In patients with severe damage, hypothalamic volume could be biased by outwardly displaced location of optic nerve. We have attempted to find an optimized method for hypothalamic volume segmentation by performing quantitative analysis on a large number of cohorts of various degrees of damage. We suggest that an individually tailored assessment is required depending on the degree of hypothalamic damage.

Disclosures: M. Lee: None. **A. Hong:** None. **J. Lee:** None. **J. Kim:** None. **Y. Kim:** None. **H. Choi:** None.

Poster

795. Anatomic Methods: Sample Preparation and Novel Probes

Location: Hall A

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Program #/Poster #: 795.23/DD2

Topic: I.03. Anatomical Methods

Support: NIH R37 AG011230
NIH R01 AG011230

Title: Age-related shrinkage of medial temporal lobe subfields is differentially exacerbated by arterial hypertension: A six-year longitudinal study of healthy adults

Authors: *A. M. DAUGHERTY[1], Q. YU[1], A. R. BENDER[2], L. TANG[1], C. L. DAHLE[1], N. OFEN[1], N. RAZ[1];
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Abstract: Hippocampal subfield volumes may change differently across the lifespan and are differentially vulnerable to cardiovascular risk factors. Yet, prior reliance upon cross-sectional designs precludes valid estimates of change trajectories and their moderators. Healthy adults (at baseline: N = 261, age 18-82 years; M = 48.18, SD = 17.96) were assessed three times over six years, with attrition of about 50% at each assessment occasion. Volumes of medial temporal lobe (MTL) subfields - subiculum, combined Cornu ammonis (CA) sectors 1 and 2, combined CA3-dentate gyrus, and entorhinal cortex - were segmented in the length of the hippocampal body on high-resolution MR images ($0.4 \times 0.4 \times 2$ mm^3) using a custom atlas based on highly-reliable manual tracing. Latent change score models estimated sequential change in regional volumes of each subfield across assessments, and hypertension diagnosis was tested as a moderator of the mean changes and age-related differences therein (all effects $p<0.01$, corrected for multiple comparisons). In the total sample, entorhinal cortex volume declined linearly from the baseline to assessment 2 ($change_{12}$ = -12.96) and to assessment 3 ($change_{23}$ = -15.04). Subiculum ($change_{12}$ = -10.25; $change_{23}$ = -11.82), CA1-2 ($change_{12}$ = -11.02; $change_{23}$ = -12.96), and CA3-dentate gyrus ($change_{12}$ = -9.20; $change_{23}$ = -10.72) also demonstrated significant linear decline that was comparable among regions. However, significant individual differences in change were noted. Participants with uncomplicated arterial hypertension (n = 42; mean age = 63.74, SD = 9.98) were older than their normotensive counterparts: t (259) = -6.61. Normotensive adults exhibited a decelerated trajectory of age-related shrinkage in the subiculum (b_{23} = 0.19) and CA3-dentate gyrus (b_{23} = 1.73). In contrast, hypertensive participants evidenced accelerated decline in older age in the CA3-dentate gyrus (b_{23} = -2.08; group difference = 3.82). Differential sensitivity of the medial temporal lobe subfields supports the role of cardiovascular risk as a

negative modifier of aging. Because cardiovascular risk can be modified by behavioral and pharmaceutical means, it can be targeted to promote neural and cognitive function into senium.

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Poster

795. Anatomic Methods: Sample Preparation and Novel Probes

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Program #/Poster #: 795.24/DD3

Topic: I.03. Anatomical Methods

Support: MPG Grant 67–11HIPPOC to UL
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Title: White matter microstructure moderates effects of hippocampal volume on memory in older adults

Authors: *A. R. BENDER[1,2], A. BRANDMAIER[1,3], S. DÜZEL[1], A. KERESZTES[1,4,5], O. PASTERNAK[6], S. KÜHN[1], U. LINDENBERGER[1,3];
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Abstract: Age-related memory deficits have been linked to differences in medial temporal lobe (MTL) structure, including limbic white matter (WM) microstructure and hippocampal (HC) volume. However, despite their functional and anatomical interdependence, the combined influences of WM microstructure and HC volume on learning and memory among older adults are rarely investigated. Moreover, in light of mixed extant findings linking HC volume with learning and memory we sought to determine whether this association varies as a function of WM microstructure. In a subsample of 337 older adults (M_{age}=69.66, SD_{age}=3.92 years) originating from the Berlin Aging Study II (BASE-II) who were eligible for MR imaging, we modeled the joint contributions of limbic WM microstructure and HC subfield volumes on the rate of verbal learning. Participants completed a standardized auditory verbal learning task of serially recalling the same 15-item word list over five successive trials. Participants also underwent magnetic resonance imaging (MRI), including structural and diffusion scans. From the latter, we sampled mean fractional anisotropy (FA) from four bilateral limbic WM tracts,

corrected for free water contamination. We segmented three HC subregions from high-resolution structural MRI data, using an established semi-automated method. We used a structural equation modeling (SEM) approach for data analyses. First, we modeled differences in learning rate by fitting a negatively accelerating exponential growth function to the scores from the five learning trials. Second, volumes of each left and right HC subfields as well as the FA of each WM tracts served as indicators to model individual latent factors. Next, we estimated individual latent factors for each of the three HC subfields and each of the four WM tracts. These served as indictors for second-order factors for HC and WM to test their overall associations with the learning slope. Last, we used a latent moderated SEM (LMS) approach to test a hypothesized interaction between HC volume and WM microstructure in explaining variance in verbal learning. LMS results showed differences in learning rate that were explained by limbic WM FA and by the interaction of HC volume and WM FA - but not by HC volume alone. Subsequent analyses showed HC volume is only associated with learning rate in individuals with WM FA values in the upper half of the distribution. We conclude that WM microstructure consistently contributes to verbal learning in older adults, but the association of HC volume depends on WM microstructure. Our results suggest that future studies relating HC volume to learning and memory in older adults should account for differences in WM.

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Poster

796. Techniques: Network Electrophysiology

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 796.01/DD4

Topic: I.04. Physiological Methods

Support: NIH RO1 R01MH098003
NIH RO1 R01NS085200
NIH Brain Initiative RF1 MH114224

Title: Simultaneous recording of multi-channel electrophysiology and whole-brain-level resting state fMRI on rats

Authors: *Y. MA[1], W. TU[2], T. NEURBERGER[1], N. ZHANG[1];
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Abstract: Multi-channel electrophysiology and resting state fMRI (rsfMRI) have been widely applied in animal studies to investigate neural activity/connectivity at whole brain level. Combining those methods provides a powerful tool to understand neural mechanisms underlying resting-state functional connectivity. During the simultaneous recording, fMRI imaging pulse

sequence induces strong electromagnetic interference on the electrophysiological recording, making it difficult to extract useful electrophysiological signal. Recent studies used a small number of imaging slices to provide a relatively long 'quiet' time for electrophysiological recording without MRI interference, which prevent the acquisition of continuous electrophysiology signals. In addition, this method is difficult to be applied to experimental setup that requires multiple slices of fMRI coverage. In this study, we developed a new animal setup for concurrent acquisition of rsfMRI with electrophysiology at multiple brain sites, and a new denoising method. Data were measured in rats under anesthesia. Results showed that our denoising method successfully removed MRI-induced artifacts, achieving sufficiently high SNR for analyzing local field potential. We also observed that the time course of gamma band (20-100Hz) power was tightly correlated to blood oxygenation level dependent (BOLD) signals in the cortex.

Disclosures: Y. Ma: None. **W. Tu:** None. **T. Neurberger:** None. **N. Zhang:** None.

Poster

796. Techniques: Network Electrophysiology

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 796.02/DD5

Topic: I.04. Physiological Methods

Support: Department of Anesthesiology
NSF Graduate Research Fellowship, DGE 1256260

Title: Relationship between electroencephalographic complexity and cortical cholinergic tone during subanesthetic ketamine: A high-density electroencephalogram study in rats

Authors: *M. A. BRITO, D. LI, J. DEAN, C. I. RYBICKI-KLER, T. LIU, A. FRYZEL, G. A. MASHOUR, D. PAL;
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Abstract: Electroencephalographic (EEG) complexity, as quantified through information-theoretic measures such as Lempel-Ziv complexity (LZC), has been used as a surrogate for the brain's repertoire of causal states and the level of consciousness. Recent studies have reported increased EEG complexity as a common feature of the psychedelic state induced by hallucinogenic drugs, including subanesthetic doses of ketamine. Ketamine is known to increase high gamma oscillations and cortical acetylcholine (ACh) levels in rodent models. Increased cortical cholinergic tone is a feature of states associated with phenomenological experience, such as wakefulness or rapid eye movement sleep, and is thought to track with the level of consciousness. However, the scope of studies aimed at investigating EEG complexity in humans during psychedelic states has been limited by lower frequency bandwidths (55Hz or lower) and a

lack of data on cortical cholinergic tone, while studies in rodent models have been limited by the use of sparse EEG channel-density. To overcome these limitations, we optimized a methodology to record high-density (30 channels) EEG data along with multi-site microdialysis of cortical ACh in a rat model. We then investigated the effect of subanesthetic ketamine on simultaneous changes in cortical complexity and cholinergic tone. After establishing baseline data during wakefulness, male Sprague-Dawley rats (n=3) were administered subanesthetic ketamine during the recording of 30-channel EEG while ACh levels in prefrontal and parietal cortices were quantified by high performance liquid chromatography. Ketamine was delivered as a bolus (5mg/kg) over 2.5 minutes followed by continuous low dose infusion (30 mg/kg/hr) for 60 minutes. Changes in EEG complexity were quantified using LZC in 5-minute epochs representing wake state, subanesthetic ketamine, and post-ketamine recovery. As compared to the wake state, subanesthetic ketamine increased cortical complexity [6.5% increase in temporal LZC (Cohen's D=3.01) and a 0.89% increase in spatial LZC (Cohen's D=0.19)] and caused an approximate 2-fold increase in ACh levels across prefrontal (226%) and parietal (146%) cortices. To our knowledge, this is the first study in rat to employ simultaneous measurement of cortical complexity using high-density EEG recordings and changes in ACh levels at multiple cortical sites using microdialysis. These results suggest a correlation between cortical cholinergic tone and EEG complexity during the dissociative state induced by subanesthetic ketamine.

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Poster

796. Techniques: Network Electrophysiology

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 796.03/DD6

Topic: I.04. Physiological Methods

Support: NIH R01 NS096008
NSF CAREER 1553482

Title: Subcortical-cortical evoked potential for electrophysiology-guided deep brain stimulation targeting for Tourette syndrome

Authors: *J. CAGLE[1], R. S. EISINGER[2], E. OPRI[1], K. D. FOOTE[3], M. S. OKUN[4], A. GUNDUZ[1];
[1]Biomed. Engin., [2]Neurosci., [3]Dept. of Neurosurg., [4]Dept. of Neurol., Univ. of Florida, Gainesville, FL

Abstract: Tourette syndrome (TS) is a lifelong condition that is highly prevalent and socially embarrassing. Deep brain stimulation (DBS) has emerged as a promising treatment option for

addressing tics in appropriately screened cases. In our patient cohort, two 4-contact macroelectrodes are placed during DBS surgery in the centromedian-parafascicular thalamic (CM-Pf) nuclei bilaterally, which is known to suppress tic activity in TS patients, and two subdural strips are placed over the primary motor (M1) cortex. Previously we have shown a significant difference of treatment outcome when the macroelectrode is misplaced in the ventral intermedius (VIM) nucleus of thalamus instead of CM-Pf nuclei, and we had developed a cognitive task utilizing attention and visual evoked potential to differentiate Vim and CM-Pf nuclei of thalamus. In addition to such cognitive tasks, we also explored connectivity markers such as stimulation evoked potentials by examining the stimulation effect in different nuclei of thalamus. To date, the stimulation evoked potentials were collected from three TS patients with chronic DBS implantation. Each patient underwent 3 minutes of stimulation while sitting still, and neurophysiological recordings from DBS electrodes and subdural strips were recorded using sensing-capable implanted neural stimulation, Medtronic Activa PC+S. The stimulation was delivered at 2Hz frequency with 300μs pulse width at 4V amplitude at each bipolar stimulation contacts. This process was repeated with inverted stimulation polarity hoping to remove stimulation artifacts after averaging. The results showed a stimulation evoked potential in M1 cortex 50ms after stimulation when stimulating the VIM nucleus but not when stimulating the CM-Pf nuclei. The result coincides with the attention based visual evoked potential tasks and further support our hypothesis on electrophysiology-guided DBS targeting in TS for improved outcomes.

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Poster

796. Techniques: Network Electrophysiology

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 796.04/DD7

Topic: I.04. Physiological Methods

Title: Functional electroencephalographic connectivity in resting state of premenopause and early postmenopause

Authors: *E. G. GONZALEZ-PEREZ[1], M. S. SOLIS-ORTIZ[2], M. F. MÜLLER-BENDER[3]; [1]Univ. De Guanajuato, Leon, Guanajuato, Mexico; [2]Univ. de Guanajuato, Leon, Guanajuato, Mexico; [3]Univ. Autónoma del Estado de Morelos, Cuernavaca, Morelos, Mexico

Abstract: Postmenopause is the stage in a woman´s life in which her hormone levels decrease causing changes in her entire body, specifically her brain. Estrogens have shown to be one of the most significant hormones to influence these changes. Women were studied in postmenopause compared to women in premenopause in their ovulatory period specifically, because during this

phase their estrogen levels are at their highest peak. The electrical activity in their brains was recorded using electroencephalograms, each group measured held 13 women between the ages of 40 and 60 years old and every EEG was done with eyes closed condition. The frequency bands considered during this analisis were: Delta, Theta, Alpha1, Alpha2, Beta1 y Beta2. Graph theory was used to evaluate brain connectivity. Postmenopausic women showed an increased power of Theta, Alpha2 and Beta 1 bands in frontal, central and temporal brain regions. In brain connectivity, postmenopausic groups showed a more global and local efficiency, and clustering coeficient for Alpha 1, Alpha 2, Beta 1 and Beta 2 bands. These analisis explain that postmenopausic women compared to premenopausic women have better functional connectivity in fast frequency bands, which is explained as a compensatory mecanism towards a posible brain disconnection.

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Poster

796. Techniques: Network Electrophysiology

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 796.05/DD8

Topic: I.04. Physiological Methods

Title: Presence of Targets and Nontargets in ERP-based Complex Trial Protocol (CTP) Significantly Increases P300 Effect as an Index of Stimuli Recognition in Evaluation of Memory Deficit and Malingering

Authors: *E. DAVYDOVA[1], E. LABKOVSKY[2], J. P. ROSENFELD[3];
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Abstract: Our previous studies demonstrated effectiveness of the Complex Trial Protocol (CTP) to detect concealed information and malingering. The CTP hit rates range from 84 to 100%. The current study investigates how presence or absence of Target and Nontarget stimuli in CTP-like, ERP-based malingering assessment affects outcome.Method: The original CTP utilizes one "Probe" (a relevant/familiar to the subject item), a few (usually 4 or 6) "Irrelevants" (which are irrelevant to the subject items), one "Target" (stimulus with an assigned significance, usually "11111"), and four "Nontargets (random, non-related to the subject stimuli, usually strings of numbers, like "22222", "33333", "444444", and "55555."In the current experiment we tested two types of stimulus (2 blocks): 1) "semantic" (with subject's birthday as probe) and 2)"episodic" (with experimenter's name as probe). There were two conditions: 1) "TARGET" condition, where Targets and NonTargets were presented (in the second part of each trial) along with Probes and Irrelevants (in the first part of each trial) and 2) "NOTARGET" condition,

where Targets and NonTargets were absent. Thus, we had four block/condition combinations or groups: 1) with a subject's birthdate as a Probe and Target/Nontargets included in the protocol (TBD), N=20; 2) with the experimenter's name as a probe and Target/Nontargets included (TNM) N=20, ; 3) with a subject's birthdate as a Probe but without Target/Nontargets (NTBD), N=17; 2) with the experimenter's name as a probe but without Target/Nontargets (NTNM), N=17.Results: A 3-way ANOVA on P300 amplitudes revealed:1) significant group difference, $F(1,29)=8.894$, $p=.006$; T>NT;2) significant block ("semantic" vs "episodic") effect $F(1,29)=16.587$,$p<.0001$, Semantic > Episodic, and nonsignificant condition ("TARGET" vs "NOTARGET") by group interaction $F(1,29)=0.486$, $p=.491$; 3) significant stimulus type ("probe" vs "irrelevant") effect $F(1,29)=68.825$,$p<.0001$, and significant condition ("TARGET" vs "NOTARGET") by group interaction $F(1,29)=4,719$, $p=.038$; and4) significant block ("semantic" vs "episodic") by stimulus type ("probe" vs "irrelevant") interaction $F(1,29)=7.441$, $p<.011$, but NO triple interaction $F(1,29)=.926$, $p=344$. Conclusions: The original CTP protocol with Target and Nontarget stimuli included in the protocol proves to be superior for detection of deception and malingering compared to an ERP protocol lacking Targets and Nontargets.Further research is required to investigate how introduction of countermeasures might affect the accuracy of ac CTP-like protocol without Target/Nontarget stimuli.

Disclosures: **E. Davydova:** None. **E. Labkovsky:** None. **J.P. Rosenfeld:** None.

Poster

796. Techniques: Network Electrophysiology

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 796.06/DD9

Topic: I.04. Physiological Methods

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Distinguished Professor Program of Jiangsu, and Postgraduate Research & Practice Innovation Program of Jiangsu Province KYCX18_2196

Title: Burst suppression latency predicts anesthesia depth

Authors: *D. WANG[1], Q. GUO[1], D. LIU[1], G. ZHANG[1], X. KONG[1], Z. XU[1], A. MANNAN[1], Q. ZHANG[1], S. XIA[1], J. YANG[1], H. ZHANG[1,2], H. DING[1,2], J.-L. CAO[1,2,3];
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Xuzhou, China; [3]Dept. of Anesthesiology, Affiliated Hosp. of Xuzhou Med. Univ., Xuzhou, China

Abstract: Background: General anesthesia produces various patterns on the electroencephalogram (EEG). Burst suppression is a characteristic phenomenon of deep anesthesia, which could be harmful to patients. The previous reports showed that burst suppression ratio (BSR) had a negative correlation with BIS when the BSR was more than 40. Unfortunately, present clinical monitoring technique is not good enough to predict the depth of anesthesia. The present study was designed to investigate how to predict the subsequent anesthetic depth by testing correlation between burst suppression latency (BSL) and BSR.
Methods: Adult C57BL/6 mice were adopted in the study. The mice were divided into 5 groups, 2 groups were anesthetized by 1.0% and 1.5% isoflurane respectively; the other 3 groups were pretreated with intraperitoneal injection of ketamine (25 mg/kg), dexmedetomidine (15ug/kg) or midazolam (0.5 mg/kg) 5 minutes before 1.0% isoflurane anesthesia. Simultaneously, EEG of all groups was recorded in frontal, parietal and occipital lobe for 2 hours.
Results: There was a negative correlation between BSL and BSR of the EEG (frontal: *P*=0.0876, r=-0.600; parietal: *P*=0.0125, r=-0.7833; occipital: *P*=0.0310, r=-0.7132, n=9) in adult mice under 1.0% isoflurane. When the isoflurane concentration was 1.5%, only occipital EEG displayed negative correlation between BSL and BSR (*P*=0.0149, r=-0.8096, n=9). In the adult mice, the pretreatment of ketamine and midazolam rather than dexmedetomidine not only decreased the BSL, but also increased the BSR during 1.0% isoflurane anesthesia. And the EEG had the consistent correlation between BSL and BSR in occipital lobe compared to isoflurane-only (ketamine: r=-0.8291, *P*=0.0057; midazolam: r=-0.7584, *P*=0.0178; dexmedetomidine: r=-0.8189, *P*=0.0069, n = 9, respectively).
Conclusions: Our study indicated that BSL could predict the subsequent anesthesia depth in subjects received both isoflurane inhalation only and combination of isoflurane inhalation with intraperitoneal injection of ketamine, dexmedetomidine or midazolam. Furthermore, ketamine and midazolam pretreatment could decrease BSL and increase BSR during isoflurane inhalation. In the clinical, anesthesiologist can adjust anesthetics in time according to BSL and chose combination rationality to avoid the occurrence of deep
anesthesia. As anesthesia deepening, the occipital lobe may be the best position to predict or detect subsequent anesthetic depth.

Disclosures: **D. Wang:** None. **Q. Guo:** None. **D. Liu:** None. **G. Zhang:** None. **X. Kong:** None. **Z. Xu:** None. **A. Mannan:** None. **Q. Zhang:** None. **S. Xia:** None. **J. Yang:** None. **H. Zhang:** None. **H. Ding:** None. **J. Cao:** None.

Poster

796. Techniques: Network Electrophysiology

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 796.07/DD10

Topic: I.04. Physiological Methods

Support: NIH Grant NS064033
NIH Grant NS089659

Title: Cortico-cortical evoked potential amplitude is predicted by diffusion imaging-based tractography

Authors: *B. H. SILVERSTEIN[1], E. ASANO[2], A. SUGIURA[2], M. SONODA[2], M.-H. LEE[2], J.-W. JEONG[2];
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Abstract: Cortico-cortical evoked potentials (CCEPs) can be utilized to identify effective networks in the human brain. Following electrical stimulation of cortical electrodes, evoked responses are recorded from distant cortical areas. A negative deflection (N1) which occurs 10 - 50 ms poststimulus is considered to be a marker for direct cortico-cortical connectivity. However, with CCEPs alone it is not possible to observe the pathways that conduct the signal or predict N1 amplitude given a stimulation site. Here we used diffusion weighted imaging (DWI)-based tractography to predict N1 amplitude. We hypothesized that CCEP voltage is proportionate to the between-electrode resistance, which we modeled according to V=IR. Assuming constant I, we defined R as the ratio of streamline length to streamline count, reflecting the length and thickness of the "wire."
Eighteen neurosurgical patients underwent both CCEPs during extraoperative recordings and DWI scans. Subdural grids of 3 mm diameter electrodes were used for stimulation and recording, with 98-128 useable electrodes per patient. CCEPs were elicited by trains of 1 Hz stimuli with an intensity of 5 mA and recorded at sample rate of 1 kHz. N1 peaks and latency were defined as the maximum of a negative deflection within 10-50 ms post-stimulus with a z-score > 5 relative to baseline. Electrodes were coregistered to DWI for tractography.
(Figure 1)

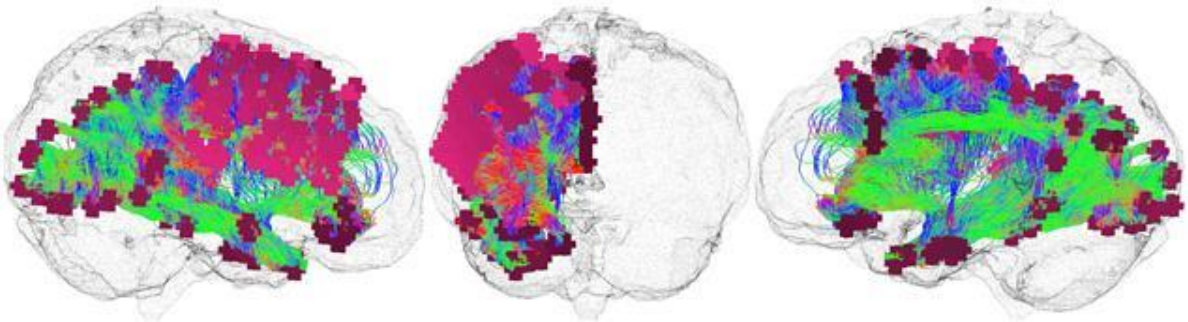

Figure 1: Representative electrode tractography from one patient. Whole-brain probabalistic tractography was estimated from 3T DWI scans (55 directions, b=1000 s/mm2, 2x2x3 mm voxels) in the MRtrix framework. Electrodes were coregistered with the DWI to identify inter-electrode streamlines. Mean streamline length and streamline count were computed to estimate R. Electrodes within 10 mm of the stimulation site were excluded from analysis.

All subjects and electrodes were pooled in a mixed model framework. We observed that voltage was best predicted by log(R): [β = -13.0, SE = 1.19, CE: -15.3, -10.7]. Thus, as R decreases, N1

peak amplitude increases exponentially. However, R did not predict N1 latency [β = 6.1e-4]. Age, recording hemisphere, and number of antiepileptic drugs were used as covariates, but no significant effects were noted.
We have demonstrated that CCEP N1 amplitude is dependent on properties of the underlying white matter network, not volume conduction. The nonlinear relationship between N1 and R suggests that there are unobserved factors which influence N1 amplitude, such as myelination, neurotransmitters, or N1 morphology.

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Poster

796. Techniques: Network Electrophysiology

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 796.08/DD11

Topic: I.04. Physiological Methods

Title: Electrodiagnostic characteristics of upper lumbar stenosis: Discrepancy between neurological and structural levels

Authors: *K. KIM[1], J. PARK[2];
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Abstract: Lumbar spinal stenosis is a common degenerative disease frequently accompanying lumbosacral radiculopathies. Conventional knowledge of lumbar spine suggests that n/n+1 level lesion will result in n+1 radiculopathy. However, the principle seems not applicable to spinal stenosis of upper lumbar levels, of relatively low incidence. This study aimed to investigate electrodiagnostic manifestation of upper lumbar stenosis. Consecutive patients were recruited from a tertiary university hospital. Inclusion criteria were 1) spinal canal stenosis at upper lumbar level (L1/2, L2/3, or L3/4) confirmed in magnetic resonance image (MRI), 2) abnormal electromyography (EMG) including active denervation potentials, and 3) MRI and EMG conducted within 3 months interval. Exclusion criteria were 1) concomitant peripheral polyneuropathy of clinical significance, 2) structural lesions at L4/5 or L5/S1 levels in MRI to explain EMG abnormalities. 24 patients sufficed inclusion criteria and 10 patients were excluded; 14 patients were enrolled in the study. All the patients showed denervation potentials in the distal lower extremity muscles innervated by L5 and S1 roots although the structural lesions were above. L2, L3, or L4 myotomes were rarely affected; only one case exhibited chronic reinnervation in the vastus medialis. Active denervation in the proximal L5 or S1 innervated muscles were observed in 8 patients. Any neuropathic findings were observed bilaterally in 10 patients versus unilaterally in 4 patients. Accordingly, all the EMG findings

could be categorized into 4 types based on symmetry, length-dependency, and myotomal distributions of electrophysiologic abnormalities: ‘motor dominant peripheral polyneuropathy’-like (symmetric, length-dependent; 5 patients), ‘bilateral polyradiculopathy’ (bilateral, asymmetric, non-length-dependent; 5 patients), unilateral polyradiculopathy (unilateral, non-length-dependent; 2 patients), and mono-radiculopathy (2 patients). In conclusion, general belief that n/n+1 level lesion results in n+1 radiculopathy did not apply to upper lumbar stenosis. Without the knowledge of electrodiagnostic characteristic of upper lumbar stenosis, it might be confused as a peripheral polyneuropathy or polyradiculitis without corresponding structural lesion.

Disclosures: K. Kim: None. **J. Park:** None.

Poster

796. Techniques: Network Electrophysiology

Location: Hall A

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Program #/Poster #: 796.09/DD12

Topic: I.04. Physiological Methods

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NIH/NIDCD Grant 2R01DC012947-06A1
NIH Grant NS011613

Title: Human neocortical neurosolver: A user-friendly software tool for cellular- and circuit-level interpretation of EEG/MEG

Authors: *B. CALDWELL[1], S. A. NEYMOTIN[2], D. DANIELS[1], M. JAS[3,4], N. PELED[3,4], R. A. MCDOUGAL[5], S. DURA-BERNAL[6], M. CANTARELLI[7], M. N. O'CONNELL[2], A. BARCZAK[2], T. M. MCGINNIS[2], P. LAKATOS[2], C. I. MOORE[1], N. T. CARNEVALE[5], M. L. HINES[5], M. HAMALAINEN[3,4], S. R. JONES[1,8];
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Abstract: EEG/MEG are currently the only methods to non-invasively record human neural dynamics with millisecond temporal resolution. These signals are correlated with nearly all healthy and pathological brain functions. However, it is still difficult to infer the underlying cellular- and circuit-level origins without simultaneous invasive recordings. This limits the translation of EEG/MEG signals into novel principles of information processing, or into new treatment modalities for pathologies. To address this limitation, with funding from the NIH BRAIN Initiative we have built the Human Neocortical Neurosolver (HNN): an open-source software tool to help researchers and clinicians without formal computational modeling or coding experience interpret the neural origin of their human EEG/MEG data. HNN provides an intuitive graphical user interface (GUI) to an anatomically and biophysically detailed model of a neocortical brain circuit, with layer-specific thalamocortical and cortico-cortical drives. Unique to HNN is an underlying neural model that accounts for the biophysics generating the primary electric currents underlying EEG/MEG signals from cortical pyramidal neuron dendrites. This construction enables direct visual and statistical comparison between model output and source localized data in equal units (nAm). Users can change model parameters in the GUI for testing hypotheses on signal differences under varied experimental conditions or in patient populations. Users can visualize both macroscale current dipole and microscale circuit activity, including layer-specific responses, cell spiking activity, and membrane voltages. The first freely-available version of HNN was released in 2018 online at http://hnn.brown.edu. Here, we give an overview of HNN and describe new developments and applications, including updated online resources for installing HNN on all major platforms or running online via Neuroscience Gateway Portal or Amazon Web Services. We describe recent expansions including, (i) updated tutorials on simulating event-related potentials (ERPs) and low-frequency oscillations, (ii) conversion of the model to the NetPyNE (http://netpyne.org) specification to enable flexible network development, (iii) development of a new web-based GUI in collaboration with MetaCell (http://metacell.us), (iv) simulation of local field potential and current source density facilitating direct comparison to animal data, and (v) inclusion of model parameter optimization tools. In total, HNN is an unprecedented tool for the EEG/MEG community to translate their human signals to underlying cellular and network-level dynamics.

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Poster

796. Techniques: Network Electrophysiology

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Topic: I.04. Physiological Methods

Support: European Commission Marie Curie Career Integration grant (FP7-PEOPLE-2013-CIG-631952)
FCT grant IF/00787/2014
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FCT grant DSAIPA/DS/0065/2018

Title: Temporal pharmacodynamics of intranasal oxytocin: A human EEG study

Authors: *M. ZELENINA[1], K. BRODMANN[2], A. AVILA[2], J. DA CRUZ[3], P. FIGUEIREDO[3], D. PRATA[1];
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Abstract: Human neuroscience research has extensively used intranasal oxytocin (OT) to modulate social behavior and its neural correlates. Therefore, it is crucial to know for how long intranasal OT has a measurable effect in human brain activity. Previous studies inferred availability of intranasal OT in the brain indirectly, from OT levels in saliva[1,2] or blood[3,4]. Existing analyses of the cerebrospinal fluid[4] and the regional cerebral blood flow[5] show heterogeneous results. Moreover, the studies stopped recording the data at around 75 min, focused on very specific brain areas, and used research-unconventional doses (40 international units (IU). In this pharmaco-EEG study, we aimed to answer: "For how long does intranasal OT, in the most commonly used research dose of 24 IU, affect the whole brain activity as measured by EEG microstates (MS) and frequency bands?". We collected EEG data from 19 healthy male participants in a double-blinded, placebo-controlled, within-subjects design with intranasal administration of 24 IU of OT/placebo, up to 102 mins post administration, split into three time points: early, middle, late. We preprocessed the data and extracted the following features: duration, occurrence and contribution of four conventional MS, transition probabilities (TP) between each unique pair of MS, and relative amplitudes of frequency bands α, β, θ, δ, differentiated between scalp locations and sides. For MS features, we performed statistical analysis with two-way repeated-measures MANOVAs, and post-hoc analysis with one-way ANOVAs and t-tests. For frequency features, we performed a preliminary exploratory analysis with a non-parametric Wilcoxon test. Our MS results showed significant differences in TP from MS 4 to MS 1 and 2, and from MS 3 to MS 4 in the late time point, and a trend in TP from MS 3 to MS 4 in the early time point. Preliminary results from frequency analysis showed significant results across the whole observation period, varying between bands and scalp locations. We conclude that OT influenced electrical brain activity up to 102 mins post-administration and agree with saliva studies that OT may stay in the system longer than previously thought. As the MS are associated with resting-state brain networks, our results may indicate that OT influences salience and attention re-orientation at 15-45 and 75-102 mins post-administration. However, need for care remains when attempting to cross-correlate or interpret OT availability between saliva, blood, CSF and brain.
1 IJzendoorn, Front Neurosci, 2012
2 Huffmeijer, Neuroendocrin. letters, 2012
3 Gossen, Neuropeptides, 2012

4 Striepens, Scientific reports, 2013
5 Paloyelis, Biol. Psychiatry, 2016

Disclosures: **M. Zelenina:** None. **K. Brodmann:** None. **A. Avila:** None. **J. da Cruz:** None. **P. Figueiredo:** None. **D. Prata:** None.

Poster

796. Techniques: Network Electrophysiology

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 796.11/DD14

Topic: I.04. Physiological Methods

Title: Electrophysiological changes in the human brain associated with intake of commercial sweeteners

Authors: S. LOPEZ-MEZA[1], G. A. OTERO.OJEDA[2], J. A. ESTRADA[4], F. J. ESQUIVEL.HERNANDEZ[5], G. GONZALEZ-GONZALEZ[3], *I. CONTRERAS[4];
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Abstract: Introduction Studies performed in both animals and humans have shown a link between non-nutritive sweetener intake and changes in systemic energy metabolism; however, their effects in the brain have not been studied in detail. **Objective** The objective of this study was to compare the effect of short-term consumption of commercially available nutritive and non-nutritive sweeteners on brain cortical electrical activity, using quantitative electroencephalography. **Methods** The sample consisted of 26 clinically healthy people with a normal body mass index. The participants underwent a washout period with restricted intake of food and beverages with added sweeteners. Subsequently, quantitative electroencephalographic (qEEG) records were obtained for all participants. After the first recording, participants were randomly divided into two experimental groups; each group consumed either sucrose (40g) or commercial sucralose (4g) daily, for a period of six weeks. After supplementation, a final qEEG record was obtained from all participants, under the same conditions used in the first session. **Results** The results show significant alterations in cortical activity in the sweetener-supplemented groups. Sucrose intake had significant effects on the left temporal-occipital region, with an increase in absolute power in theta activity and a decrease in the absolute power of delta waves in the left frontal lobe. The sucralose group had an increase in absolute power in theta waves in the occipital lobe and the ventral midline. **Conclusions** Our results show that short-term, frequent intake of nutritive and non-nutritive sweeteners promotes changes in the cortical

activity of the brain, which can have significant effects on the cognitive processes of the people who consume them regularly.

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Poster

796. Techniques: Network Electrophysiology

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 796.12/DD15

Topic: I.04. Physiological Methods

Support: James S. McDonnell Foundation
Canadian Institute of Health Research (fellowship to CD)
Fonds de Recherche du Québec – Nature et technologies (studentship to YM)

Title: Brain network motifs are markers of loss and recovery of consciousness

Authors: *C. DUCLOS, Y. MAHDID, D. NADIN, S. BLAIN-MORAES;
McGill Univ., Montreal, QC, Canada

Abstract: Functional motifs are patterns of inter-connections between nodes of a complex network. As the basic building blocks of directed networks, motifs could contribute to the understanding of the neural building blocks of consciousness. This study explored the re-organization of 3-node network motifs during loss and recovery of anesthetic-induced unconsciousness. Nine healthy subjects (5 men; 24.4 ±1.0 yo) underwent a controlled anesthetic protocol with propofol (15-min induction) and isoflurane (3h maintenance), while brain activity was recorded through 128-channel electroencephalography (EEG). Five-minute segments of EEG were extracted for the following time points: 1) baseline; 2) induction; 3) unconsciousness; 4) 30-min prior to recovery of consciousness (ROC); 5) 10-min prior to ROC; 6) 5-min prior to ROC; 7) 30-min post ROC; and 8) 180-min post-ROC. EEG data were bandpass filtered between 0.1 and 50 Hz, visually inspected, and segmented into theta (4-8 Hz) and alpha (8-13 Hz) frequency bands. A binarized weighted and directed phase lag index matrix was used to calculate the frequency of occurrence of a motif against 100 random networks. To quantify inter- and intra-subject similarity of motif topological configurations across eight time points, we measured the cosine similarity between network motif configurations across time points. Repeated measures ANOVAs were carried out over all time points for motif frequency and cosine similarity. P-values were corrected using a Greenhouse-Geisser correction. Of the five possible 3-node motifs, three were significant across all time points, when compared to random networks (motifs 1, 2, 7). Repeated measures ANOVAs across all time points showed a significant change in the frequency of theta motif 7 only ($F(11,88) = 3.35$, $p < 0.05$), while cosine similarity

showed a significant change for all motifs, for both alpha and theta (F-values(11,88) > 3.5, p-values < 0.05). A post hoc Dunn-Sidak test revealed that cosine similarity differed significantly during unconsciousness for alpha motifs 2 and 7, and for all three theta motifs (p-values < 0.05). Our results confirm that anesthetic-induced unconsciousness does not suspend motifs, but rather causes a topological re-organization in network motifs. Overall, motifs reveal granular shifts in networks across states of consciousness, and could reveal the neural building blocks of consciousness.

Disclosures: **C. Duclos:** None. **Y. Mahdid:** None. **D. Nadin:** None. **S. Blain-Moraes:** None.

Poster

796. Techniques: Network Electrophysiology

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Topic: I.04. Physiological Methods

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DARPA Contract N66001-17-C-4002
L'Oreal USA For Women in Science

Title: Multi-scale neural resampling to map and monitor neural circuits in non-human primates

Authors: *A. L. ORSBORN[1,2,3,4], J. CHOI[5], C. WANG[6], C. CHIANG[6], J. VIVENTI[6,7,8], B. PESARAN[4];
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Abstract: Neural computations governing behavior are performed across many spatial scales, from individual neurons to distributed populations of neurons. Measuring neural activity relevant to behavior requires both large coverage and high spatial resolution. For a fixed number of recording contacts, there are inherent trade-offs between the total brain area studied and sampling density. Devices such as micro-wire arrays (e.g. Utah array) and linear probes (e.g. Neuropixels) provide dense sampling of spatiallylocalized signals but cover small areas of cortex (~20mm^2) or a single cortical column. No existing recording technology provides highly-resolved dense sampling of large areas. To overcome these limitations, we propose a repeated resampling strategy to effectively build super-resolution composite datasets. We designed a modular neural implant for non-human primates that permits resampling. The implant accommodates a range of hardware to make spatially co-registered repeated measurements. A novel artificial dura (AD) provides chronic subdural access. The AD is divided into a

chronically-implanted cover over dural edges and a removable mating piece over the brain surface (AD hat). We embed a μECoG array into the AD hat, which provides repeatable array positioning within the chamber in 4 orientations. We also align a microdrive containing an array of penetrating electrodes with the AD hat to enable simultaneous spike-field-ECoG recordings. We implanted this system in two male rhesus macaques, over sensorimotor cortices exposing a 254mm^2 area of cortex for study. A μECoG array (244 200 μm diameter contacts, spaced 0.75 mm) was repeatedly implanted in different orientations over months. Recordings were made as animals observed visual stimuli and performed reaching tasks. We find that μECoG responses mapped across the cortex are highly consistent over days for a given μECoG array placement. Moreover, we find that μECoG maps measured across different placements can be converted into a common chamber-based coordinate system to yield similar maps. Fitting spatial maps with spline models allowed us to estimate the spatial alignment of maps and spatial resolution of our measurements. This modular subdural implant allows repeated neural resampling with many measurements, which could overcome coverage- density tradeoffs. Resampling strategies could also create composite longitudinal datasets to overcome longevity limitations of chronic implants, which will be critical for learning studies. Multi-scale composite datasets will be essential for studying large portions of the brain at high resolution to link neural circuit activity to behavior.

Disclosures: A.L. Orsborn: None. **J. Choi:** None. **C. Wang:** None. **C. Chiang:** None. **J. Viventi:** None. **B. Pesaran:** None.

Poster

796. Techniques: Network Electrophysiology

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Program #/Poster #: 796.14/DD17

Topic: I.04. Physiological Methods

Support: James S. McDonnell Foundation
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FRQNT
CIHR

Title: Contrasting amplitude and phase-based measured of functional connectivity across states of consciousness

Authors: *Y. MAHDID, C. DUCLOS, J. DA SILVA CASTANHEIRA, S. BLAIN-MORAES; McGill, Montreal, QC, Canada

Abstract: Functional connectivity and graph theory measures, which are based on either envelope- or phase-based coupling modes, may provide powerful insight into the neural

correlates of consciousness. However, these coupling modes have generally been used mutually exclusively in the literature, and a lack of consensus persists around which coupling mode is best suited for identifying the neural correlates of consciousness. This study aims to assess the prediction accuracy of envelope- and phase-based functional connectivity in the prediction of states of consciousness.
Nine healthy subjects (5 men; 24.4 ± 1.0 yo) underwent a controlled anesthetic protocol (propofol induction and isoflurane maintenance), while brain activity was recorded through 128-channel electroencephalography (EEG). EEG was bandpass filtered between 0.1 and 50 Hz, visually inspected, and segmented into the alpha α (8–13 Hz) frequency band, which shows most changes under anesthetic-induced unconsciousness. Data was divided into 10-sec windows across 5 consciousness states (Baseline, Induction, Unconsciousness, Pre-Recovery of Consciousness and Recovery). Mean source activity of the 82 cortical regions of interest (ROI), defined by the Automated Anatomical Labeling Atlas, was extracted to generate a single time series for each ROI, across all subjects and consciousness states. For each 10-sec window and each consciousness state, amplitude envelopes were generated via a Hilbert transform and Phase-lag Index (PLI) was calculated for all ROI pairs. Each subject's whole-brain amplitude envelope correlation (AEC) and PLI functional connectivity matrix was averaged to produce group-level matrices for both AEC and PLI, across states of consciousness. Each 10-sec window was then used to train a linear Support Vector Machine (SVM) classifier to detect each consciousness state, with a mixed subject design. Each window value for each subject's consciousness state was normalized between 0 and 1, and was then separated in a testing and a training set with a 30%-70% split (765 windows for training, 1770 windows for testing). A 5-fold cross validation scheme was used to select the best penalty parameter C for the Linear SVM and the reported generalization accuracy was obtained by training the best classifier on the 30% training split before testing on the remaining 70%.
AEC and PLI both showed state-dependent changes across states of consciousness. In predicting state of consciousness, PLI and AEC showed 54% and 97% accuracy, respectively, suggesting that AEC has stronger prediction accuracy in a mixed subject setting than PLI.

Disclosures: Y. Mahdid: None. **C. Duclos:** None. **J. Da Silva Castanheira:** None. **S. Blain-Moraes:** None.

Poster

796. Techniques: Network Electrophysiology

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 796.15/DD18

Topic: I.04. Physiological Methods

Title: A mobile system for concurrent high density EEG, EMG and closed-loop tCS

Authors: N. YASAR, R. APPARIES, T. POULSON, A. M. WILDER, S. HIATT;
Ripple Neuro, Salt Lake City, UT

Abstract: Electroencephalography (EEG) has long been a leading tool for non-invasive measurement of cortical activity in humans for both clinical and research purposes. Similarly, electromyography (EMG) is a useful non-invasive tool for studying and treating movement disorders or as an indicator of performance in cognitive and other studies. More recently, the use of Transcranial Stimulation (tCS) to non-invasively modulate cortical activity has seen increasing popularity for a number of applications. Although several systems exist for each application, few systems offer concurrent EEG and EMG recording and tCS stimulation in a mobile system. The ability to record and stimulate in a freely moving subject is both useful for research involving movement and natural behavior, as well as long-term clinical interventions. We have developed a low-cost system capable of concurrent high-density EEG and EMG with simultaneous tCS, selectable on any of the EEG recording channels. The system features on-board processing to allow for triggering or modulation of tCS based on the electrophysiological response, and offers up to 512 channels of recording at a resolution of 24 bits and a sampling rate of up to 7.5 ksps. It is capable of several commonly used modalities of tCS, including Direct Current Stimulation (tDCS), Alternating Current (tACS), monopolar or bipolar Pulsed Current (tPCS), and Random Noise (tRNS). The simulation output can also be programed with arbitrary waveforms to take advantage of future modalities as they are developed. The stimulation parameters can be actively configured (manually or preprogrammed), with a compliance voltage of ± 9-30V, and current limit of 100µA - 15mA. Limits on these adjustable settings can be preset to ensure safe boundaries for different stimulation modalities. The system is easily portable as it is small (measuring 183 x 95 x 36mm), light-weight (700g), and features WiFi connectivity for wireless streaming of data. Data can also be stored on the 512GB internal memory for stand-alone operation. An internal battery allows for up to 2 hours of recording, while a hot-swappable battery allows for endless wireless recording (4-6 hours of use per battery between charge).

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Poster

796. Techniques: Network Electrophysiology

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Program #/Poster #: 796.16/DD19

Topic: I.04. Physiological Methods

Support: Ball Aerospace under contract to the U.S. Air Force

Title: Visual blindness oscillating in phase with the EEG alpha rhythm

Authors: *K. E. ALEXANDER[1], J. R. ESTEPP[1,3], S. M. ELBASIOUNY[2,1];
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Abstract: The neural mechanisms underlying the posterior alpha (8-12 Hz) rhythm measured in the electroencephalogram (EEG) are still largely unknown. However, a prominent theory is that alpha oscillations are the result of repeated T-type Ca^{+} channel burst firing in the thalamo-cortical visual relay cells. Each burst results in large, excitatory postsynaptic potentials in their target cells in the primary visual cortex, which appear as alpha peaks in the EEG. After each burst, the cells enter a refractory period that appear as alpha troughs in the EEG. Therefore, we hypothesized that thalamo-cortical visual relay cells do not relay low intensity visual afferentations from the optic nerve to the primary visual cortex during these refractory periods. To test this hypothesis, visual stimuli of threshold intensity will be presented to participants during times of high amplitude alpha oscillations. The visual stimuli will be Gabor patches during an eyes-open condition and light flashes in an eyes-closed condition. In the eyes-open condition, the stimuli will be presented separately to each visual hemifield to control for phase asymmetry between the hemispheres. And, the alpha phase relative to stimulus onset will be measured over the contralateral visual cortex. In the eyes-closed condition, visual hemifields cannot be isolated, so a centered light flash will be used and trials in which left and right occipital alpha oscillations are out of phase will be rejected. In both conditions, alpha phase relative to stimulus onset will be measured after an interval accounting for the neuronal conduction delay since it is theorized that the phase of the measured alpha wave reflects the past state of thalamo-cortical neurons. We expect that stimuli presented with a corresponding trough of the alpha oscillation will not be responded to by the participant. In this way we will provide further evidence of thalamo-cortical burst firing as the underlying generator of alpha oscillations.

Disclosures: K.E. Alexander: None. **J.R. Estepp:** None. **S.M. Elbasiouny:** None.

Poster

796. Techniques: Network Electrophysiology

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 796.17/DD20

Topic: I.04. Physiological Methods

Support: Ball Aerospace under contract to the U.S. Air Force.

Title: The effects of mental workload on P300 amplitude for use in cognitive probing

Authors: *C. L. WINTERMUTE[1], J. R. ESTEPP[1,3], K. E. ALEXANDER[1], A. M. PIASECKI[4], S. M. ELBASIOUNY[2,1];
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Abstract: Passive brain-computer interfaces (pBCI) provide support to a human-machine system by sending implicit inputs from neurological signals of the human to his or her machine teammate without generating an explicit output the user intends or even perceives. These neurological signals can be in reaction to cognitive probes the pBCI deploys in order to establish the user's cognitive state. It can be beneficial to adapt a user's experience in a system with a pBCI, such as preventing task-irrelevant stimuli from distracting the user during high workload, thus conserving cognitive resources needed for the primary task. Further, the multiple resource theory predicts a relationship between responses to cognitive probes and task load. The goal of this project was to confirm the presence of this relationship when probing different sensory channels independent of a visual primary task. To achieve that, we used electroencephalography (EEG) to monitor cortical activity in participants while they completed a series of continuous performance paradigms, specifically an n-back working memory task and a tracking task, at varying task difficulty levels. A task-irrelevant, oddball stimulus design was simultaneously deployed as a cognitive probe in a secondary task to elicit a P300 event-related potential (ERP). The oddball used auditory and tactile stimuli to avoid interfering with the visual sensory channel required of the primary task. The hypothesis was that the oddball P300 could be used to index the relative mental workload the participant was undergoing in both continuous tasks, and for both oddball sensory modalities, with some generalizability between primary task conditions. We expected to measure a decrease in P300 amplitude relative to increased mental workload experienced by the participant; further, we expected this attenuation of P300 amplitude to be observable in both primary tasks. The significance of this research will be the observation of how cognitive probes can be utilized effectively in ancillary sensory channels without competing against chiefly visual primary tasks, the flexibility in selecting those ancillary sensory channels, and initial findings about how generalization of the cognitive probe between primary tasks may be achieved.

Disclosures: C.L. Wintermute: None. **J.R. Estepp:** None. **K.E. Alexander:** None. **A.M. Piasecki:** None. **S.M. Elbasiouny:** None.

Poster

796. Techniques: Network Electrophysiology

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 796.18/DD21

Topic: I.04. Physiological Methods

Support: Supported by PAL Program UNAM-School of Chemistry. Key: 3000/3070

Title: Evaluation and quantification of the electrical activity of different isolated preparations, with the application of melatonin

Authors: *E.-B. NARANJO-RODRIGUEZ[1], O. ESPEJO-GONZÁLEZ[1], I.-G. CASTRO-TORRES[2], A.-. S. LIRA-ROCHA[1];
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Abstract: Melatonin [(MT) (N-acetyl-5-methoxytryptamine)] participates in various physiological processes, which allow different species to have a specific behavior. MT, indole derived from tryptophan, is a hormone synthesized and secreted, with a circadian pattern by the pineal gland and peripheral vertebrate tissues. In this work, with conventional rat tissue isolated, the spontaneous electrical activity of duodenum, ileum, colon and uterus was recorded. Aorta (stimulated with carbachol [10^{-8}, 10^{-7}, 10^{-6} M]) and vas deferens (stimulated with electrical activity; F = 0.1 Hz, V = max, D = 1 msec), all were treated with MT [10, 20, 40, 80, 160 and 320 μg/mL]) and the electrophysiological response in brain slices (extracellular records of the hippocampus); with low frequency stimulation trains (1Hz), with MT [15, 30, 45 and 90 μM] the values of the spike were quantified, and compared with the positive control. The analysis of data, considered: Amplitude (AMP), Frequency (FREC) and Area under the curve (ABC). For the analysis of the data, these were captured, stored and analyzed with statistics, by coupling the registration system to a computer. We conclude that the electrical activity of duodenum, ileum, colon and uterus decreased with the application of MT. The similar effect in aorta and the vas deferens. In brain slices, the MT produced specific modulation of plasticity in pyramidal neurons of the hippocampus. The responses obtained were dependent on the concentration, an effect that is produced by the presence of MT receptors in them, allowing us to study the mechanism of action of MT. **Support Proyect: PAL. FQ. UNAM. Key: 3000-3073.**

Disclosures: E. Naranjo-Rodriguez: None.

Poster

796. Techniques: Network Electrophysiology

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 796.19/DD22

Topic: I.04. Physiological Methods

Support: DGAPA-UNAM IN228409

Title: Electrical brain activity in left and right handed while performing a mental rotation task

Authors: *A. ALCÁNTARA QUINTERO, I. G. GALÁN, Y. DEL RÍO-PORTILLA;
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Abstract: Laterality or handedness is measure by manual preference o manual development (Mcmanus et. al., 2013). Manual preference has been classified as left or right, depending on the hand people uses to write; nevertheless, it also includes the hand preference use to perform different actions (Annett, 1970). The left hemisphere is known for being involved in language processing and the right hemisphere for visuospatial processing; although, this has just been studied in right handed people, in left-handers there is no clear pattern of functional brain organization. Several studies have shown brain activity differences, associated to manual preference (Shimoda, Takeda, Imai, Kaneko, & Kato, 2008). These studies show how EEG is an optimal way to find out differences in networking development. The purpose of this study was to understand the performance of brain functional organization in left and right handed, while answering a mental rotation task. The sample included 20 left handed and 20 right handed participants. Participants were evaluated with different tests of visuospatial skills and were EEG recorded; baseline and during a mental rotation task: two simultanously portrayed 3D rotated shapes were to be compared and asked if both shapes were the same o different is spite of the rotation. The main results showed a significant behavioral perfomance in left handers, whom obtained more correct answers ($p<0.05$). Regarding to electrical brain activity, results showed that right-handers had a higher absolute power in the Theta1 band (F4) and in Gamma band (F7, C4) during the mental rotation task. A pattern of increased interhemispheric temporal coupling for Delta, Theta and Gamma bands in the posterior temporal regions during the task, was found in right-handers. Related to Intrahemispheric temporal coupling, right-handers presented an increased in temporal coupling on both hemispheres, mostly of fronto-temporal and medial regions for Theta1 (F2-T6, T6-P4), Theta2 (F4-FZ), Beta1 (F1-C3, F8-P4, F8-O2, CZ-PZ), Beta2 (F1-P3, F1-T5, F1-CZ, F1-PZ, T3-CZ, F2-O2, F8-O2) and Gamma (F1-C3, T5-FZ,T5-CZ, P3-CZ). Unilateral control could present advantages such as quickness, due to less conductivity between hemispheres and would avoid duplication, which is beneficial in complex functions (Ringo, 1994 and Corballis, 2009). Although, these data showed that eventhough right-handers have more intrahemispheric activity than interhemispheric, these is too much compared to left-handers, whom in conclusion have less temporal coupling making their visuospatial rotation processing more efficient, providing a better development in this type of tasks.

Disclosures: A. Alcántara Quintero: None. **I.G. Galán:** None. **Y. del Río-Portilla:** None.

Poster

796. Techniques: Network Electrophysiology

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 796.20/DD23

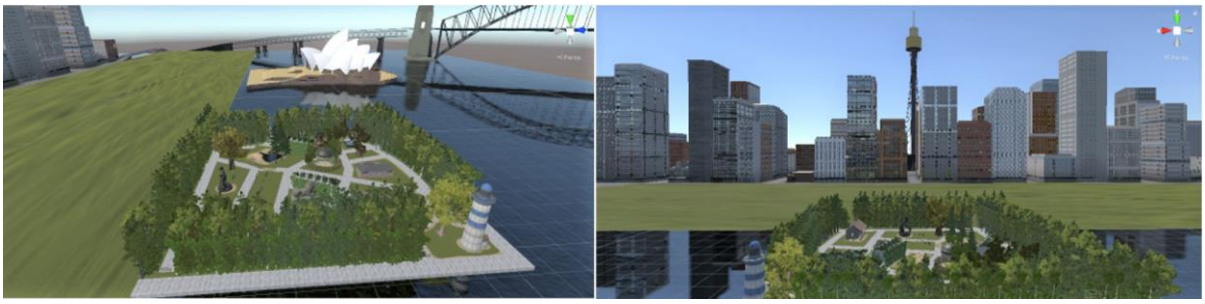
Topic: I.04. Physiological Methods

Support: ARC DP180100656

Title: Investigating the impact of landmarks on spatial learning during active navigation

Authors: J. LU[1], A. WUNDERLICH[2], *A. K. SINGH[1], T.-T. N. DO[1], K. GRAMANN[2,1], C.-T. LIN[1];
[1]Sch. of Computer Sci., Univ. of Technol. Sydney, Sydney, Australia; [2]Tech. Univ. of Berlin, Berlin, Germany

Abstract: It is well accepted that landmarks play a significant role in spatial navigation but their effects on spatial learning and the accompanying brain dynamics in actively moving participants have not been explored yet. This study proposes a systematic approach to compare the brain dynamics during active physical navigation addressing spatial knowledge acquisition based on allocentric and egocentric reference frames using local and global landmarks. To this end, different spatial navigation tasks will be utilized using high-density EEG synchronized to head-mounted virtual reality. In a pilot experiment we investigated participants' behavior during active exploration of a medium scale VR environment called "Sydney park" (see Figure 1). The environment consists of local landmarks (e.g. bench, lake, table etc.) and global landmarks (lighthouse, Sydney Opera House, Sydney Tower Eye) combined with roads, junctions, bushes, trees etc. similar to the environment of Sydney Royal Botanical Gardens. In this experiment scenario, participants were asked to explore the "Sydney Park" following auditory navigation instructions. The route was defined in a way that balanced participants' exposure to local and global landmarks. At the end of a navigation phase, we asked participants to perform a map drawing task followed by combined wayfinding and pointing tasks to test their spatial knowledge about the navigated environment. The collected data was analyzed using the Gardony Map Drawing Analyzer and customized Matlab scripts.
The results from behavioral data suggest that the participants were able to explore the "Sydney Park" effectively as shown by the quality of their map-drawings. It can thus be concluded that participants were able to develop a mental representation of the "Sydney Park" and that the scenario is acceptable for a full study with EEG. In a next step, we plan to perform the actual experiment with EEG and other physiological measures to investigate the impact of landmarks on spatial learning and its neural correlates.
Figure 1. Sydney Park scenario: top view (left); side view (right)



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Poster

796. Techniques: Network Electrophysiology

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 796.21/DD24

Topic: I.04. Physiological Methods

Title: Mitigating the effects of electrode biofouling for improved long-term measurement of dopaminergic signaling

Authors: B. T. SEATON[1], D. F. HILL[2], S. L. COWEN[3], ***M. L. HEIEN**[1];
[1]Chem. and Biochem., [2]Dept. of Physiol., [3]Dept. of Psychology, Univ. of Arizona, Tucson, AZ

Abstract: Dopamine is an important neurotransmitter that governs many physiological and behavioral systems. Disruption of dopaminergic signaling is involved in chronic pain, Parkinson's disease, and mental disorders. Fast-scan cyclic voltammetry (FSCV) is an electrochemical technique that allows dopaminergic release to be studied in real time. FSCV measurement requires the subtraction of nonfaradaic background current, necessitating a stable background signal over the course of the study for reliable detection of dopamine. Long-term (days to months) FSCV studies thus present a challenge, as the implantation of electrodes in the brain elicits a cascade of immune responses that target the electrodes and degrade voltammetric performance, an effect generally referred to as "biofouling". In FSCV, biofouling manifests as a shift in the nonfaradaic background signal that begins days after implantation and worsens over the course of weeks, confounding dopamine detection. This shift appears to be the result of two biofouling-induced events: a cathodic shift in the Ag/AgCl reference electrode potential due to dechlorination and an increase in reference electrode impedance due to glial encapsulation. These two factors were investigated using scanning electron microscopy/energy-dispersive X-ray spectroscopy (SEM/EDS) and electrochemical impedance spectroscopy (EIS), respectively. A three-electrode headstage that utilizes a platinum counter electrode was designed to compensate for the increased impedance. This headstage significantly reduced ($n = 4$, two-tailed t-test, $p < 0.05$) the FSCV background signal shift in comparison to a conventional two-electrode headstage *in vivo* using Sprague-Dawley rats. However, a shift was still apparent due to the change in reference electrode potential, which declined progressively for 2 to 3 weeks after implantation until settling at ca. 200 mV cathodic to the original potential ($n = 4$). Thus, a reference electrode that keeps its original potential after implantation is vital in obtaining a stable FSCV signal in long-term studies. The potential stabilities of alternate reference electrode materials subjected to *in vitro* biofouling environments are being investigated. In conjunction with the 3-electrode headstage, a stable reference electrode will provide a permanently stable FSCV signal that will allow for reliable dopamine detection over the course of weeks to months, improving the validity of long-term dopaminergic signaling research (e.g. chronic pain and Parkinson's disease).

Disclosures: **M.L. Heien:** None. **D.F. Hill:** None. **S.L. Cowen:** None. **B.T. Seaton:** None.

Poster

796. Techniques: Network Electrophysiology

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Topic: I.04. Physiological Methods

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NIH R01 NS025529
Army Research Office W911NF-16-1-0474
Saks Kavanaugh Foundation

Title: Synchronous recording of dopamine neurochemical and striatal electrical activity in non-human primates

Authors: *H. N. SCHWERDT[1,2], K.-I. AMEMORI[1], D. J. GIBSON[1], L. STANWICKS[1], T. YOSHIDA[1], S. AMEMORI[1], R. LANGER[3,2], M. J. CIMA[4,2], A. M. GRAYBIEL[1];
[1]Brain and Cognitive Sciences, McGovern Inst. for Brain Res., [2]Koch Inst. for Integrative Cancer Res., [3]Dept. of Chem. Engin., [4]Dept. of Materials Sci., MIT, Cambridge, MA

Abstract: Impaired dopamine neurotransmission is implicated in mood disorders and Parkinson's disease. These disorders also involve abnormal changes in the neuronal activity in the striatum, a major recipient of dopamine. We developed systems to monitor concurrently dopamine and neural electrical activity in non-human primates to examine the multiple modes of striatal signaling involved in key mood and motor behaviors that are compromised in many disorders. Multiple sensors were implanted into the striatum of two rhesus macaques to selectively measure sub-second dopamine concentration changes and oscillatory local field potentials (LFPs) by employing simultaneously fast-scan cyclic voltammetry and electrophysiology. Physiological parameters including pupil diameter, licking and pulse oximetry were also recorded in a monkey to identify cryptic behavioral states. These multi-modal measurements were made as the monkeys performed a reward-biased visual saccade task in which eye movements to targets appearing on the left or right were rewarded with a small or large amount of liquid food. Dopamine concentration changes were greater for large reward trials than for small reward trials in the ventral striatum of the first monkey. These results concord with the well-established role of ventral striatal dopamine signaling reward value. Most measurements in both monkeys were taken from the dorsal striatum where dopamine changes and LFPs displayed diverse site-dependent patterns related to different aspects of motivation. Early analysis suggests changes in dopamine concentration are significantly modulated following

initial trial start cue, peripheral target cue, and reward events as a function of reward condition and target position (left or right) as well as striatal site. Behaviorally contingent dopamine changes were further reflected in the LFPs measured at neighboring sites. These neural signals were also related to measures of autonomic response (heart rate variability and pupil diameter) and vigor (licking), but the dynamics of such relationships are under investigation. The early work described here suggests heterogeneous functions of dopamine that are closely tied to LFP activity in mediating various aspects of motivation. These findings strengthen the rationale for targeted strategies for a number of disorders to help alleviate symptoms originating from dysfunction at specific brain sites. Further investigations are needed to understand the site-specific functions of dopamine and striatal activity in motor and mood behaviors, which could help identify new therapeutic targets.

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Poster

796. Techniques: Network Electrophysiology

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Program #/Poster #: 796.23/DD26

Topic: I.04. Physiological Methods

Support: NIH T-32-NS076401
NIH DA 020140-09

Title: Kainate induces oscillations in *ex vivo* hippocampal sections on perforated micro electrode arrays

Authors: *J. C. RODRIGUEZ DIAZ[1], K. S. JONES[2];
[1]Neurosci. Grad. Program, [2]Pharmacol., Univ. of Michigan, Ann Arbor, MI

Abstract: Coordinated and synchronized activity in the brain can result in oscillatory activity. Oscillations play crucial roles in many cognitive processes such as memory formation and attention. GABAergic interneurons are crucial for synchronizing neuronal activity leading to gamma oscillations (30-60 Hz).Abnormal oscillatory activity in the hippocampus has been implicated in the pathology of some mental disorders including schizophrenia, however, the neurobiological mechanism underlying these abnormal oscillations are not yet fully understood. We set out to develop an assay that would allow for the study of gamma oscillations in hippocampal sections using microelectrode arrays. Extracellular electrophysiological recordings were performed using 60- channel perforated microelectrode arrays (pMEAs). Oscillatory activity in the gamma band was induced pharmacologically with kainate application. Established

oscillations were inhibited by bath application of the GABAA receptor antagonist bicuculline. Bath application of kainate-induced and maintained oscillatory activity in the gamma band in both CA1 and CA3 regions of the hippocampus. CA1 oscillations had a narrow band with a peak at around 30 Hz while in CA3 the oscillations were broader. Kainate-induced oscillations in CA1 and CA3 were abolished by application of the GABAA receptor antagonist bicuculline. These studies suggest that kainate-induced oscillatory activity can serve as a model of *in vivo* GABA-dependent gamma oscillations in the hippocampus. Furthermore, pMEAs provide a tool to study oscillations in nearby regions during chemically induced oscillations. Future studies will focus on determining the oscillations sensitivity to glutamate receptor antagonists and comparing these with oscillations induced in an animal model of schizophrenia.

Disclosures: J.C. Rodriguez Diaz: None. **K.S. Jones:** None.

Poster

796. Techniques: Network Electrophysiology

Location: Hall A

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Program #/Poster #: 796.24/DD27

Topic: I.04. Physiological Methods

Support: Packard Center for ALS Research at Johns Hopkins
Department of Defense, W81XWH1810175
ALS Association 18-DDC-436

Title: Role of human induced pluripotent stem cell-derived spinal cord astrocytes in the functional maturation of motor neurons in a multielectrode array system

Authors: *A. TAGA[1], R. DASTGHEYB[1], C. W. HABELA[1], J. A. JOSEPH[1], J.-P. RICHARD[1], S. GROSS[1], G. LAURIA[2], G. LEE[1], N. HAUGHEY[1], N. J. MARAGAKIS[1];
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Abstract: Objective and rationale: The ability to generate human induced pluripotent stem cell (hiPSC)-derived neural cells displaying region-specific phenotypes is of particular interest for modeling central nervous system (CNS) biology *in vitro*. With the increasing number of differentiation techniques, the electrophysiological characterization of hiPSC-derived neurons has become crucial to provide accurate measures of their function. We describe a unique method by which spinal cord hiPSC-derived astrocytes (hiPSC-A) are cultured with spinal cord hiPSC-derived motor neurons (hiPSC-MN) in a multielectrode array (MEA) system to record electrophysiological activity over time.
Methods: Through the critical steps of caudalization and ventralization, we generated spinal cord hiPSC-A and -MN. We then optimized the co-culture paradigm for MEA recording and

investigated astrocyte variables that influenced MN maturation. Immunocytochemistry and quantitative PCR were used to analyze astrocyte and neuronal populations. MEA recordings were performed weekly over a four-week period, to obtain electrophysiological parameters including spike and burst rate and the percentage of spiking and bursting electrodes. Finally, we used MEA recording to test the electrophysiological effects of drugs targeting hiPSC-MN receptors (i.e. AMPA/Kainate receptor and GABA receptor) and hiPSC-A transporters (i.e. EAAT2 and Cx43).
Results: We show that hiPSC-A enhance hiPSC-MN electrophysiological maturation in a time-dependent fashion. The sequence of plating, density, and age in which hiPSC-A are co-cultured with MN, but not their respective hiPSC line origin, are factors that influence neuronal electrophysiology. When compared to co-culture with mouse primary spinal cord astrocytes, we observe an earlier and more robust electrophysiological maturation in the fully human co-cultures. These findings are supported by immunocytochemistry and real time PCR studies in parallel cultures demonstrating human astrocyte mediated changes in the structural maturation and protein expression profiles of the neurons. Interestingly, this relationship is reciprocal and co-culture with neurons influences astrocyte maturation as well. Pharmacological assays confirmed increased expression over time of hiPSC-MN receptors and hiPSC-A transporters in co-cultures.
Conclusions: This fully human *in vitro* platform for the electrophysiological evaluation of spinal cord astrocyte/MN interactions has the potential to more accurately model human diseases with spinal cord pathology, including spinal muscular atrophy (SMA) and amyotrophic lateral sclerosis (ALS).

Disclosures: A. Taga: None. **R. Dastgheyb:** None. **C.W. Habela:** None. **J.A. Joseph:** None. **J. Richard:** None. **S. Gross:** None. **G. Lauria:** None. **G. Lee:** None. **N. Haughey:** None. **N.J. Maragakis:** None.

Poster

796. Techniques: Network Electrophysiology

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Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 796.25/DD28

Topic: I.04. Physiological Methods

Support: Personal Funds (RLC)

Title: Monitoring activity of *Drosophila* larvae with impedance measures

Authors: *N. S. F. DE CASTRO[1], R. L. COOPER[2];
[1]Biol., Univ., Lexington, KY; [2]Dept Biol, Univ. of Kentucky Dept. of Biol., Lexington, KY

Abstract: Monitoring *Drosophila* larval movement with electrical detection allows one to record movements without the use of lights and cameras. This may be a more suitable technique in some experimental paradigms such as those using light sensitive proteins in optogenetic techniques. In determining when an larva starts to move or continue to moves after a light induced activation of Channel Rhodopsins, expressed either in body wall muscles or neurons, is of interest as one can determine that the recovery period or if the light stimulus is inducing a cessation of movement. We have developed a technique using an impedance measure of the media the larvae are in as a index of larvae movement. As a proof of concept, we record with IR camera the larval movement simultaneous with impedance measures. The two techniques parallel each other in their ability to index larval movements. The disadvantages of impedance measures is the environmental disturbances such as air movement over the preparation or drying out of the media; however, these environmental conditions need to be controlled when performing behavioral assays using a camera or an impedance measure. Bright LED light used in optogenetic experiments tend to saturate cameras unless filters are used and different filters maybe necessary depending on the LED spectrum and sensitivity of the camera. Impedance measure are independent of the type of LED or brightness.

Disclosures: N.S.F. De Castro: None. **R.L. Cooper:** None.

Poster

797. Electrical Methods to Modulate Neural Activity II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 797.01/DD29

Topic: I.08. Methods to Modulate Neural Activity

Support: H2020-FETPROACT-2018-01 NeuHeart (#824071)
Bertarelli Foundation

Title: Spatially selective intraneural recordings of pig vagus nerve activity during alterations in physiological parameters

Authors: *M. OTTAVIANI[1], L. GIANGRECO[3], A. CUTRONE[2], F. DEDOLA[2], F. VALLONE[2], M. CRACCHIOLO[2], F. BERNINI[1], A. MAZZONI[2], F. RECCHIA[1,4], S. MICERA[2,5];
[1]Inst. of Life Sicences, [2]The Biorobotics Inst., Sant'Anna Sch. of Advanced Studies, Pisa, Italy; [3]Univ. of Padova, Padova, Italy; [4]Lewis Katz Sch. of Med., Temple Univ., Philadelphia, PA; [5]Ecole Polytechnique Federale De Lausanne, Lausanne, Switzerland

Abstract: Bioelectronic medicine (BM) uses implantable neural interfaces to treat chronic diseases through the modulation of selected neural circuits regulating specific organ and system functions. Given the numerous afferent and efferent vagal fibers innervating multiple organs,

vagus stimulation is one of the most promising applications in BM. At the same time, being the vagus the most complex visceral nerve, its precise modulation is possible only using closed-loop control approaches. Several steps are required to achieve this goal since the design of optimal neural interfaces is limited by the inadequate knowledge of the way vagal neural activity regulates specific physiological processes.
In this study, we recorded vagus nerve activity with different types of neural interfaces during alterations of physiological parameters. In 9 anesthetized farm pigs, left (n=4) and right (n=5), cervical vagus nerves were surgically implanted with a tripolar cuff electrode and a self-opening neural interface (SELINE) to record electroneurograms. Physiological variables such as respiratory volume/rate, arterial blood pressure, heart rate, and glycemia were altered, respectively, by mechanical ventilation and intravenous infusions of angiotensin II or sodium nitroprusside or 20% glucose solution or insulin. Spectral analysis of the neural recordings revealed that changes in vagal activity in response to those alterations are reflected by variations of low-frequency (< 40 Hz) and high-frequency components. Interestingly, we were able to find specific spectral modulations associated with each manipulation of physiological variables. This paves the way to algorithms decoding online vagus activity for closed-loop applications. Results strongly varied with electrode type: while recordings acquired from cuff electrodes had poor spatial resolution and selectivity (with high redundancy among channels), SELINE displayed higher selectivity by detecting, through its multiple active sites, spatially distinct and stimulus-specific changes in low and high-frequency neural activities. Subsequent histological examination of the nerve with the SELINE probe left in place allowed the identification of fiber fascicles adjacent to specific recording sites. These novel findings support the possibility to map the topographical heterogeneity of vagal electrical activity within the nerve as a preliminary step towards the development of highly selective BM interventions.

Disclosures: **M. Ottaviani:** None. **L. Giangreco:** None. **A. Cutrone:** None. **F. Dedola:** None. **F. Vallone:** None. **M. Cracchiolo:** None. **F. Bernini:** None. **A. Mazzoni:** None. **F. Recchia:** None. **S. Micera:** None.

Poster

797. Electrical Methods to Modulate Neural Activity II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 797.02/DD30

Topic: I.08. Methods to Modulate Neural Activity

Support: MEXT/JSPS KAKENHI Grant Number JP16H05862

Title: Noise reduction in MEG measurement during transcranial alternating current stimulation

Authors: *S. SHIBUSAWA[1,2], A. OTSUKA[2], K. AMANO[2,1];
[1]Osaka Univ., Osaka, Japan; [2]Natl. Inst. of Information and Communications Technology, Ctr. for Information and Neural Networks, Osaka, Japan

Abstract: Transcranial alternating current stimulation (tACS) is a promising tool to non-invasively manipulate neural oscillations, and is known to be effective for affecting several brain functions such as motor (Brignani et al., PLoS One, 2013), memory (Reinhart & Nguyen, Nat Neurosci, 2019) and perception (Minami et al., Curr Biol, 2017). However, the direct effects of tACS on brain oscillations have remained unclear because broadband noise and the peaked noise at the stimulation frequency make MEG measurements difficult.
In a typical tACS setting, the cables extending to the anode and cathode electrodes runs parallelly and causes an antenna effect, which amplifies the noises originating from the stimulation current. From the aspect of MEG measurements during tACS, it is better to make the antenna effect as small as possible by maximally twisting the cables. This will, however, limit the degree of freedom in electrode arrangement. Here we used simNIBS to simulate the difference in current density distribution between a conventional electrode arrangement and the arrangement where the electrodes are rotated by 90 deg from the conventional arrangement and the cable side of the electrodes are facing closely with each other so that the cables are maximally twisted.
The simulation was performed for the stimulation protocol of our previous study where the peak alpha frequency was manipulated by the current stimulation applied to the parieto-occipital area (Minami et al., Curr Biol, 2017). As a result, it was found that the stimulated brain areas did not change depending on the orientation of the electrodes. The current density in the brain was rather increased with the twisted electrode arrangement so that the current intensity can be reduced. This is better for noise reduction and helps to prevent trapping and flipping of the MEG sensor, which means loss of brain activity information near the stimulation brain areas. When MEG was measured during tACS in both arrangements, the arrangement with maximally twisted cables significantly reduced the broadband noise and the harmonics of the stimulation frequency. Simulation of the current density distribution generated by tACS revealed that the arrangement with the rotated electrodes enables us to reduce current intensity to obtain the current density distribution comparable to a conventional configuration. Reduction of both current intensity and antenna effect with this setting leads to noise reduction of the MEG sensor and prevents trapping and flipping, enabling high signal-to-noise ratio measurements. Our results contribute to the simplification of noise modeling in the separation of noise generated by tACS and brain activity.

Disclosures: S. Shibusawa: None. **A. Otsuka:** None. **K. Amano:** None.

Poster

797. Electrical Methods to Modulate Neural Activity II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 797.03/DD31

Topic: I.08. Methods to Modulate Neural Activity

Support: NICHD - 1R03HD094608-01A1 (DJG)

Title: Improving an open-source commercial system to reliably perform activity-dependent stimulation

Authors: *S. BUCCELLI[1,2], M. D. MURPHY[3], Y. BORNAT[4], D. T. BUNDY[3], R. J. NUDO[3], D. J. GUGGENMOS[3], M. CHIAPPALONE[1];
[1]Inst. Italiano Di Tecnologia, Genova, Italy; [2]Univ. of Genova, Genova, Italy; [3]Dept. of Physical Med. and Rehabil., Univ. of Kansas Med. Ctr., Kansas City, KS; [4]Univ. of Bordeaux, Bordeaux, France

Abstract: Activity-dependent stimulation (ADS) protocols are designed to manipulate and strengthen in vivo neural connections and offers a promising tool for promoting neurophysiological reorganization following a brain injury. The effectiveness of these protocols relies on the accurate detection of events from the extracellular field of one area and the timing of the delivery of stimulation pulses at fixed, short-duration latencies to a separate region. Typically, this pairing is done by using single- or multi-unit as the trigger event, which may limit the functional application of this protocol. In order to expand the potential scope of this therapy we are developing ADS protocols in which low frequency signals (i.e. < 300Hz) can be used as the trigger event by utilizing a particular phase and a power above threshold within specific frequency bands of the local field potential signal. A challenge of ADS regardless of signal type is that trigger detection can suffer in awake and behaving animals due to biological signal sources such as movement and chewing, necessitating the use of methods that can robustly distinguish between neural unit activity and biological noise, which may negative impact the ability to strengthen the targeted connections. Here, we improved a low-cost commercial system to reliably perform both spike detection and local field potential filtering in awake rats. We implemented a spike detection state machine on a commercial field-programmable gate array (FPGA) based on multiple user-programmable thresholds. A series of offline and online analyses showed that our implementation was able to appropriately trigger stimulation during epochs of biological noise such as chewing with an overall accuracy higher than 97%. Notably, this implementation improves upon the capabilities of a commercial, low-cost neurophysiological acquisition system (Intan Technologies) with minimal disruption to existing workflows designed to use it. Our improvements have been made open-source and are freely available to all scientists working on closed-loop neuroprosthetic devices.

Disclosures: S. Buccelli: None. **M.D. Murphy:** None. **Y. Bornat:** None. **D.T. Bundy:** None. **R.J. Nudo:** None. **D.J. Guggenmos:** None. **M. Chiappalone:** None.

Poster

797. Electrical Methods to Modulate Neural Activity II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 797.04/DD32

Topic: I.08. Methods to Modulate Neural Activity

Support: DARPA Targeted Neuroplasticity Training (TNT)

Title: Biological sex differences in response to vagus nerve stimulation: Investigation into cardiovascular and immune system effects

Authors: F. YAGHOUBY, K. JANG, U. HOANG, ***S. VASUDEVAN**;
U.S. Food and Drug Admin., Silver Spring, MD

Abstract: Vagus nerve stimulation (VNS) has been approved for the treatment of epilepsy, depression and cluster headache. While VNS has been reported to be an effective treatment for other conditions such as rheumatoid arthritis and tinnitus, the importance of biological sex differences for off-target effects has been overlooked, despite the existence of anatomical and physiological differences between men and women. Our objective is to study the biological sex differences associated with VNS on the cardiovascular and immune systems. This is being studied using chronic rodent models implanted with wireless Electrocardiogram (ECG) devices and custom VNS cuff implants. Under approval by the Institutional Animal Care and Use Committee (IACUC) at the FDA, male and female Lewis rats (n = 16) were first implanted with a wireless physiological monitoring device for continuous ECG recording. After three weeks, each animal was implanted with a custom cuff electrode around the left cervical vagus nerve. Upon complete recovery from surgeries, a daily stimulation protocol was triggered and continued for 8 weeks using a wireless programmable pulse generator. To characterize the immune system effects, blood samples were collected on a weekly basis and the expression of inflammatory cytokines was examined. Cardiovascular variables from ECG and cytokine concentration levels were compared between male and female animals at different time points of the experiment to evaluate VNS effects. Two groups of rats including treatment (n=8) and sham (n=8) were used in this study with an equal number of male and female animals (n=4) in each group. Comprehensive analysis of ECG signals was performed to quantify cardiovascular effects. ECG features and cytokine levels were averaged for each week and compared between groups at different time points of the experiment. Sex-specific cardiovascular responses were observed for selected ECG variables. Additionally, immune system effects reflected by cytokine concentrations showed a notable increase after surgeries with slight differences between male and female rats. Biological sex differences in safety assessment of Vagus nerve stimulation (VNS) have been primarily neglected, despite sex-specific anatomical and physiological differences. In this animal study, we investigated the off-target effects of VNS on cardiovascular

and immune systems and the role of sex differences in safety assessments. In a cohort of male and female rats, significant differences were observed for heart rate variability analyses. However, inflammatory biomarker assessment did not reveal significant effects between the two groups.

Disclosures: F. Yaghouby: None. **K. Jang:** None. **U. Hoang:** None. **S. Vasudevan:** None.

Poster

797. Electrical Methods to Modulate Neural Activity II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 797.05/DD33

Topic: I.08. Methods to Modulate Neural Activity

Support: NSF INSPIRE (CBET-1343193)

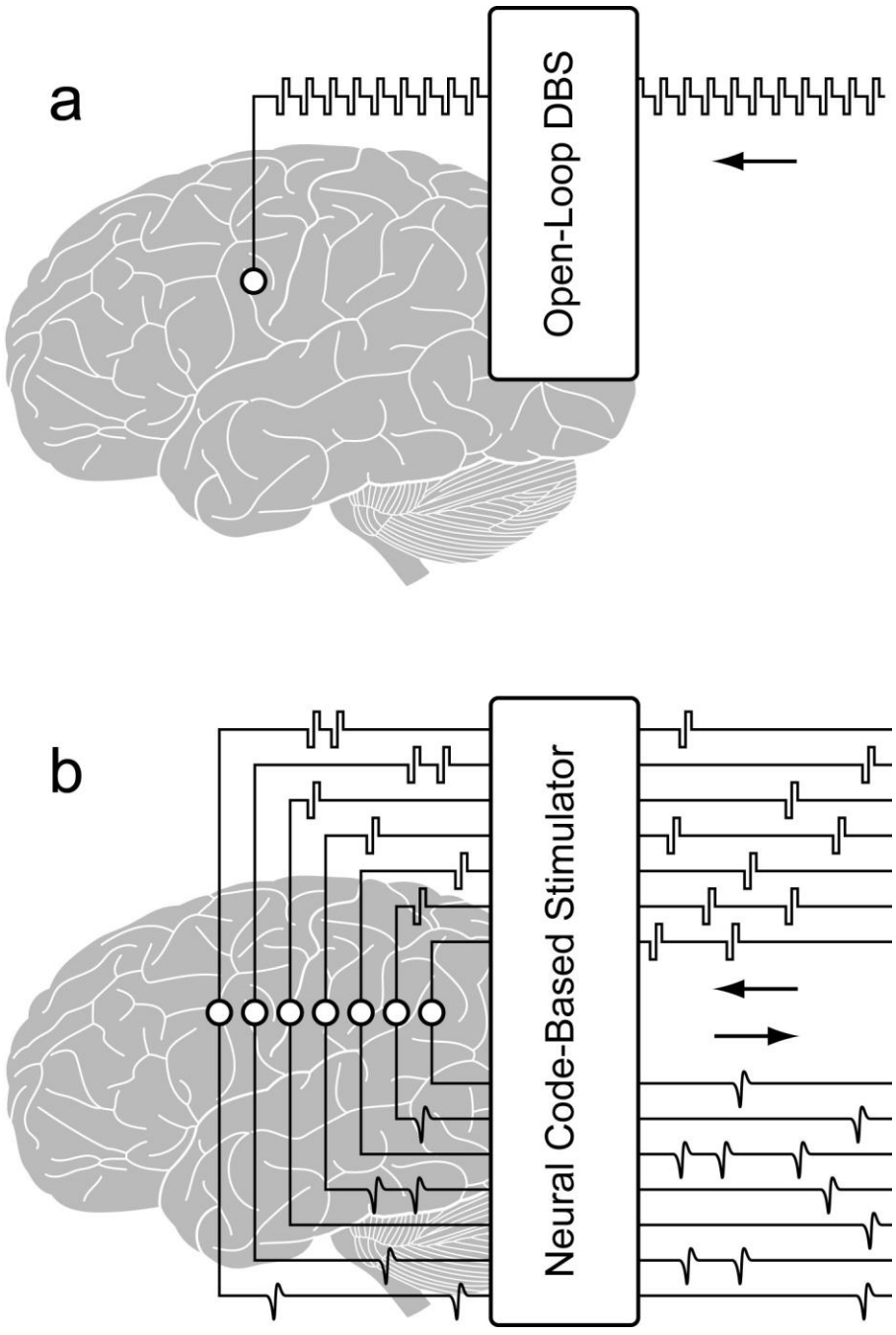
Title: A multi-channel asynchronous neurostimulator with artifact suppression for neural code-based stimulations

Authors: *S. ELYAHOODAYAN, W. JIANG, H. XU, D. SONG;
Biomed. Engin., USC, Los Angeles, CA

Abstract: A novel 32-channel neurostimulator for generating neural code-based, precise, asynchronous electrical stimulation pulses is designed, fabricated and characterized. This system can deliver charge-balanced, constant current biphasic pulses, with arbitrary pulse patterns in multiple electrodes using a multiplexer to save power and area. The design also features a stimulus artifact suppression technique that can be integrated with commercial amplifiers. Using an array of CMOS switches, electrodes are disconnected from recording amplifiers during stimulation, while the input of the recording system is shorted to ground through another CMOS switch to suppress ringing in the recording system. The timing of the switches used to block and suppress the stimulus artifact are crucial and are determined by the electrochemical properties of the electrode. This system allows stimulation and recording from the same electrodes to monitor local field potentials with short latencies from the region of stimulation for achieving feedback control of neural stimulation. In this way, timing between each pulse is controlled by inputs from an external source and stimulus magnitude is controlled by feed-back from neural response from the region of stimulation. The system was implemented with low-power and compact packaged microchips to constitute an effective, cost-efficient and miniaturized neurostimulator. The device has been first evaluated in phantom preparations and then tested in hippocampi of behaving rats. Benchtop results demonstrate the capability of the stimulator to generate arbitrary spatio-temporal pattern of stimulation pulses dictated by random number generators to control magnitude and timing between each individual biphasic pulse. In vivo results show that evoked potentials elicited by the neurostimulator can be recorded ~2ms after the termination of stimulus

pulses from the same electrodes where stimulation pulses are delivered, whereas commercial amplifiers without such an artifact suppression typically result in >60ms recovery period. This neurostimulator design is desirable in a variety of neural interface applications, particularly cortical prostheses aiming to restore cognitive functions by reinstating neural code transmissions in the brain.

[Support contributed by: NSF CBET-1343193]



Disclosures: **S. Elyahoodayan:** None. **W. Jiang:** None. **H. Xu:** None. **D. Song:** None.

Poster

797. Electrical Methods to Modulate Neural Activity II

Location: Hall A

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Program #/Poster #: 797.06/DD34

Topic: I.08. Methods to Modulate Neural Activity

Support: NSF Grant 1637892
NSF Grant 1527202

Title: Evoked haptic sensations in the foot through high-density transcutaneous nerve stimulation

Authors: L. PAN, L. VARGAS, X. HU, H. HUANG;
UNC/NC State Joint Dept. of Biomed. Engin., North Carolina State Univ. and Univ. of North Carolina-Chapel Hill, Raleigh, NC

Abstract: Evoking haptic sensation on upper limb amputees via peripheral nerve stimulation have been investigated intensively in the past decade, but the related study on lower limb amputees is limited. This study aimed to evaluate the feasibility of using non-invasive transcutaneous nerve stimulation to evoke haptic sensation of amputated foot in transtibial amputees. A high-density electrode grid (4x4) was placed over the skin surface above the intersection of the sciatic, tibial, and common peroneal nerves. We hypothesized that electrical stimulation delivered to distinct electrode pairs created unique electric fields, which can activate selective sets of sensory axons innervating different skin regions of the foot. Five transtibial amputee subjects (three unilateral and two bilateral) were tested by scanning all possible electrode pairs. All subjects reported various haptic percepts at distinct regions of the foot corresponding to specific electrode pairs. Compared with the evoked sensation in the upper limb through transcutaneous nerve stimulation, the evoked haptic sensations of the foot had lower spatial resolution. Although sensation was perceived at different regions of subjects' phantom foot, sensation at the heel was rare in a majority of the subjects. These results demonstrated the capability of our non-invasive nerve stimulation method to evoke haptic sensations in the foot of transtibial amputees. The outcomes can help us understand the neurophysiological mechanism of missing limb sensation in lower-limb amputees, and can also facilitate future development of strategies to manage phantom pain and enhance embodiment of prosthetic legs.

Disclosures: L. Pan: None. **L. Vargas:** None. **X. Hu:** None. **H. Huang:** None.

Poster

797. Electrical Methods to Modulate Neural Activity II

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Program #/Poster #: 797.07/DD35

Topic: I.08. Methods to Modulate Neural Activity

Support: NIH R01 NS085167
NIH R01 NS094384
DARPA HR0011-15-2-0017
DARPA N66001-15-2-4057
DARPA N66001-17-2-4011

Title: Parametric characterization of implanted and non-invasive vagus nerve stimulation strategies in rat

Authors: *J. E. BUCKSOT[1], K. MORALES CASTELAN[2], S. K. SKIPTON[2], S. A. HAYS[1]; [1]Bioengineering, Univ. of Texas At Dallas, Richardson, TX; [2]Behavioral and Brain Sci., Univ. of Texas at Dallas, Richardson, TX

Abstract: Vagus nerve stimulation (VNS) has rapidly gained interest as a treatment for a variety of disorders. A number of methods have been employed to stimulate the vagus nerve, but the most common is through a cuff electrode implanted on the cervical vagus nerve. Recently, two non-invasive methods have gained traction: transcutaneous cervical VNS (tcVNS) and transcutaneous auricular VNS (taVNS). Despite promising clinical results, there has been little direct comparison of these methods to the traditional implant. In this study, we compared both non-invasive strategies to stimulation with an implanted cuff in rats using activation of the Hering-Breuer reflex, a well-established biomarker of VNS. We found that the threshold to activate the vagus using an implant was 0.582 ± 0.053 mA, and there was no detectable muscle twitching in the neck at intensities below 2.5 mA. The threshold to activate the vagus using tcVNS was 28.36 ± 2.25 mA. The threshold to cause twitching of the neck muscles with tcVNS was 2.18 ± 0.18 mA, indicating substantially stronger stimulation intensities are needed to elicit activation of the vagus nerve. With taVNS, we found no activation of the Hering-Breuer reflex at any parameter. These results demonstrate that tcVNS can activate the cervical branch of the vagus nerve, however, the required stimulation intensities are well above the tolerable intensities used clinically. These results provide greater insight into activation of the vagus nerve with each strategy and provide a framework for selecting stimulation parameters and implementations for future studies.

Disclosures: J.E. Bucksot: None. **K. Morales Castelan:** None. **S.K. Skipton:** None. **S.A. Hays:** None.

Poster

797. Electrical Methods to Modulate Neural Activity II

Location: Hall A

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Program #/Poster #: 797.08/DD36

Topic: I.08. Methods to Modulate Neural Activity

Support: NIH R01NS094396

Title: Electrical stimulation waveform modulates spatial and temporal activation of cortical neurons *in vivo*

Authors: *K. C. STIEGER[1,2], J. R. ELES[1], K. A. LUDWIG[5,6], T. D. Y. KOZAI[1,2,3,4,7];
[1]Bioengineering, [2]Ctr. for The Neural Basis of Cognition, [3]Ctr. for Neurosci., [4]McGowan Inst. for Regenerative Med., Univ. of Pittsburgh, Pittsburgh, PA; [5]Biomed. Engin., Univ. of Wisconsin Madison, Madison, WI; [6]Neurolog. Surgery, Univ. of Wisconsin, Madison, WI; [7]Neurotech Ctr., Univ. of Pittsburgh Brain Inst., Pittsburgh, PA

Abstract: Although electrical stimulation has been used for over a century to investigate the functional role of neural circuits, the direct neurobiological response to stimulation is highly variable and remains poorly characterized within the vast parameter space. Stimulation of spatially localized neuronal populations could increase the reliability of activation and limit damage during long stimulation trains. Current hypotheses suggest that electrical stimulation activates proximal axons resulting in poor spatial localization and rapid accommodation at higher frequencies (> 90 Hz). Asymmetric waveforms have the potential to selectively activate specific neuronal compartments by taking advantage of the nonlinear properties of voltage-gated sodium channels. Utilizing male C57BL/6J-Tg(Thy-1-GCaMP6s) mice we used in-vivo two-photon microscopy to image neuronal calcium activity in layer 2/3 neurons and widefield mesoscale imaging to image larger population activity during 30s stimulation trains while varying polarity and waveform asymmetry. Our preliminary data suggest distinct spatial and temporal differences based on stimulation waveform. Specifically, in mesoscale imaging we observed decreases in the peak and average area of activation during the 30s stimulation train in the first stimulation paradigm. However, compared to a second stimulation paradigm, we observed increases in peak and average area of activation. Using two photon imaging we observe decreases in the number of neurons activated, the neuronal activation time, and mean and maximum normalized changes in fluorescence, and a slight increase in the percentage of activated neurons within 100μm of the electrode in the first paradigm compared to the second. These findings suggest that stimulus waveform and polarity may play a major role in the spread of activation and entrainment of neurons during electrical stimulation, which may be critical for research in neural circuits in addition to clinical therapeutic use.

Disclosures: K.C. Stieger: None. **J.R. Eles:** None. **K.A. Ludwig:** None. **T.D.Y. Kozai:** None.

Poster

797. Electrical Methods to Modulate Neural Activity II

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Program #/Poster #: 797.09/DD37

Topic: I.08. Methods to Modulate Neural Activity

Support: DK100460
DK114546

Title: Selective DRG neuromodulation by flexible parylene based electrode array

Authors: *T. GUO, L. CHEN, S. ILHAM, N. NOLTA, M. HAN, B. FENG;
Univ. of Connecticut, Storrs, CT

Abstract: *Background*: The dorsal root ganglions (DRG) consisting of clustered afferent somata in the spinal cord foramina have emerged as novel neuromodulatory targets for alleviating symptoms like chronic pain. Compared with other neuromodulatory targets, DRG offer more selectivity not only than the spinal cord due to the distinct dermatomes innervated by different DRG, but also than the peripheral nerves due to the larger spatial distribution of the afferent somata in contrast to the tightly wrapped axons in fascicles. Indeed, our recent GCaMP6f recordings indicate that high-threshold colorectal afferents that are putative visceral nociceptors have neural somata concentrated in the caudal region of mouse L6 DRG. In this preliminary study, we developed a flexible stimulating electrode array, the first of this kind that could potentially allow selective targeting of the caudal region of the DRG to alleviate visceral pain. *Methods*: The multichannel electrode array was micro-fabricated on a flexible material (paryleneC) to conform to the surface curvature of the DRG. In each channel, we enhanced the spatial selectivity of electrical stimulation by surrounding the stimulating electrode with a concentric returning electrode. The preliminary electrode array consisted of four channels for stimulating the anterior, posterior, medial, and lateral region of one DRG. We deposited gold as the electrode material via E-beam evaporation and covered the gold wires with another layer of paryleneC. The electrode surfaces were exposed by reactive ion etching and modified with iridium oxide films by cyclic reduction/oxidation reactions. *Results*: Fabricated electrode array showed low impedance (<10 kΩ) as measured by electrochemical impedance spectroscopy, suitable for safe delivery of 100 μA currents under the voltage limit of 1V. GCaMP6f fluorescent recordings from L6 DRG in transgenic mice confirmed local activation of the caudal DRG by the novel flexible electrode array. *Conclusion*: The current study reported an innovative flexible electrode array that allowed selective activation of a sub-region of DRG somata to limit the off-target side effects. One potential application of this electrode array is to target the caudal region of the DRG to relieve nociceptive visceral pain.

Disclosures: **T. Guo:** None. **L. Chen:** None. **S. Ilham:** None. **N. Nolta:** None. **M. Han:** None. **B. Feng:** None.

Poster

797. Electrical Methods to Modulate Neural Activity II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 797.10/DD38

Topic: I.08. Methods to Modulate Neural Activity

Title: Visual fatigue reduction in normal adults by introducing broadband chaotic codes for the modulation of code modulated visual evoked potentials (c-VEP)

Authors: Z. SHIRZHIYAN[1], A. KEIHANI[1], M. FARAHI[1], E. SHAMSI[1], M. GOLMOHAMMADI[2], A. MAHNAM[3], A. H. JAFARI[1], *M. RAZA[4];
[1]Med. Physics & Biomed. Engin. Department, Sch. of Medicine, Tehran Univ. of Med. Sciences, Tehran, Iran, Tehran, Iran, Islamic Republic of; [2]Res. Ctr. for Biomed. Technologies and Robotics (RCBTR), Tehran Univ. of Med. Sciences, Tehran, Iran, Tehran, Iran, Islamic Republic of; [3]Dept. of Biomed. Engineering, Fac. of Engineering, Univ. of Isfahan, Isfahan, Iran, Isfahan, Iran, Islamic Republic of; [4]Section of Neuroscience, Dept. of Neurol., Baqiyatallah Univ. of Med. Sci., Tehran, Iran, Islamic Republic of

Abstract: Pseudo random binary codes such m-sequences are usually used in code modulated brain computer interfaces to evoke code modulated visual evoked potentials (c-VEPs). These codes are favorable because of their broadband spectrum and correlation properties and provide high speed with low cross interference of target stimuli in BCIs. However, these codes cause high visual fatigue. In this study, we generated broadband chaotic code to evoke c-VEPs and examining whether they could be used in designing more comfortable code modulated BCIs or not. Four lagged versions of m-sequence and chaotic code with 31-bit length were used visual stimuli and presented to evoke c-VEP (code modulated VEPs) in normal subjects (n=44, 21 females), then the EEG responses to corresponding codes were recorded. We used Canonical correlation analysis (CCA) and spatiotemporal beamforming (STB) methods for analysis of EEG signals. Additionally, we evaluated the subjective visual fatigue using self-reported VAS scores for both types of codes. The results of analysis indicate that chaotic codes decoded from their evoked responses successfully as well as m-sequence codes. The total average accuracies of all subjects were 93.6 ± 11.9 % and 94 ± 14.4 % for chaotic and m-sequence codes respectively. The statistical analysis of obtained accuracy did not show significant difference in accuracy rates However, there was significant visual fatigue reduction by using of chaotic codes compared to m-sequence (paired t-test (t (43) =4.054, p=0.0005)). The newly introduced chaotic codes for evoking c-VEPs evaluated successfully by CCA and STB methods. The chaotic codes cause low fatigue rates compared to m-sequences because of their inherent properties of chaos theory

which is more compatible with visual neural system. Therefore, we suggest use of binary chaotic codes in order to design comfortable and ergonomic code modulated BCIs.

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Poster

797. Electrical Methods to Modulate Neural Activity II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 797.11/DP15/DD39

ControlExtraData.DynamicPosterDisplay:
Dynamic Poster
Topic: I.08. Methods to Modulate Neural Activity

Title: Real-time application of machine learning algorithms to electroencephalography for predicting brain states

Authors: *M. OGANESYAN, I. TARASENKO, N. VYSOKOV;
Brainpatch, London, United Kingdom

Abstract: Commercial electroencephalography (EEG) devices are becoming cheaper and are rapidly entering the consumer market, but with the high inter-trial variability and low signal-to-noise ratio (SNR) the performance of data analysis remains a challenge. At the same time, modern machine learning techniques are used to discriminate between brain states or responses. However, most of the published research has at least one of two key limitations: need for some degree of human involvement at the preprocessing stage for complex problems, or simplistic binary classification with disregard for intermediate brain states.
In this work, we report a pipeline capable of processing an 8 channel EEG signal from consumer-grade equipment (OpenBCI) and predicting the state of a subject's brain in real time, with no human involvement. We have used relaxation/concentration as a positive control, and to compare performance of existing approaches with our system. The training dataset was collected by recording relaxed (eyes closed), idle and concentrated states, with subjects performing a range of standard working memory or mental performance tests. At real-time inference stage, the state (binary or multiclass classification) was determined by first dynamically pre-processing the data, generating a robust feature space, and finally classifying using a random forest. We achieved a high degree of accuracy (>80%), F1 score (>0.8), and reproducibility of our pipeline for determining the brain states in real time.
Thus, our approach is capable of effectively distinguishing between both the extreme forms of relaxation and concentration, as well as the idle states in between. The low computational requirements of a random forest compared to popular deep learning techniques allow for portability to embedded low-cost consumer grade devices, while high confidence predictions

across ‘unseen’ subjects allow for commercialization of this technology in an industrial and office setting. Furthermore, of particular scientific interest is the capability of the random forest to track EEG features that yield the greatest prediction power out of a wide range of autogenerated interaction features (unlike the black box behavior of deep learning architectures), thereby potentially unmasking inner workings of a particular brain state.

Disclosures: **M. Oganesyan:** A. Employment/Salary (full or part-time):; BrainPatch. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BrainPatch. **I. Tarasenko:** A. Employment/Salary (full or part-time):; BrainPatch. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BrainPatch. **N. Vysokov:** A. Employment/Salary (full or part-time):; BrainPatch. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BrainPatch.

Poster

797. Electrical Methods to Modulate Neural Activity II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 797.12/DD40

Topic: I.08. Methods to Modulate Neural Activity

Title: Evoked movements and muscle activations through transcutaneous stimulation near the spinal cord

Authors: Y. ZHENG[1], ***X. HU**[2];
[2]BME, [1]Univ. of North Carolina at Chapel Hill, Chapel Hill, NC

Abstract: Functional electrical stimulation (FES) can help individuals with neurological disorders to restore the motor function of upper extremities. However, the application of conventional FES is limited because stimulation at the muscle belly activates muscles in a non-physiological way (i.e., inaccessible to deep muscles, highly synchronized activation of muscle fibers, and non-physiological recruitment order of motor units), which can lead to fast fatigue and limited motions. To address these issues, we sought to elicit arm and hand motions by transcutaneously stimulating near the spinal cord (C5 to T1) with an electrode array. Joint kinematics were captured using a motion capture system, and electromyography (EMG) signals were recorded to quantify the muscle activation patterns. Our results showed that the near spinal cord stimulation was able to elicit various independent or coordinated motions, which included flexion/extension of the elbow, wrist, and fingers, and forearm pronation/supination, by adjusting the stimulation location and intensity (5-10 mA). Both H-reflex and highly asynchronized muscle activities with a long latency (50 ms) after stimulation onsets were observed, which demonstrated the activation of sensory axons or/and dorsal roots and the involvement of spinal-

supra circuitry. Compared with the conventional FES, our approach has two advantages. First, various upper arm and hand motions can be elicited through an electrode array with a low current intensity. Second, our approach can recruit motor units in a more physiological way through the recruitment of central pathways, which can lead to more fatigue-resistant motions and also faciliate neuroplasticity of the central nervous system. Our approach can potentially address different issues of conventional FES, and improve the application of electrical stimulation for rehabilitation/assistance of individuals with impaired motor function.

Disclosures: **X. Hu:** None. **Y. Zheng:** None.

Poster

797. Electrical Methods to Modulate Neural Activity II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 797.13/DD41

Topic: I.08. Methods to Modulate Neural Activity

Support: Innovation and Technology Fund (ITF), Innovation and Technology Commission, Hong Kong Special Administrative Region Government (Ref. No: ITS/151/17)

Title: Therapeutic potential of deep brain stimulation for the treatment of spinocerebellar ataxia

Authors: *P. ASTHANA[1], G. KUMAR[1], C. TIN[2], C. H. E. MA[1];
[1]Dept. of Biomed. Sci., [2]Dept. of Biomed. Engin., City Univ. of Hong Kong, Kowloon Tong, Hong Kong

Abstract: Spinocerebellar ataxia (SCA) is a genetically inherited progressive neurodegenerative disorder characterized by poor coordination of gait, hands, speech, and eye movements. Neuronal degeneration occurs in cerebellum, which is related to motor control. Until now, there is lack of medication and surgical intervention for treating SCA. Deep brain stimulator (DBS) has been used extensively in patients with essential tremor, Parkinson's disease, primary dystonia and obsessive-compulsive disorder. We therefore test the therapeutic potential of DBS in treating SCA. In present study, conditional knockout mice ablating a transcription factor expression specifically in mature Purkinje’s cells (PCs) was generated without showing any loss of PCs and exhibited ataxia phenotype. We delineated abnormal movements of SCA and monitor disease progression by synchronising high-speed video kinematics with multi-channel electromyography (EMG) recording, rotarod test, pole climb test and walking track analysis. Mice were implanted with multichannel electrodes in cerebellum and gastrocnemius muscle for DBS and EMG recording, respectively. After DBS, SCA mice exhibited improved motor coordination by showing increased retention time in rotarod test, increased stances length in footprint walking test, decreased variation in stance and swing phase duration in video kinematics test, increased spontaneous walking speed, and increased root mean square)

amplitude of gastrocnemius muscle as compared with baseline. In conclusion, our pilot study demonstrated improved motor coordination in SCA mice after DBS in cerebellum.

Disclosures: P. Asthana: None. **G. Kumar:** None. **C. Tin:** None. **C.H.E. Ma:** None.

Poster

797. Electrical Methods to Modulate Neural Activity II

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Topic: I.08. Methods to Modulate Neural Activity

Support: KU Leuven Research Funding EGM-D2929-C24/17/091
EIT Health Innovation by Ideas, NEURO-WEAR
SB PhD fellow at FWO

Title: Epicranial cortical stimulation: A novel minimally invasive neuromodulation method

Authors: A. KHATOUN, B. ASAMOAH, ***M. MC LAUGHLIN**;
KU Leuven, Leuven, Belgium

Abstract: Rationale Electrical brain stimulation methods can treat a range of medically refractory neurological and psychiatric disorders. These methods fall into two categories: invasive brain stimulation, such as deep brain stimulation and invasive cortical stimulation (ICS); and non-invasive methods such as transcranial electric stimulation (TES). ICS can successfully treat neuropathic pain and has been investigated as a treatment for movement disorders. However, significant risks and cost are associated with the surgical implantation. TES on the other hand is noninvasive with significantly lower risks and cost. However, TES effects are often weak and stimulate a large area. Epicranial cortical stimulation (ECS) has been proposed as a novel, minimally invasive brain stimulation method where electrodes are implanted on the skull. By overcoming some limitations of TES and ICS, ECS may fit a specific niche and could offer beneficial therapy to certain patient groups. **Objective** Use rat experiments and human head computational models to investigate the feasibility of using concentric-ring electrodes with ECS to achieve focused and strong electric fields in the cortex. **Methods** Wistar rats (n=6) were implanted with a concentric-ring ECS electrode to target the motor cortex. Limb movements were quantified using an accelerometer. We then investigated the feasibility of concentric-ring ECS in humans by using a human head computational model. We modeled the electric field generated by concentric-ring ECS and compared it to ICS and TES. **Results** Using the concentric-ring electrodes we focused stimulation to selectively target one specific limb. Thus demonstrating that concentric-ring ECS can target small brain areas in rodents. The computational model results helped bridge the gap between rodent and human. The human head model showed that for a 1 mA current, the electric field in the brain is stronger with ECS (~4

V/m) than with TES (~0.3 V/m) but ECS generates a weaker electric field than ICS (~40 V/m). An insulating back layer on the ECS electrodes allows increasing stimulus amplitude up to 10 mA without stimulating the skin. ECS at 10 mA generated an electric field strength approximately equivalent to that of ICS at 1 mA. Concentric-ring ECS electric field was also relatively focused, as predicted from the high selectivity observed in the rat experiments. **Conclusions** Concentric-ring ECS can generate comparatively strong and focused electric fields in the brain. Specific patient groups may benefit from chronic, minimally invasive, focused neuromodulation. Further studies using chronic ECS in larger animals are needed to explore safety and long-term feasibility.

Disclosures: A. Khatoun: None. **B. Asamoah:** None. **M. Mc Laughlin:** None.

Poster

797. Electrical Methods to Modulate Neural Activity II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 797.15/DD43

Topic: I.08. Methods to Modulate Neural Activity

Support: NWO SSM06011

Title: Modulated electrocortical current density dynamics in major depression following mindfulness-based cognitive therapy

Authors: P. L. A. SCHOENBERG[1], J. M. HENRY[1], *D. R. VAGO[1], A. E. M. SPECKENS[2]; [1]Vanderbilt Univ. Med. Ctr., Nashville, TN; [2]Radboud Univ. Med. Ctr., Nijmegen, Netherlands

Abstract: Mindfulness-Based Interventions (MBIs) are steadily infiltrating mainstream healthcare as non-pharmacological alternatives with evidence-based efficacy for depression and anxiety, common co-morbid symptoms among chronic conditions. Mindfulness-Based Cognitive Therapy (MBCT) shows high clinical utility for mood disorders, whilst mechanistic specificity has not been fully disentangled. **Aim:** Extant research has focused largely on psychological clinical scale outcomes. Here, we examined neurophysiological mechanisms related to clinical outcomes for treating depression with MBCT. Specifically, the following regions of interest and connectivity across multiple frequency spectra were examined: (1) the prefrontal and anterior cortical hubs (such as FPC and ACC) involved in executive functioning; (2) the insula and Posterior Cingulate Cortex (PCC) related to self-referential processing, including visceral interoceptive awareness and 'default-mode' function; and (3) fronto-parietal connectivity associated with regions specialized in inhibitory control. **Method:** we conducted a Randomized Clinical Trial (RCT) in 43 patients with Major Depressive Disorder (MDD), without significant other co-morbidity, exposed to either MBCT vs. wait-list control (WL). We recorded patients' electroencephalographic (EEG) data before and after the 8-week treatment interval (or 8-weeks

waitlist). LORETA based current density vector magnitude localization and connectivity dynamics were examined concomitant to an affective Go/NoGo paradigm pre-to-post treatment for patients in both groups. **Results:** Confirming our hypotheses, significant modulation was apparent in the ACC, part of the inhibitory and executive network that would be required to mediate affective bias towards negative stimuli. Findings highlighted decreases in current density magnitude within the insular cortex and PCC, specific to theta, beta, and gamma-2 spatial frequency bands. **Significance:** This first examination of complex neurophysiological parameters in MBCT contributes greater insight into the multi-dimensional functional and connectivity network dynamics underlying its clinical efficacy and action.

Disclosures: P.L.A. Schoenberg: None. **J.M. Henry:** None. **D.R. Vago:** None. **A.E.M. Speckens:** None.

Poster

797. Electrical Methods to Modulate Neural Activity II

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Program #/Poster #: 797.16/DD44

Topic: I.08. Methods to Modulate Neural Activity

Title: Two-photon calcium imaging in mice shows neural effects of transcranial current stimulation

Authors: *J. DUIJNHOUWER, P.-O. POLACK, B. KREKELBERG;
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Abstract: Transcranial current stimulation (tCS) is a non-invasive technique that has shown therapeutic potential in human behavioral studies. Yet, little is known about its mechanisms of action. To help fill this void, we used two-photon imaging in awake, behaving mice expressing GCaMP6f to study the effects of tCS at the neuronal level. As the mice also expressed tdTomato in GAD2 positive neurons, we were able to distinguish GABAergic interneurons from pyramidal neurons. We measured the responses to drifting gratings of layer 2/3 neurons in primary visual cortex during transcranial alternating current stimulation (tACS; 10 Hz) with current strengths of 50, 100, 200 μA, or no current. We found that, for the neurons that were significantly tuned to the orientation and/or the motion-direction of the gratings, the overall response increased with current strength, showing a slight increase over the 0-100 μA range and a marked jump at 200 μA. Inspection of the tuning parameters using a sensitive Bayesian analysis revealed that for some neurons this response increase resulted mostly from an increase of the response to the preferred orientation, while for others it was orientation non-specific (offset). Tuning width and preferred-orientation/direction were not affected by the electrical stimulation. These findings did not differ qualitatively between the sub-populations of pyramidal neurons and interneurons.

Disclosures: **J. Duijnhouwer:** None. **P. Polack:** None. **B. Krekelberg:** None.

Poster

797. Electrical Methods to Modulate Neural Activity II

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Program #/Poster #: 797.17/DD45

Topic: I.08. Methods to Modulate Neural Activity

Support: NRF Grant 2017M3C1B2085292

Title: Acquisition of sensory neural signals from stretchable penetrating multi-shank neural interface of peripheral nerve in rat

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Abstract: Recently, a variety of approaches to the development of the peripheral neural interface has been taken. The flexible penetrating microelectrodes which can directly contact the nerve fibers within the fascicles have a better spatial selectivity and were able to minimize mechanical mismatch between neural interface and nerve fiber.
Here, the suggested neural interface which was developed by applying the advantage of the transversally penetrating microelectrode can also reduce the stress caused by surrounding body tissues pulling on both the nerve and the implanted electrodes. Also, this neural interface can increase the chances of a selective neural signal acquisition due to its regular spacing between the four shanks.
The neural interface with four shanks is fabricated based on photosensitive polyimide material as structural substrate. In each shank of the neural interface are located eight channels, which allows the interface to have the total 32 channels. The structure between each shank of the neural interface has the meander structure designed for reduction of the stretching force from the sciatic nerve. Each fabricated sensing electrode has the impedance of 300 kOhm, which is confirmed to be appropriate for acquisition of the neuro sensory signal.
12-week-old male SD rats were anesthetized, and 4 shanks of the electrode were inserted into the right sciatic nerve. Shanks are implanted in a row with regular intervals in the nerve. Ground and reference electrode are connected subcutaneously. The neural interface was connected to the recording device (Intan technologies, US) and the laptop for the neural signal acquisition. Nonconductive object was used to physically stimulate the right paw of the rat. With each of the paw stimulation, the sensory signal was acquired from a few of the 32 channel electrodes. The experiment for recording and decoding of the neural signals with varying kinds of stimulation is under progress. Also, further experiment on chronic implantation and neural sensory signal

acquisition, and the evaluation of long-term stress on the sciatic nerve is planned to be carried out.

Disclosures: **W. Choi:** None. **H. Park:** None. **J. Kim:** None. **S. Oh:** None. **J. Kim:** None.

Poster

797. Electrical Methods to Modulate Neural Activity II

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Program #/Poster #: 797.18/DD46

Topic: I.08. Methods to Modulate Neural Activity

Support: NIH Grant NS089679
NIH Grant NS111685

Title: Metalized printed microstructures (MPMs): A novel approach for high-density, geometrically-customizable neural interfaces

Authors: J. GLEICK, T. GARDNER, *T. M. OTCHY;
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Abstract: Implantable neural interfaces are engineered devices designed to study and treat the nervous system: cochlear implants restore hearing, deep brain stimulation alleviates Parkinsonian symptoms, and vagal neuromodulation attenuates inflammatory responses for a range of chronic diseases. The enormous potential of these systems - both for therapeutic and basic research applications - has spurred the development of new electrode arrays to interface with targets throughout the nervous system. To enable targeting of more discrete ensembles of neurons - and thus achieve greater specificity - the trend in neural interfacing is toward arrays of ever larger numbers of densely-placed electrodes. However, current electrode fabrication approaches are limited in both the geometry and density that can be achieved.
We aim to overcome this hurdle, increasing the planar reach and spatial densities of electrode sites, while maintaining an electrochemical profile suitable for *in vivo* studies, using our rapid, high-resolution resonant direct laser writing system (rDLW; see Pearre et al. 2018; arXiv:1803.07135). We print geometrically complex acrylic microstructures directly onto the electrode pads of traditionally-fabricated thin-film electrode arrays. These polymer microstructures are subsequently metalized via gold vapor deposition (i.e., sputtering), producing a highly-conductive surface for *in vivo* electrical interfacing. This approach extends the electrochemically active surface out of the two-dimensional plane, potentially allowing for more intimate and efficacious contact with targeted neural structures. In addition, we anticipate that this rDLW-based fabrication process will enable the realization of electrode arrays with geometries, densities, and minimum feature sizes that have not been achievable with current fabrication methods. In addition, our fabrication method supports the rapid production of

different designs using basic CAD software, enabling the on-demand, study-specific prototyping of new electrode configurations within hours. Here, we demonstrate the potential of this fabrication approach with bench-top mechanical testing, *in vitro* electromechanical testing, and acute *in vivo* recordings.

Disclosures: J. Gleick: None. **T. Gardner:** None. **T.M. Otchy:** None.

Poster

797. Electrical Methods to Modulate Neural Activity II

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Topic: I.08. Methods to Modulate Neural Activity

Support: DFG, EXC1086 "BrainLinks-BrainTools"
EU, FP7-HEALTH-2013-INNOVATIO-1602547,"EPIONE"

Title: On stability and longevity of implantable flexible neural electrode arrays

Authors: *T. STIEGLITZ[1,2,3], P. CVANCARA[1], M. VOMERO[1,2], J. PFAU[1,2], F. PIEPER[4], G. ENGLER[4], E. ZUCCHINI[5], E. DELFINO[5], G. GRANATA[6], M. ASPLUND[1,2], S. RASPOPOVIC[7], A. K. ENGEL[8], L. FADIGA[5], P. M. ROSSINI[6], S. MICERA[9];
[1]Microsystems Eng-IMTEK, [2]BrainLinks-BrainTools Cluster of Excellence, [3]Bernstein Ctr. Freiburg, Univ. of Freiburg, Freiburg, Germany; [4]Univ. Med. Ctr. Hamburg-Eppendorf, Hamburg, Germany; [5]Univ. of Ferrara, Fondazione Inst. Italiano Di Tecnologia, Ferrara, Italy; [6]Neurol., Catholic Univ. of The Sacred Heart, Rome, Italy; [7]Dept. of Hlth. Sci. and Technol., ETH Zürich, Zuerich Eth-Zentrum, Switzerland; [8]Dept. of Neurophysiol. and Pathophysiology, Hamburg, Germany; [9]Ecole Polytechnique Federale De Lausanne, Lausanne, Switzerland

Abstract: Flexible neural probes have been established as tools for neuroscience research. While many studies report on short-term implantation, the question remains whether thin-film metallization as electrode material embedded in a flexible polymer is applicable for translational research in chronic settings. We have established micromachining process technology of polyimide with embedded platinum tracks and electrode sites with a total thickness of 10 µm. Electrode sites were coated with iridium oxide to reduce the noise floor in recordings and increase the maximum reversible charge injection rate in stimulation applications. Designs range from flexible shaft electrode with 30 µm width to epicortical arrays with close to 500 recording electrodes in the central nervous system in different animal models (rat, ferret, non-human primate). Electrode site diameters vary from 15 to 1 mm depending on the neuroscientific specification as well as the arrays size. In the peripheral nervous system, transversal intrafascicular multielectrode arrays (TIME) have been developed with 14 electrode sites of 80 µm diameter and probe width of 220 µm for stimulation of peripheral nerves. Human clinical

trials in 7 subjects after limb amputation were conducted. Manufacturing of probes in a cleanroom is of utmost importance to prevent entrapment of dust particles that eventually burns during processing and leave pinholes that reduce insulation in recording applications and might lead to electrolysis of water and destruction of the insulation layer during electrical stimulation. Integration of adhesion layers provided compound stability of the thin-film metallization with the polyimide that serves as substrate and insulation layer at the same time. Reliable assembling of the electrode arrays to cables and connectors is key to ensure longevity. First failures might already occur due to (wrong) handling during implantation within the surgical intervention procedure. (Mis-) use of implantation shuttles, additional glues and surgical tweezers cause disintegration of connectors from the arrays, clotting of electrode sites and destruction of insulation layers or interconnecting lines on the probes since these probes are different in handling than tungsten wires. We were able to conduct chronic experiments with functional recordings in different laboratories and animal species for more than a year in the CNS. Human clinical trials went up to six months with stable stimulation thresholds. Therefore, we conclude that flexible micromachined electrode arrays are suitable for chronic implantation in translational research when proper manufacturing and handling is considered.

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Poster

797. Electrical Methods to Modulate Neural Activity II

Location: Hall A

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Program #/Poster #: 797.20/DD48

Topic: I.08. Methods to Modulate Neural Activity

Support: DARPA N66001-17-2-4010

Title: Electrical stimulation of the vagus nerve modulates intrinsic reward value during decision-making

Authors: A. Z. RAJALA[1], E. M. MUELLER[1], M. E. MALONE[1], J. P. NESS[2], W. ZENG[3], W. B. LAKE[4], R. L. JENISON[1], A. J. SUMINSKI[5], ***L. C. POPULIN**[1];
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Abstract: Electrical stimulation of the vagus nerve (VN) is an effective method to modulate and change the function of the nervous system in a controlled and timely manner due to its direct access to neuromodulatory centers and arousal mechanisms via its projections to the nucleus

tractus solitarius. Pairing stimulation of the VN with behavior is known to increase cortical plasticity during auditory discrimination and motor tasks and drive functional rehabilitation after injury. Importantly, vagus nerve stimulation (VNS) has also been implicated in the improvement of cognitive performance in patients. While the timing of stimulation with respect to behavior appears to be important in sensorimotor tasks, it remains unclear if similar modulation is induced by VNS during different epochs of higher order cognitive tasks. Here we test the hypothesis that applying VNS at different epochs in a temporal discounting task changes the subjective value of the upcoming reward. Two male rhesus monkeys (Macaca mulatta) were chronically implanted with cuff electrodes(2mm ID, 7mm inter-electrode spacing, LivaNova Inc) on the cervical VN using sterile technique. Following recovery, they were tested in a temporal discounting task that required them to choose between an immediate small reward (SS) or a large reward given after a long delay (LL). Eight fractal images represented each of the 4 SS and LL conditions. The SS delay was constant at 0 sec with 4 reward magnitudes (0.2, 0.3, 0.4, and 0.5 mL) while the LL reward magnitude was constant at 0.59 mL with 4 delay times (2, 4, 8, and 16 sec). The task required fixating a red dot straight ahead, after which two images appear to the right and left of the fixation representing the SS and LL. When the fixation dot was turned off, the subject made an eye movement towards one of the images indicating his reward choice. A set of 16 blocks of 10 trials each contained all possible combinations of SS and LL and were presented in either ascending or descending order. VNS was performed using trains of 8 biphasic (cathode leading) pulses 100-250mA or 450-600mA, 200us per phase, 30Hz and was delivered at image presentation on every trial. Behavioral data were modeled using a hyperbolic discounting function and a probability choice model to estimate the rate of temporal discounting and the randomness of choice. VNS at the time of image presentation reduced the rate of temporal discounting but increased the randomness of choice as a function of increasing stimulation amplitude in the ascending condition. The data suggest that VNS modulates cognitive function in the context of the temporal discounting task. Future work will examine the neural mechanisms underlying these changes.

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Poster

797. Electrical Methods to Modulate Neural Activity II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 797.21/DD49

Topic: I.08. Methods to Modulate Neural Activity

Support: DARPA NESD (N666001-17-C-4013)
Private gift

Title: Patterned cortical microstimulation by wireless ensembles of chronically implanted microelectronic chiplets in freely moving rat model

Authors: J. LEE[1], F. L. LAIWALLA[1], ***A.-H. LEE**[2], E. MOK[1], V. LEUNG[4], S. SHELLHAMMER[5], L. LYNCH[1], Y.-K. SONG[3], L. LARSON[1], A. V. NURMIKKO[1]; [1]Sch. of Engin., Brown Univ., Providence, RI; [2]Grad. Sch. of Convergence Sci. and Technol., Seoul Natl. Univ., Seoul, Korea, Republic of; [3]Seoul Natl. Univ., Suwon/Gyeonggi-do, Korea, Republic of; [4]Electrical engineering, Univ. of California San Diego, La Jolla, CA; [5]Qualcomm, San Diego, CA

Abstract: To achieve high-density and multi-areal cortical interfaces, we have proposed an approach where microscale, autonomous, wireless devices offer an alternative to e.g. current monolithic microelectrode array. Other groups have proposed related and free-floating microstimulator (Muller et al., 2019 and Etienne-Cummings et al., 2018). At present, demonstrating scalability is a critical bottleneck as published works are so far limited to only a few stimulation channels which will be not enough for a cortical prosthesis application. Here, we describe and demonstrate an independent 56 channels microscale (~500 µm size) ensemble as a wireless networked system of "Neurograins" for time-programmable patterned cortical electrical microstimulation. In our system, each neurograin harvests energy transcutaneously near 1 GHz radio frequency (RF) for power and communicates bi-directionally through a custom inductive wireless system. Along with the RF circuits, the chiplets house digital logic and a programmable current source, enabling up to 25 uA bipolar current injection Individual chips have a unique laser-written address as an additional customized feature. The chiplets were post-processed to integrate PEDOT: PSS planar electrodes for epicortical use or equipped with intracortical penetrating microwires. Radio-frequency power and telecommunications management are handled by software defined radio which serves a wearable external "Epidermal Skinpatch" unit for mobile use. The Skinpatch transmits commands for the full ensemble of neurograins by time-domain multiplexing setting stimulation parameters for each chip. Network protocol and the hardware is capable of control more than 1000s of neurograins, though only 56 chiplets were in this work due to the anatomical constraints of the rat animal model. Selective patterned stimulation by the neurograin array was first validated in ex-vivo mouse brain slice experiment with a single chip evoking significant local field potential changes in the target cortical area. To characterize the chronic performance of the system, we have implanted 56 chips with intracortical microwires to multiple cortical areas of rats. Bilateral craniotomy was performed to maximize the neurograin interarea coverage across the motor, the somatosensory and the visual cortices. The freely moving animals performed a standard detection task to learn to associate cortical microstimulation with a reward at report ports in a chamber. The results of ex-vivo and in-vivo experiments validate the capability of ensembles of our microdevices system to selectively modulate neural activity through patterned electrical stimulation.

Disclosures: J. Lee: None. **F.L. Laiwalla:** None. **A. Lee:** None. **E. Mok:** None. **V. Leung:** None. **S. Shellhammer:** None. **L. Lynch:** None. **Y. Song:** None. **L. Larson:** None. **A.V. Nurmikko:** None.

Poster

797. Electrical Methods to Modulate Neural Activity II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 797.22/DD50

Topic: I.08. Methods to Modulate Neural Activity

Title: Effect of estrous cycle on stimulation thresholds of the dorsal nerve of the clitoris to reflexively activate the external urethral sphincter in rats

Authors: *R. JUAREZ, Sr[1], Y. CRUZ[2];
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Abstract: Pelvic functions are under control of the nervous system. Innervation of pelvic organs can be damaged during pelvic surgeries or during natural reproductive processes, such as childbirth. This is supported by previous observations in an animal models of vaginal distension in rats. The application of electric current to nerves can be used as a treatment for nerve regeneration due to the fact that this treatment induces the release of neurotrophins in rats. The external urethral sphincter (EUS) neural circuit can be activated reflexively through mechanical stimulation of the clitoris, suggesting that the EUS neuromuscular circuit may be reflexively modulated by transcutaneous electrical stimulation (TES) of the dorsal nerve of the clitoris (NDC). In addition, it has been shown that the receptive field of the pudendal nerve changes across the estrous cycle. Thus, the objective of the present study was to determine the electrical current threshold for TES of the DNC that triggers the activity of EUS in female rats, and to compare the differences between two phases of the estrous cycle; diestrus and estrus. Adult female Wistar rats were used 4 in diestrus and 4 in estrus. The animals were anesthetized with urethane. The electromyograms (EMG) of the EUS were recorded, the electrical stimuli were applied to clitoral skin using a stimulator, and the current was kept constant. The TES of the clitoris sheath was applied by bipolar electrodes. Current stimuli of 10 µA to 14 mA were applied until the EUS response was observed. The results show that the EUS EMG activity was triggered by TES and that the stimulation thresholds are affected by the estrous cycle conditions of the rat, estrus rats require less current (2.6±2.5mA) to trigger the reflex than animals in diestrous (8.8±1.5 mA). Is concluded that different electrical stimulation parameters should be used depending on the estrous cycle and the area of interest to be stimulated. FUNDING: CONACYT RJM 623059; SEP-DEGESO.

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Poster

797. Electrical Methods to Modulate Neural Activity II

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Topic: I.08. Methods to Modulate Neural Activity

Support: NSF IGERT 120104
NSF CBET-1351692

Title: Fully implanted millimeter-sized wireless neural stimulators based on magnetoelectric materials

Authors: *A. WICKENS[1], J. CHEN[1], S. DUTTA[1], Z. CHEN[1], N. VERMA[1], B. AVANTS[1], P. T. M. KAN[2], R. GARCIA[2], S. A. SHETH[3], C. KEMERE[1], J. T. ROBINSON[1];
[1]Rice Univ., Houston, TX; [2]Baylor Col. of Med., Houston, TX; [3]McGovern Med. School-UTHealth, Houston, TX

Abstract: Miniature electrical neural stimulators enable less invasive surgical implantation and the ability to target tiny nerves or brain areas. However, as these neural stimulators become smaller, we must engineer new ways to deliver power. Conventional power deliver relies on long wires to deliver power from an implanted battery or subcutaneous antenna. These leads can limit device placement and cause device failure due to lead breakage or infection. To address this critical need, several wireless neural stimulation technologies have been demonstrated; however most of these technologies cannot generate effective stimulation amplitudes at therapeutic frequencies when placed more than a few millimeters away from the power transmitter. Approaches that can generate sufficient power have limited channel count or stimulation frequency.
Here we show that magnetoelectric devices can harness enough power from an externally applied magnetic field to deliver effective therapeutic stimulation at frequencies approaching 100 Hz. These materials show excellent power densities even as the devices are made small allowing them to be fully implanted and wirelessly powered. We demonstrate that these mm-sized wireless devices can be used to power different types of conventional stimulation electrodes when implanted in rabbits, pigs, and freely moving rats. Furthermore, these miniature electrical stimulators can be adapted to power many individually addressable stimulation channels while still maintaining a small overall device footprint.

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Poster

797. Electrical Methods to Modulate Neural Activity II

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Program #/Poster #: 797.24/DD52

Topic: I.08. Methods to Modulate Neural Activity

Support: NSF Piper Health Solutions Seed Grant
NSF Integrative Graduate Education and Research Traineeship

Title: Effects of transcutaneous electric nerve stimulation on proprioceptive discrimination

Authors: A. LEVITSKY, J. KLEIN, P. ARTEMIADIS, *C. A. BUNEO;
Arizona State Univ., Tempe, AZ

Abstract: Proprioceptive loss is a common sequelae of several neurological conditions. However, the clinical evaluation and treatment of proprioceptive loss remains largely inadequate. Recent studies employing robots have greatly improved our understanding of limb proprioception in both neurologically intact subjects as well as patients, but the extent to which proprioception is modifiable by interventions such as exogenous neuromodulation is unclear. To investigate this, we used a proprioceptive discrimination task and signal detection analysis to characterize upper limb proprioceptive function following the application of transcutaneous electric nerve stimulation (TENS) delivered to the cervical spine. The right arms of human subjects were coupled to a trough that was held by a 7 degree-of-freedom robot arm. Sensitivity to imposed displacements of the endpoint of the arm was evaluated using a “same/different” task, where on each trial, subjects’ hands were moved from a reference position, along a distracter loop, to a judgment position located 1-4 cm away. At the end of each displacement, subjects were required to respond ‘same’ if the judgment position was the same as the reference position or ‘different’ if it was not. These responses were used to compute sensitivity and bias. Four groups of 20 subjects were tested. All groups had electrodes applied to the cervical spine at the C3/C4 level. One group served as a sham and received no stimulation. The remaining groups received TENS at one of 3 frequencies (30 Hz, 300 Hz, and 3 kHz) for 10 minutes prior to performing the task. No stimulation was provided during task performance. Sensitivity and bias were analyzed statistically using 2-factor mixed ANOVAs, with distance as a within-subjects factor and frequency as a between-subjects factor. A significance level of $\alpha = 0.05$ was used for all tests. As expected, sensitivity increased monotonically with displacement distance, an effect that was statistically significant. Although no main effect of frequency on sensitivity was found ($p=.162$), there was a significant interaction between frequency and distance. Bias also varied with distance, tending to be greatest at 1-2 cm but decreasing precipitously for larger distances. Although the effect of distance was statistically significant, there was no statistically significant effect of frequency ($p=.158$) and no significant interaction effect ($p=.902$). In summary,

transcutaneous electrical stimulation of cervical spinal nerve afferents appears to have beneficial effects on proprioceptive discrimination, but these benefits depend on both stimulation frequency and discrimination distance.

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Poster

797. Electrical Methods to Modulate Neural Activity II

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Program #/Poster #: 797.25/DD53

Topic: I.08. Methods to Modulate Neural Activity

Title: Kinetic augmentation of deep brain stimulation programming optimization across multiple motor symptoms in essential tremor

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Abstract: Successful programming of Deep Brain Stimulation systems in the treatment of movement disorders is influenced by two factors: (i) electrode placement, and (ii) post-surgical optimization of the setting of stimulation parameters (contacts, polarity, amplitude, pulse width, frequency). Currently, optimization involves a clinician manually sweeping through a multitude of stimulus parameters to identify the most beneficial setting for the patient and often relies on trial and error. Furthermore, improvements in symptoms in response to changes in these settings are based on clinical judgment, and less than ideal. In this study, we developed a computationally efficient, symptom-based, kinetic assessment to augment DBS programming. We tested the notion that stimulation programming that utilized an objective assessment of motor symptoms would allow for selection of parameters based on quantitative measures rather than being solely reliant on clinical judgment. We evaluated the feasibility of a kinetic assessment alongside standard programming methods as a means of objective optimization and verification of successful DBS programming. The subject was a 69-year-old male with a 22-year history of essential tremor (ET) prior to undergoing DBS surgery. Six months post-surgery, and multiple programming sessions later, he presented with worsening tremor and gait ataxia, which may occur in ET. At this time, balance testing using a force plate was undertaken both pre- and post-programming. Balance testing consisted of ten, 20-second trials, half with eyes open and half with eyes closed. Balance score was calculated as the average COP excursion across the trials respectively. Furthermore, the postural sway signal was divided into 4 frequency bins following a continuous wavelet transform to glean out contributions of postural (0-4 Hz) and ET (4-10 Hz) oscillations pre- and post-programming. Our findings demonstrate a significant improvement in multi-directional postural sway, fall-risk, and a reduction in tremor (sway oscillations >4 Hz)

under both testing conditions post-programming. In this first of a kind feasibility study, we demonstrated the use of an objective balance measurement tool for augmenting and validating current DBS programming standard of care. DBS has been shown to be effective in the significant suppression of tremor. Our findings extend this to balance and fall risk. This kinetic assessment provides both time- and cost-effective method to help optimize programming of DBS systems.

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Poster

797. Electrical Methods to Modulate Neural Activity II

Location: Hall A

Time: Wednesday, October 23, 2019, 1:00 PM - 5:00 PM

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Topic: I.08. Methods to Modulate Neural Activity

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Title: Histological evaluation of anatomical differences of cervical vagus nerve in pig to inform vagal nerve stimulation

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Abstract: Cervical vagal nerve stimulation (VNS) is an FDA approved treatment for epilepsy and depression and is currently being evaluated for treatment of numerous other disorders including pain, anxiety, cognition and memory, as well as inflammatory disorders. VNS also received European market approval for heart failure, bronchoconstriction and diabetes; however approval for these indications was based on studies in animals such as dogs and rats, whose vagal nerve size may not have been representative of humans. When subjected to double-blinded, randomized, sham controlled studies for subsequent U.S. approval, many of these CE-marked VNS indications failed to meet their primary efficacy endpoints. More than 100,000 patients have undergone VNS, but despite the efficacy of vagal nerve stimulation in a subset of

patients, many fail to reach stimulation levels that result in alleviation of symptoms without triggering unwanted side effects.
Post-hoc studies of the patient population have suggested that VNS may not engage the intended fiber pathways in humans, despite engagement in preclinical studies in mouse, rat, or dog. Stimulation parameters were limited in these studies as they first activated unintended fibers that cause side effects such as cough, voice alteration, and dyspnea. Discrepancies between stimulation amplitude needed for intended effect versus unwanted side effect could be directly related to the relative size of the vagus nerve in across animal models, variations in fascicle organization, or variations in branching patterns. To address translating improvements in VNS from the lab to the clinic, neuroanatomical evaluation of the cervical vagus and surrounding nerves with respect to placement of the epineural cuff is critically important.
We evaluated the utility of the porcine model in approximating the clinical environment, due to the similar size and fascicular organization of porcine and human vagus nerves. Using Masson's trichrome stain, microdissection, ultrasound and MicroCT we determined the organization and distribution of fascicles throughout the cervical vagus trunk, as well as their relationship to cervical branches that may be involved in side-effects, including the superior and recurrent laryngeal branches. Leveraging this anatomical mapping, we seek to inform vagal nerve stimulation in terms of cuff placement for target engagement, without causing unwanted side effects through activation of muscles innervated by the vagus.

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Poster

797. Electrical Methods to Modulate Neural Activity II

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Title: Cortical changes induced by neuromodulation during a working memory task

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Abstract: Transcranial alternate current stimulation (tACS) is emerging as an effective and versatile clinical tool to prime brain activity prior to or during neurorehabilitation and can be applied to foster plasticity induction [1]. However, neurophysiological changes induced by tACS are only partially understood [2].
High-density electroencephalography (hdEEG) is now an effective methodology for brain research, because it allows to perform accurate source localization from its signals [4]. hdEEG is especially useful in this context, given its application in a wider variety of experimental framework with respect to traditional brain imaging techniques.
We developed a platform based on source localization from hdEEG aiming at investigating the cortical changes induced by a rehabilitation protocol, involving a cognitive (or motor) task, with/without tACS. Here we present the results related to testing our system with a protocol involving a working memory (WM) task [5] with the goal of: (i) investigating which brain regions and in which frequency bands are modulated during a working memory task, and (ii) correlate behavioral effects of tACS neuromodulation during task with change in brain signals.
Neural activity via hdEEG was assessed focusing on changes of activity across the cognitive network. We first reconstructed neural oscillations in the cortex [3] and we then applied event related synchronization and desynchronization analysis on the reconstructed signals, and investigated how WM load and tACS modulate brain plasticity.
Preliminary results of data without stimulation indicated a frequency and location specific modulation of brain signals. Moreover, we found an increase in task performance following the stimulation.
Further, we will extend the study to neurological patients with cognitive impairments (e.g. Huntington disease). This will shed light on the neural machineries underlining the beneficial effects of a NIBS-based rehabilitation protocol and will exploit usability of our platform for investigation of rehabilitation of neurological disease.
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